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1A – Treatment of Acute Pancreatitis

O01

Restoration of the Passability of the Choledoch Distal Part in Case of the Acute Biliary Pancreatitis

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Introduction: ERCP is widely used procedure with significant risk of complication. It is necessary to search safer alternative.

Patients & Methods: Patients with diagnosed biliary pancreatitis were included to prospective study from January 2008 to December 2010. The including criterion was disorder of passability of the terminal part of choledoch without cholelithiasis. ERCP were performed in 133 patients. The dilatation of choledoch more then 10 mm, reflux to the main pancreatic duct, the delay of contrast evacuation to the duodenum were observed in all cases. The endoscopic balloon dilatation of papilla as first stage was performed in all cases.

Results: The positive effects (reduction of clinical symptoms, normalization of biochemical indices, and decrease of the choledoch diameter during repeated ERCP) were observed in 101 cases. This group hadn’t complications. Absent or short-term positive effect was in 32 patients. Endoscopic papillosphincterotomy (EPST) was carried out (after preliminary preparation) in this group. The following complications were observed: bleeding in 3 cases, progressing of pancreatitis in 5 cases. Complications were stopped by conservative treatment. And one patient had severe acute pancreatitis which had had open operation.

Conclusions: Endoscopic cylinder dilation is effective and safe method of restoring the passability of the terminal part of choledoch in case of the acute biliary pancreatitis. EPST should be performed in case of absence or short-term positive clinical effect of cylinder dilatation as second stage.

O02

Refeeding Wisdom in Mild Acute Pancreatitis

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Introduction: The concept of enteral nutrition currently is widely accepted and replaced pancreatic rest. In mild acute pancreatitis, oral refeeding is recommended as soon as possible, but when and what to restarting oral refeeding is still controversial.

Objectives: To investigate the effect of early oral refeeding on patients with mild acute pancreatitis.

Patients & Methods: Patients with mild acute pancreatitis was randomized to Control group (n = 77) and Earlier refeeding group (n = 80). In Control group, oral refeeding was initiated when symptoms release and laboratory results returned to normal. In Earlier refeeding group, patients restarted eating when they felt hungry and wanted to eat. Patients were evaluated daily for severity of the disease before refeding. Recurrence of pain, transitional abdominal distention, glycemic rise, serum levels of enzymes, and length of hospitalization were monitored after refeding. Diet advancement and hospital discharge were determined according to the standard established before.

Results: The days of oral refeding after abdominal pain onset and the length of hospitalization was 4.63 ± 1.59d, 6.9 ± 2.1d in Earlier refeeding group and 6.83 ± 2.31d, 10.1 ± 3.4d in Control group, respectively (p = 0.00). The number of patients with pain relapse and transitional abdominal distension after oral refeding was 8 (10.4%), 6 (7.8%) in Earlier refeeding group and 3 (3.75%), 2 (2.5%) in Control group. (p = 0.1342, p = 0.1626, separately.) While, the number of serum amylase or lipase elevated higher than upper limit of maximum (ULM) after refeding was 2 in Earlier refeeding group and 0 in Control group (p = 0.1626).

Conclusion: The time interval between symptom onset and refeeding and length of hospitalization (LOH) were dramatically shortened when patients restarted oral refeding just according to their subjective feeling of hunger. The remission of symptom and normalization of serum amylase or lipase is not imperative in patients with mild acute pancreatitis.
Treatment Results of Necrotizing Pancreatitis in a Prospective Multicenter Cohort of 639 Patients


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Introduction: In recent years, treatment of necrotizing pancreatitis has changed towards more conservative and less invasive strategies but prospective data are lacking.

Objectives: We describe treatment results in a prospective multicenter cohort covering the entire clinical spectrum of necrotizing patients.

Patients & Methods: From 2004 to 2008, 639 consecutive patients with necrotizing pancreatitis from 21 Dutch hospitals were prospectively included in this observational cohort study. Data on disease severity, interventions (i.e., radiological, endoscopical, surgical) and outcome were recorded.

Results: Overall mortality was 15% (n=96). Organ failure occurred in 240/639 patients (38%), with 35% mortality. Treatment was conservative in 397/639 patients (62%) with 7% mortality. An intervention was performed in 242/639 patients (38%), with 27% mortality; this included early emergency laparotomy in 35/639 patients (5%), with 78% mortality. The longer the time between admission and intervention, the lower the risk of mortality: 0–14 days; 56%, 14–29 days; 26% and >29 days; 15%. P < 0.001; this difference persisted after correction for disease severity. 208/639 patients (33%) underwent intervention for infected necrosis, with 19% mortality. Catheter drainage was most often performed (63%) as first intervention, without additional necrosectomy in 35% of patients. Primary catheter drainage had fewer complications than primary necrosectomy (42% vs. 64%, P = 0.003), mainly due to less post-intervention new onset organ failure (17% vs 31%, p = 0.02).

Conclusion: Two-thirds of patients with necrotizing pancreatitis can be treated without an intervention and have relatively low mortality. In patients with infected necrosis, delayed intervention and catheter drainage as first treatment improves clinical outcome.

1B – Prognostic Markers in the Course of Pancreatitis

Difference in the Early Activation of Inflammation Markers in Acinar-Cell Rich Compared to Fibrotic Human Pancreas Exposed to Surgical Trauma and Hypoxia

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Introduction: Postoperative pancreatitis often precedes other complications after pancreato-duodenectomy operation. We have shown that the risk for postoperative complications increases significantly, when there are more than 40% of acinar cells in the transection line of pancreas. We hypothesized that the intra-operative pancreatic injury leads to immediate activation of inflammation cascade in the transection line of the remnant of pancreas, and that this activation might be different in acinar-cell rich compared to fibrotic pancreas.

Objectives: The aim of this study was to analyse the expression of inflammation markers in the transection line of human pancreas after pancreato-duodenectomy both in acinar-cell rich and fibrotic pancreata.

Materials & Methods: In pancreato-duodenectomy operation, several pancreatic samples from six patients, 3 with acinar-cell rich and 3 with fibrotic pancreas, were exposed to surgical trauma, and thereafter to hypoxemia for 15 min, 1h, 2h, 4h or 6h, to mimic the conditions at the transection line of the pancreas remnant in the patient. Immunohistochemical analysis of inflammation markers was performed on formalin-fixed, paraffin-embedded samples.

Results: In the acinar-cell rich pancreata, intra-acinar cell NFkB -activation, and intra-acinar and intra-ductal MCP-1 expression increased from mild/none at 15 min to 1h, 2h, 4h or 6h, to mimic the conditions at the transection line of the pancreas remnant in the patient. Immunohistochemical analysis of inflammation markers was performed on formalin-fixed, paraffin-embedded samples.
detected during the 6h monitoring, but due to the fewer overall number of acinar cells, the tissue expression of these markers remained lower.

**Conclusions:** In human pancreas which is rich in acinar cells the inflammation cascade begins almost immediately after induction of injury by surgical trauma and hypoxemia. Fibrosis may protect the pancreas from developing clinically relevant inflammation.

### O05
**Validation Study of Revised Atlanta Classification for Acute Pancreatitis Including Moderately Severe Acute Pancreatitis: A Mortality Analysis**

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**Background:** The Atlanta classification of patients with acute pancreatitis has been considered inadequate for predicting outcome. Recently, a revised version to include a patient group with moderately severe acute pancreatitis has been proposed.

**Objective:** To validate this revised classification using an existing data set.

**Methods:** Data from 290 patients were reviewed. Patients with predicted severe acute pancreatitis (APACHE-II >6) from 78 hospitals in the UK were previously studied in a trial of lexipafant. Organ failure was assessed daily for the first week, and all clinically relevant local complications were recorded. The associations between early organ failure, local complications and in-hospital mortality were analysed.

**Results:** Of the 286 patients included in the analysis, 165 (58%) had early organ failure of whom 59 (36%) had associated local complications. Twelve patients (4%) had local complications without organ failure. A total of 35 in-hospital deaths (12%) were due to acute pancreatitis. Thirty-four of the 35 deaths (97%) were in patients who had organ failure. In-hospital mortality was 36% in patients with both early organ failure and local complications and 12% in patients with early organ failure without local complications. Among patients with local complications without early organ failure (n = 12), only one (8%) died in-hospital.

**Conclusion:** Patients with predicted severe acute pancreatitis and no early organ failure have a low mortality risk irrespective of local complications. Our data support the concept of moderately severe acute pancreatitis to describe patients with local complications without early organ failure.

### O06
**The Harmless Acute Pancreatitis Score – Clinical Implications on Management of Patients with Acute Pancreatitis**

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**Introduction:** The Harmless Acute Pancreatitis Score (HAPS) is a scoring system to identify patients with non-severe acute pancreatitis.

**Objectives:** The aim of our retrospective review was to evaluate the reproducibility of the HAPS outside its original settings.

**Patients & Methods:** Baseline information of all hospitalized cases of acute pancreatitis at the Karolinska University Hospital, Stockholm between 2004 and 2009 were collected from the available registries. The focus was on the parameters that constitute the HAPS: abdominal status, levels of creatinine and hematocrit. In the cases where hematocrit was missing we replaced it with hemoglobin, which was strongly statistically correlated when both were present.

**Results:** In total, 531 patients with both first-time and recurrent acute pancreatitis were included. Among the patients who were available for analysis according to the original HAPS (n = 353) it was predicted a non-severe course in 79 patients of whom only 1 patient actually had a severe course (95% CI: specificity 96.3% and positive predictive value 98.7%). When analyzing the entire material with hemoglobin instead of hematocrit (n = 531) the HAPS predicted a non-severe course in 182 patients of whom only 2 patients had severe complications (95% CI: specificity 94.3% and positive predictive value 98.9%).

**Conclusion:** The HAPS has a high specificity to predict non-severe course of acute pancreatitis and is therefore a suitable tool in clinical praxis where early screening is of importance in order to treat the patients at an optimal level of care.
Characterization of Amino Acid Transporters in Healthy or During Acute Pancreatitis Mouse Exocrine Pancreas


Introduction: The exocrine pancreas accumulates extracellular amino acids (AA) against a marked concentration gradient. Accumulation of radiolabeled AA has been envisaged as a non-invasive test of exocrine pancreatic function. Despite the importance of pancreatic acinar cell AA uptake for the synthesis of digestive enzymes and thus for functional diagnostic methods, few studies have been performed as yet to characterize AA transporter expression, cellular localization, or its regulation.

Objectives: The aim of this study is to characterize AA transporter expression in healthy and acute pancreatitis mouse models.

Materials & Methods: We analysed the RNA expression levels of 35 genes from seven different AA transporter families by quantitative real time PCR and confirmed the acinar localization of the proteins by immunofluorescence.

Results: We could identify the RNA expression and confirm the localization at acinar cells of four transporters. The broad range neutral AA transporters, LAT1 and LAT2 (Slc7a5 and 8) as well the glutamine transporters, Snat3 and 5 (Slc38a3 and 5), were localized on the basolateral membrane of acinar cells. During acute pancreatitis, the RNA expression of the glutamine transporter Snat5 decreased 10 fold. The expression of several other genes was modified during pancreatitis.

Conclusion: The presence and the localization of different epithelial AA transporters could be confirmed in acinar pancreatic cells. We observed changes in the expression of several genes during acute injury. This new knowledge might lead towards the development of new non-invasive imaging methods to monitor the functional state of the exocrine pancreas.

Primary Acinar Cell Culture is Appropriate for Research of Early Pathophysiologic Events in Pancreatitis

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Introduction: Together with isolated pancreatic acinar cells and tumor cell lines, primary acinar cell culture could be a relevant model for research of early pathophysiologic events in pancreatitis. Because of that, we aimed at evaluating the number and viability of acinar cells, its morphology and enzyme activity on primary culture.

Methods: Pancreatic tissue was obtained from male Swiss mice. Acinar cells were isolated by enzymatic and mechanical tissue dissociation, filtration and centrifugation. Cell viability was assessed by trypan blue exclusion. Acinar cells were cultured in DMEM Hams, fetal bovine serum 15% and streptomycin-penicillin. Morphology and amylase activity (colorimetric method) were assessed at 24 hour intervals. Morphological changes and acinar and stellate cell proliferation were evaluated by inverted and confocal microscopy.

Results: Seven experiments were performed. Mean acinar cell number was 4.12 3 10^4 cells/ml and viability was of 77%. At day 2, viable acinar cells were attached to the bottom of the plate and amylase secretion increased fourfold. Intracellular amylase decreased by 60% at day five. From day 5, stellate cells were activated in periacinar areas. At day 9, acinar cells started the senescence and stellate cells proliferated to reach a 90% confluence.

Conclusions: Acinar cells are viable up to 9 days, and intracellular amylase concentration was maintained up to day 5 in primary culture. Primary acinar cell culture is thus appropriate for research of early pathophysiologic events in pancreatitis. Factors secreted by acinar cells in primary culture appear to play a role in stellate cells activation.

Cathepsin D Regulates Trypsin Activity in Pancreatic Acinar Cells by Controlling Cathepsin B Activity


Introduction: Premature intracellular activation of trypsinogen is considered to be a key event in the pathogenesis of acute pancreatitis. Cathepsin B has been shown to be a trypsin activator while cathepsin L inactivates trypsin. We have characterized the role of the
2B – Metabolic Changes in Pancreatic Cancer Cells

**O10**

**Predictive Factors of Tumor Control in Patients with Pancreatic and Non-pancreatic Well Differentiated Digestive Endocrine Carcinomas Treated with Lanreotide**

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**Introduction:** The antiproliferative effect of somatostatin analogs was recently demonstrated.

**Objective:** To identify factors associated with tumor control in a group of patients with well differentiated digestive endocrine carcinoma (WDEC) treated with lanreotide.

**Patients & Methods:** A retrospective study was conducted in 68 patients with WDEC treated with lanreotide alone, progression-free survival being the primary endpoint. The influence of the following factors was searched for by uni- and multivariate analysis: age, gender, discovery mode, origin of the primary tumor, metastatic spread Ki 67 proliferation index, grade of uptake on somatostatin receptor scintigraphy, pre-treatment tumor evolutivity, extent of liver involvement, resection of primary tumor, prior treatments, tumor markers.

**Results:** Tumor progression was observed in 39/68 pts (57.4%). The median progression-free survival was 29 months. In univariate analysis, resection of primary tumor (p=0.0005), Ki67 index ≤ 5% (p=0.0001), stable disease before treatment (p=0.0005), liver tumor involvement ≤ 25% (p=0.005) and decreased levels of chromogranin A ≥ 50% or normalization at 6 months (p=0.0006) were predictive of disease stability during lanreotide treatment. At multivariate analysis, Ki67 index ≤ 5% (HR = 0.323, p = 0.027), pre-treatment stability (HR = 0.252, p = 0.012) and liver tumor invasion ≤ 25% (HR = 0.344, p = 0.036) were significantly associated with disease stability under lanreotide. Gender, age, nature of the primary tumor, discovery mode, functionality, presence of extrahepatic metastases were not predictive factors of tumor control by lanreotide.

**Conclusion:** Patients suffering from WDEC with Ki67 proliferation index ≤ 5%, stable disease before treatment and moderate liver invasion (≤ 25%) are the best responders to lanreotide treatment. There is no difference between pancreatic and non-pancreatic tumors. These data if confirmed in prospective trials will help rationalizing the use of somatostatin analogs in an antiproliferative aim.

**O11**

**Cachexia vs. Obesity: How Do Body Mass and Body Fat Distribution Influence the Postoperative Course After Pancreatectoduodenectomy?**


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**Introduction:** Prognosis after pancreatectoduodenectomy for primary adenocarcinoma of the pancreas is not only determined by tumor and surgeon but also by the patient’s physical condition.

**Objectives:** Our study aimed to assess the effect of patient’s body mass index (BMI) and fat distribution on the postoperative course.

**Methods:** 408 patients who underwent a Whipple operation at our department between 2001 and 2010 were followed-up in a prospective database. Preoperative CT-scans were analysed double-blinded for the following parameters: abdominal wall (AW), hip girdle (HG) and visceral (VF) fat thickness and “depth” of the surgical site. These and preoperative parameters including weight and height were stratified to equally sized subgroups. Additionally, post-operative parameters including mortality, non-surgical and surgical complications (delayed gastric emptying, pancreatic fistula, bleeding, relaparotomy, intraabdominal abscess and wound infection) were analysed and statistically correlated with BMI and fat distribution.
Abstracts

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Papers

012
Diabetes Associated with Disease of Exocrine Pancreas: A Prospective Observational Study

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Introduction: Scanty data are available on diabetes mellitus associated with exocrine pancreatic disease.

Objectives: 1. to define the prevalence, risk factors, and etiopathogenetic aspects of diabetes mellitus associated with exocrine pancreatic disease. 2. to evaluate the role of glucose metabolism, insulin resistance and insulinemia in prognosis of cancer pts

Methods: A prospective observational study was performed on pts proposed for pancreatic surgery from 1/2008 to 9/2010. 357 pts were characterized for gender, age, weight, BMI, history of diabetes, hypogl. therapy, family history, blood glucose, insulinemia, HbA1c, GADA, IA-2A, IAA, ZnT8A, b cell function (HOMA2B), insulin resistance (HOMA2-IR and -S). In pts undergoing cancer resection disease-free and overall survival were assessed.

Results: 35.3% of pts were diabetic (28% with known and 7.3% with newly diagnosed diabetes); normoglycaemia was present in 45.8% of pts while impaired fasting glucose (IFG: 101–125mg/dl) was present in 18.9%. In pts with known diabetes, onset was 34 months before admission (median). The treatment was insulin in 42.6%, OHA in 38.3%, insulin +OHA in 4.3% and diet in 14.9%. In a multivariate analysis, significant risk factors for diabetes were age, familiarity for diabetes and diagnosis of ductal adenocarcinoma. HOMAs showed that in diabetic pts the main defect is insulin secretion, being insulin resistance less affected. Islet autoantibodies (table) were present in a subgroup of pts. Finally, in cancer pts insulinemia and insulin resistance (HOMA2IR) were independent risk factor for tumor progression in Cox regression analysis.

Conclusions: diabetes associated with exocrine pancreas disease is a complex clinical entity with unique characteristics.

013
Influence of Obestatin Administration on the Course of Cerulean Induced Acute Pancreatitis in Rats

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Introduction: Previous studies have shown that administration of obestatin inhibits the development of acute pancreatitis and accelerates the healing of acetic acid-induced gastric ulcers. Aim of the present study was to determine the influence of obestatin administration on the course of cerulein-induced acute pancreatitis and pancreatic recovery.

Material & Methods: Acute pancreatitis was induced by cerulein given i.p. 5 times with 1 h intervals at the dose of 50 μg/kg/dose. Obestatin was administered twice a day at the dose of 8 nmol/kg/dose, starting the first dose 24 h after the last injection of cerulein. Severity of acute pancreatitis were examined 0 h or 1, 2, 3, 5, 7 and 10 days after the last injection of cerulein.

Results: Administration of cerulein led to the development of acute oedematous pancreatitis in all rats and maximal severity of this disease was observed 24 h after induction of pancreatitis. Treatment with obestatin reduced morphological signs of pancreatic damage such as pancreatic oedema, leukocyte infiltration and vacuolization of acinar cells, and led to earlier regeneration of the pancreas. Biochemical indexes of the severity of pancreatitis such as serum activity of pancreatic digestive enzymes were significantly reduced in animals treated with obestatin. These effects were accompanied with an increase in pancreatic DNA synthesis and a decrease in serum level of pro-inflammatory interleukin-1β. Administration of obestatin improved pancreatic blood flow in rats with acute pancreatitis.

Conclusions: Treatment with exogenous obestatin reduces severity of acute pancreatitis and accelerates pancreatic recovery in this disease.

3A – Experimental Acute Pancreatitis

014
Influence of Obestatin Administration on the Course of Cerulean Induced Acute Pancreatitis in Rats

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Conclusions: Treatment with exogenous obestatin reduces severity of acute pancreatitis and accelerates pancreatic recovery in this disease.
**O14**

**Proteomic Analysis of the Acidic Soluble Proteins of the Pancreas in Experimental Acute Pancreatitis**


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**Introduction:** Alterations of protein expression within the initiation phase of acute pancreatitis (AP) play an important role in the development of this disease.

**Objective:** To determine the acidic proteins that are differentially expressed in the soluble fraction of rat pancreas during the early phase of cerulein-induced AP.

**Material & Methods:** AP was induced by two intraperitoneal injections of 20 ug cerulein per kilogram body weight at hourly intervals. Subcellular fractionation was carried out in the postnuclear homogenate of pancreata and the proteins from the soluble fraction were separated by 2D-PAGE using pH gradients of 3–5.6. The differentially expressed proteins that appeared or whose expression level was more than three-fold increase in cerulein-treated rats compared to non-treated rats were identified by MALDI-TOF-TOF MS analysis. Changes in some altered proteins were further assessed by Western blotting.

**Results:** Soluble acidic proteins overexpressed in the early phase of cerulein-induced AP were detected: proteases (Carboxipeptidases A1, A2 and B1), inflammatory markers (Alpha-1-inhibitor III, Alpha-1-macroglobulin), neutrophil elastase proteins (Thioredoxin-like1), molecular chaperones (Tumor rejection antigen gp96), redox regulation and antioxidant enzymes (Peroxiredoxin-2), serine protease homologs (Haptoglobin), serine protease inhibitors (Serpin B6), TGF-beta signal transduction pathways elements (STRAP).

**Conclusion:** Soluble acidic protein overexpression in early phases of cerulein-induced AP was mainly related to the protection of the pancreas, protein breakdown phenomena and regulation of the TGF-beta signaling cascade.

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**O15**

**IL-6 Transsignaling Links Myeloid NF-κB and Epithelial Stat3 to Promote Acute Lung Injury in Acute Pancreatitis**


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**Introduction:** Acute lung injury (ALI) is the limiting complication of multiorgan failure (MOF) during severe acute pancreatitis (AP) and is associated with the high mortality. How local damage is linked to systemic complications, remained unelucidated so far.

**Objectives:** The aim of this study is to investigate the underlying mechanism of ALI during AP, by using genetic mouse models and pharmacological approaches in mice.

**Materials & Methods:** Stat3, Socs3 and RelA/p65 were functionally inactivated in the pancreas (Stat3Δpanc, Socs3Δpanc and RelaΔpanc). RelA/p65 was knocked out in myeloid cells (RelaΔmye). IL-6-/- mice and opt_sgp130Fc mice were also analyzed. Experimental AP was induced by repetitive injections of caerulein. For inhibition experiments, the small-molecule inhibitor of STAT3 S3I-201 was utilized.

**Results:** Rapid NF-κB activation in the pancreas results in recruitment of myeloid cells that secrete IL-6 in an NF-κB-dependent manner. Subsequently, IL-6 transsignaling induces phosphorylation of Stat3 on Y705 in the pancreas and the lung, thereby amplifying local inflammation and ALI. Genetic and pharmacological interventions prove that the IL-6 transsignaling-dependent gp130/Stat3 cascade, but not NF-κB, is the relevant target of ALI.

**Conclusions:** Here, we show that IL-6 transsignaling and myeloid involvement of the NF-κB and Stat3 cascade in different compartments play an important role in this context. This study further identifies the IL-6 dependent gp130/Stat3 cascade as a possible molecular target of ALI during AP.
3B – Acinar-Duct Cell Interactions

016
The Effects of Tryptophan-Free Diet on Pancreatic Exocrine Secretion in the Rats
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Introduction: Tryptophan, aminoacid precursor of serotonin, melatonin and kynurenin, plays an important role in the regulation of gastrointestinal functions. As an essential aminoacid tryptophan must be supplied in the normal diet. The effect of sustained deficit of this substance on pancreatic exocrine function has not been investigated yet.

Aim: To assess the effects of tryptophan-free diet on pancreatic enzyme secretion in the rat.

Material & Methods: The study was performed on Wistar rats weighing 250g. Animals were divided on two main groups: one group was maintained on normal diet, another group of rats received tryptophan-free diet. Rats from each group were maintained on above diets for 1, 3 or 7 days. To assess the pancreatic exocrine secretion, the samples of pancreato-biliary juice were collected in 15 minutes aliquots to measure the amylase outputs. The blood specimens were taken for determination of CCK employing ELISA.

Results: In the groups of rats kept on normal diet, basal amylase secretion was relatively stable after 1, 3 or 7 days of experiment. In the rats with tryptophan-free diet the significant reduction of amylase output have been observed after 1, 3 and 7 days (by 10%, 36% and 74% respectively). These changes were accompanied by a marked decrease of CCK plasma levels.

Conclusion: Pancreatic exocrine secretion was significantly reduced in the rats with tryptophan-free diet.

017
Ethanol Inhibits CFTR Activity in Guinea Pig Pancreatic Duct Cells
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Background: Ethanol (EtOH) is known to contribute to the development of acute pancreatitis; however its cellular effects are poorly understood. Ishiguro et al. found that low concentrations (0.3 – 30 mM) of EtOH augment, whereas high concentration (100 mM) inhibits secretin-stimulated pancreatic ductal fluid secretion. Since cystic fibrosis transmembrane conductance regulator (CFTR) plays a crucial role in maintaining fluid secretion, our aim in this study was to examine the effects of ethanol on basal and forskolin-stimulated CFTR currents in native pancreatic duct cells.

Methods: We used the patch clamp technique to study the effects of EtOH (1, 10 and 100 mM) on whole cell CFTR currents in single, guinea pig pancreatic duct cells prepared by a combination of enzymatic treatment and mechanical separation of intact pancreatic ducts.

Results: Exposure of duct cells to 1 and 10 mM EtOH had no significant effect on basal CFTR currents even after 15 minutes. In contrast, 100 mM EtOH significantly increased whole cell currents in ~ 80% of recordings. Notably, the same osmotic concentration of mannitol (100 mM) caused the same activation in whole cell currents, indicating that the stimulatory effect of EtOH is more probably due to its osmotic effect. Administration of forskolin (5μM) activated CFTR currents by 8–10 fold in magnitude. These forskolin-activated currents reached a maximum after 5 minutes of administration and were time-independent in response to voltage steps. 100 mM EtOH reversibly blocked the forskolin-stimulated currents by 60±11%, whereas 1 and 10 mM EtOH did not affect it.

Conclusions: Our data showed that 100 mM EtOH decreases forskolin-stimulated CFTR Cl– currents in pancreatic duct cells. However, low concentrations (1 and 10 mM) of EtOH affected neither the basal nor the stimulated CFTR currents.

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018
Investigation of Pancreatic Ductal Fluid and HCO3− Secretion in SLC26a6 Knockout and Wild-Type Mice
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Background: Pancreatic ductal epithelial cells produce HCO3−-rich isotonic fluid secretion. The exact mechanism of epithelial HCO3− secretion by the pancreas is poorly understood. However, apical cystic fibrosis transmembrane conductance regulator (CFTR) and SLC26 Cl−/HCO3− exchangers are required for these functions.

The aim of this study was to evaluate the role of SLC26a6 (PAT1) in pancreatic anion and fluid secretion.

Methods: We isolated interlobular ducts from the pancreas of wild-type (WT) and PAT1 knockout (KO) mice. Anion exchange activity was determined measuring the intracellular pH (using the pH-sensitive fluorescent dye BCECF-AM). We used the inhibitory stop and alkali load methods to determine the HCO3− efflux across the luminal membrane. Fluid secretion into the closed luminal space of the
cultured ducts was analysed using a swelling technique. Digital images of the ducts were analysed using Scion Image software (Scion Corp.) to obtain values for the area corresponding to the luminal space.

Results: Exposing the ducts to 0.2 mM H$_2$DIDS and 0.2 mM amiloride caused an acidification of pH, due to inhibition of the basolateral Na$^+$/HCO$_3^-$ cotransporters and Na$^+$/H$^+$ exchangers. HCO$_3^-$ secretion was significantly lower in PAT1 KO vs. WT mice. We also analysed the recovery of pH, from an alkali load induced by exposure to 20 mM NH$_4$Cl in a HCO$_3^-/CO_2$-containing solution. The recovery from alkalosis was significantly lower in PAT1 KO vs. WT mice. The forskolin stimulated fluid secretory rate was significantly lower in KO vs. WT mice both in the absence and in the presence of HCO$_3^-/CO_2$.

Conclusion: Our results suggest that SLC26a6 plays a crucial role in pancreatic ductal secretion.

This study was supported by OTKA, MTA/DFG and NFÜ.

4 – Role of Inflammatory Cells in Acinar Cell Injury

O19

Effects of S-Propargyl-Cysteine (SPRC) in Caerulein-Induced Acute Pancreatitis

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Introduction: Hydrogen sulfide (H$_2$S) is synthesized endogenously from L-cysteine by two pyridoxal-5’-phosphate-dependent enzymes, cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE). S-propargyl-cysteine (SPRC), an H$_2$S releasing drug, may modulate the endogenous H$_2$S production.

Objectives: The present study was aimed to investigate the effects of SPRC in an in vivo model of acute pancreatitis (AP) in mice.

Material & Methods: AP was induced in mice by hourly caerulein injections (50 µg/kg) for 10 hours. Mice were treated with SPRC (10 mg/kg) or vehicle (distilled water). SPRC was administered 3 h before the induction of pancreatitis. Mice were sacrificed 1 h after the last caerulein injection. Blood, pancreas and lung tissues were collected and processed to measure the plasma amylase, plasma H$_2$S, myeloperoxidase (MPO) activities and cytokine levels in pancreas and lungs.

Results: Significant reduction of inflammation, both in pancreas and lung was associated with SPRC treatment. Furthermore, the anti-inflammatory effects of SPRC were associated with reduction of pancreatic and pulmonary pro-inflammatory cytokines and increase of anti-inflammatory cytokine. Plasma H$_2$S concentration showed significant difference in H$_2$S levels between control, vehicle and SPRC treatment groups.

Conclusion: These data provide evidence for anti-inflammatory effects of SPRC by modulating endogenous H$_2$S production.

O20

Inflammation Amplifies the Regenerative Response to Pancreatic Tissue Loss

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Introduction: Regeneration of the pancreas after pancreatitis or partial resection is very limited and volume increase of the organ has not been reported. Nevertheless, histological markers of cell cycle activation have been observed following tissue damage.

Objective: The aim of this ongoing study is to evaluate in models of pancreatic injury (acute and chronic pancreatitis) and major tissue loss (60% pancreatectomy) the potential for regeneration.

Methods: Acute and chronic pancreatitis were induced in mice by multiple injections of cerulein. 60% pancreatectomy was achieved by resection of the pancreatic tail. The expression of regeneration markers, cell cycle regulators, growth factors and tissue inflammation were analyzed by immunohistochemistry and qRT-PCR.

Results: Proliferating pancreatic cells were observed following both cerulein treatment and 60% pancreatectomy. Double staining with amylase and Ki67 indicated that proliferation was mainly confined to acinar cells, confirming their proliferating potential. However, qualitative assessment of the remnant pancreas indicated that there was no volume growth, suggesting that the cell cycle was activated but not completed. To further investigate whether inflammation could enhance the pancreatic regenerative capability, inflammation was induced by cerulein injections following resection. In comparison to the single treatments, the combined pancreatic injury resulted in a strongly accelerated proliferative response. In addition, the cell cycle inhibitors p15 and p21 were differentially regulated in the combined injury model.

Conclusions: Inflammation combined with tissue loss accelerates cell cycle activation in the pancreas. The role of cell cycle inhibitors in hampering completion of mitosis and volume regeneration is currently investigated using knocked out animals.

O21

Probiotics Decrease Bacterial Translocation During Acute Destructive Pancreatitis in Rats

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Objective: Pancreatic infection is a major cause of morbidity and mortality in patients with acute destructive pancreatitis (ADP). Improvements of content of intestinal microflora may decrease the rate of bacterial translocation from the gut.

Aim: To investigate the effects of probiotics on bacterial translocation to internal organs during ADP.

Pancreatology 2011;11:99–227
Methods: In 160 Wistar rats ADP was induced by intraperitoneal injection of 250 mg/100 g of 20% L-arginine solution twice during 1 hour. Rats in group 1 received L. plantarum, group 2 – B. bifidum, group 3 – B. subtilis, control (C) group – normal saline by gavage daily just after ADP induction. Concentration of microorganisms in pancreas, liver, spleen, lungs, portal and system blood, peritoneal cavity were investigated during 24–120 hours by bacteriological methods.

Results: In C group bacterial translocation to internal organs started after 12 hours in 13.4% and appeared in 100% of animals after 48 hours with E.coli, K. pneumonia, other Enterobacteria spp., S. aureus, B. fragilis and C. alibicans. Probiotics significantly decreased amount of microorganisms in pancreas and other organs since 72 hours in 1 group, 96 hours – in 2 group and 120 hours – in 3 group. Besides L. plantarum administration was followed by increasing of citrulline concentration in blood since 48 till 96 hours.

Conclusion: Probiotics decrease bacterial translocation during ADP in rats. In case of L. plantarum improvement occurs partially through enhancing of intestinal mucosal metabolism.

O22
Myeloid, But Not Pancreatic, RelA/p65 is Required for Fibrosis in a Mouse Model of Chronic Pancreatitis
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Introduction: The role of transcription factors such as NF-kB in chronic pancreatitis (CP) is largely unknown.

Objectives: Our aim was to analyze the role of the pro-inflammatory transcription factor RelA/p65, a member of the NF-kB family, in different cellular compartments during CP.

Material & Methods: RelA/p65 was functionally inactivated in the pancreas (relaF/F), in myeloid cells (relaF/Fmye) or both (relaF/Fpanc,mye) using the Cre-loxp strategy. Experimental CP was induced with repetitive injections of caerulein over 6 weeks. Pancreata were investigated histologically and biochemically. An in-vitro co-culture assay of pancreatic stellate cells (PSC) and macrophages was established. Gene-arrays from pancreata and macrophages with functional inactivated RelA/p65 were performed.

Results: After long-term caerulein stimulation, relaF/Fpanc mice displayed typical signs of CP whereas relaF/F littermates showed only mild alterations. The pancreas of relaF/Fpanc,mye mice showed numerous macrophages and activated a-SMA positive PSCs. However, additional inactivation of RelA/p65 in myeloid cells (relaF/Fmye) resulted in an attenuation of fibrosis. In-vitro, RelA/p65 deficient LPS-stimulated macrophages downregulated transcription and increased degradation of fibronectin in co-cultured PSCs. Using gene-arrays, matrix metalloproteinase-10 (MMP-10) was identified as a potential candidate for this observation.

Conclusion: Our study describes for the first time a compartment-specific role of RelA/p65 during CP. In acinar cells, RelA/p65 exerts protective effects during chronic inflammation, whereas in myeloid cells, RelA/p65 is able to promote fibrogenesis. We have identified MMP-10 in macrophages as a RelA/p65 dependent potential anti-fibrogenic factor during CP.

5 – Epigenetics and Role of MicroRNA in Pancreatic Cancer

O23
Antisense Inhibition of Microrna-21 and -221 in Tumor-Initiating Stem-Like Cells Modulates Biological Functions of Pancreatic Cancer Including Tumorigenesis, Metastasis, and Chemoresistance
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Introduction: Our preliminary studies identified a small population of pancreatic cancer cells with stem-like properties.

Objectives: Performed gene expression analysis showed a significant difference in the expression of more than 1300 genes in stem-like Side Population (SP) cells, among which the difference in microRNA expression between SP and non-SP cells was identified as the most interesting candidate for our further studies.

Material & Methods: Pancreatic cancer stem-like cells from highly metastatic cell line L3.6pl were identified and characterized by flow cytometry. The gene expression was assessed by Affymetrix and the results were further confirmed by quantitative RT-PCR. The antagonism transfection was performed using microRNA-21 and -221 oligonucleotide antisense. Tumor cell apoptosis, cell cycle progression, chemoresistance, and invasion were quantitated by propidium iodide staining and Boyden chamber assay, respectively.

Results: In our study, some microRNAs, including miR-21, miR-221, miR-221, and miR-30c-2 were significantly upregulated in stem-like SP cells. Interestingly, in these cells both miR-21 and miR-221 were involved in the modulation of expression of more than 200 genes, including RASSF6, RAB2B, TP63, TP53INP1, TP53INP2, TET1, MAPK10, MAP2K6, CDK6, TNFRSF11B, SOCS6, STK33, and SMAD7. The administration of antagonim-21 and -221 significantly reduced the SP fracture, decreased SP cell differentiation, positively affected L3.6pl cell proliferation, invasion, and chemoresistance against gemcitabine and 5-Fluorouracil.

Conclusion: Our results demonstrate the significance of both microRNA-21 and -221 in tumor-initiating capability of stem-like tumor cells in pancreatic cancer. Both microRNAs contribute to the most important biological functions of pancreatic cancer including apoptosis, metastasis, and chemoresistance, and may further serve as a potential target for pancreatic cancer therapy.
O24

GATA6 is Required for the Maintenance of the Epithelial Phenotype in Pancreas Cancer Cells

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Introduction: Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal cancer. Molecular genetic studies have identified the major genetic aberrations involved in PDAC, including activating mutations in the K-RAS oncogene and loss of function of the p16INK4A, TP53 and SMAD4 tumour suppressor genes. Recently, the gene coding for the transcription factor GATA6 was found to be amplified and overexpressed in 10–15% of PDAC, but its role in this malignancy remains unclear.

Objectives/Methods: In order to understand the role of GATA6 in PDAC, we knocked down GATA6 in a panel of PDAC cell lines, including PaTu 8988S, PaTu 8988T, SK-PC-1, Panc-1 and A13B and overexpressed it in a smaller subset of lines (SK-PC-1, Panc-1). In both cases we checked cell proliferation and migration, the capacity to invade matrigel and grow in 3D and the expression of a number of genes.

Results: GATA6 knock-down consistently resulted in reduced proliferation, associated with mesenchymal features: reduction of E-cadherin expression and increased migration and invasion capacity. Indeed, those cell lines that expressed the highest levels of GATA6 (PaTu 8988S and A13B) were the more epithelial ones, while cell lines with low levels of GATA6 (PaTu 8988T) showed a mesenchymal-like phenotype. Consistently, E-cadherin expression was induced upon ectopic overexpression of GATA6 in Panc-1.

E-cadherin expression has been shown to be regulated by the endodermal transcription factors FOXA1 and FOXA2. We found that GATA6 is able to directly activate the transcription of both FOXA1 and FOXA2 in PDAC cells, thus indirectly activating the expression of E-cadherin. GATA6 loss in these cells induces a reduction in FOXA1/2 levels, which in turn results in down-regulation of E-cadherin and partial Epithelial-to-Mesenchymal Transition.

Conclusion: Our findings indicate that the GATA6-FOXA1/2 axis constitutes a new mechanism involved in the regulation of E-cadherin expression and EMT in PDAC cells. It remains to be determined how this relates to the amplification of GATA6 in tumors.

O25

Identification of Targets Acting Synergistically with Erlotinib in Pancreatic Cancer Using a Kinome-Wide Loss-of-Function Screen

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Introduction: Pancreatic cancer is characterized by a high degree of resistance to chemotherapy. The EGFR inhibitor erlotinib is the only small-molecule inhibitor which has been shown to provide a small survival benefit in combination with cytotoxic chemotherapy.

Objectives: Identification of targets whose inhibition acts synergistically with erlotinib, thereby overcoming drug resistance in pancreatic cancer.

Methods: We employed a kinome-wide siRNA-based loss-of-function screen in BxPC3 cells in the presence or absence of erlotinib to identify kinases that are synergistically lethal with erlotinib. Cell viability was used as a read-out. Targets were characterized individually by various in vitro assays using knock-down and overexpression strategies.

Results: 9 out of 779 tested kinases led to a synthetic lethality in combination with erlotinib. The effect on cell viability could be verified individually after knock-down of all 9 kinases. Two of them, the kinases SNF1L and RPS6KA2, were characterized in greater detail. Knock-down of SNF1L predominantly induced apoptosis, whereas overexpression conferred significant rescue from drug-induced apoptosis. RPS6K2 was shown to act downstream ERK, and knock-down of RPS6K2 by siRNA or by using a specific inhibitor led to cell cycle arrest, whereas RPS6K2 activation significantly enhanced cell cycle progression.

Conclusion: By applying a synergistic lethality screen using a kinome-wide RNAi-library approach, we identified SNF1L and RPS6KA2 as potential drug targets whose inhibition synergistically enhanced the effect of erlotinib on tumor cell growth and survival. These kinases therefore represent promising drug candidates suitable for the development of specific inhibitors for pancreatic cancer therapy.
Abstracts

**O26**

miR-143 and miR-21 Expression in Pancreatic Cancer

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**Introduction:** The clinical management of pancreatic cancer has improved in last decade, however there is still space for improvement in its early detection, diagnosis and treatment strategies.

**Objective:** microRNA (miRNA) detection in pancreatic tumour biology might represent a new diagnostic and prognostic biomarkers.

**Materials & Methods:** Expression levels of miR-143 and miR-21 were analyzed by qRT-PCR using TaqMan assay, in samples from 31 patients with different histological types of pancreatic cancer: ductal adenocarcinoma (PDAC), adenocarcinoma of Vater’s papilla (PVC), cancer of distal common bile duct (CBD) and MEN1-associated pancreatic neuroendocrine tumour (MEN1-PNET). Correlations between miR-143 and miR-21 expression levels and clinic-pathological features of patients were also evaluated.

**Results:** MiR-143 was up-regulated in all pancreatic tumours compared to normal adjacent non-cancerous tissues with the only exception of two MEN1-PNET samples (p < 0.0001). Conversely, miR-21 was up-regulated only in PDAC tissues and in other two samples, one from MEN1-PNET and one from distal CBD cancer (p = 0.99). Interestingly, miR-21 expression was found to significantly differ in PDAC versus PVC samples (p = 0.0049). Association data of relevance for miR-143 expression was according to preoperative serum levels of CA 19-9 (p = 0.0016), while miR-143 expression was negatively correlated to lymph node spreading (p = 0.0032). Furthermore correlation between miR-143 and miR-21 expression levels in patients with PDAC was observed (p = 0.023).

**Conclusions:** Deregulation of miR-143 and miR-21 may reflect histological features and biological behaviour of different pancreatic tumours. Furthermore, association data with clinical parameters suggest a prognostic significance for miR-143 and miR-21 in pancreatic cancer.

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**6A – Molecular Biology of Pancreatic Adenocarcinoma**

**O27**

Snail Cooperates with KrasG12D in a Gene Dose Dependent Fashion to Accelerate Pancreatic Ductal Adenocarcinoma Progression in Genetically Engineered Mice

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1: Pancreatic ductal adenocarcinoma (PDAC) is a dismal disease with 5-year survival rates below 3%. The transcription factor Snail plays a crucial role in epithelial-mesenchymal transition (EMT) and is overexpressed in PDAC.

2: We investigated the role of Snail for pancreatic carcinogenesis and EMT in a genetically engineered mouse model of PDAC.

3: A conditional Snail expression model was generated by targeting the Rosa26 locus with a lox-Stop-lox (LSL) silenced Snail cassette (LSL-R26Snail/+). Expression of Snail in the pancreas was activated by the Cre driver line Ptf1aCre/+

4: Mice with Snail expression from 1 Rosa26 allele (Ptf1aCre/+; LSL-R26Snail/) developed normally. Increasing gene dose by expressing Snail from 2 Rosa26 alleles resulted in dramatic growth retardation due to impaired exocrine pancreatic function. In the context of concomitant KrasG12D expression, R26Snail/+ mice developed aggressively locally invasive PDAC. Median survival was shortened to 6 months compared to 16 months in Ptf1aCre/+; LSL-KrasG12D/ mice. All PDAC from Ptf1aCre/+; LSL-KrasG12D/+; LSL-R26Snail/+ mice showed a well differentiated morphology without signs of EMT or increased metastasis. Doubling Snail expression levels by using LSL-R26Snail/+ mice dramatically accelerated PDAC formation and reduced median survival to 2 months.

5: Snail expression accelerates pancreatic tumor progression in a gene dose dependent fashion; however, it does not induce overt EMT and metastasis of PDAC. Our findings provide new insights into Snail gene function as tumor promoter in vivo. Investigation of the underlying mechanisms will open potential therapeutic strategies for this dismal disease.
**O28**

PanIN Formation Requires a Novel Nupr1/p8-RelB-IER3 Pathway

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**Introduction:** PDAC develops within a hypovascularized microenvironment that imposes a stringent selection of cancer cells resistant to oxygen and nutrient deprivations. However, the molecular mechanisms by which PDAC cells become resistant to these stresses remain largely unknown. In addition, the ways these mechanisms impact the formation of preneoplastic lesions (PanIN) remain poorly understood. Among potentially implicated stress proteins, Nupr1/p8 is an interesting candidate because of its anti-apoptotic function and its systematic over-expression in PDAC.

**Objectives:** We made the hypothesis that Nupr1/p8 is induced in response to the adverse microenvironment of the tumor and triggers the expression of genes involved in cell resistance.

**Material & Methods:** MiaPaCa2 cells were used for in vitro studies. Metabolic stress was induced by treating cells with EBSS. Gene expression was assessed by DNA microarray analysis and confirmed by qRT-PCR and western blot. Cell viability was estimated by MTT and apoptosis by Caspase 3/7 activity. siRNAs against Nupr1/p8, RelB, RelA, BIRC3 and IER3 were used alone or in combination.

**Results:** In this study, we showed that: 1. Nupr1/p8 expression is activated in response to starvation, such expression being necessary for cell survival in nutrient deprived conditions; 2. Nupr1/p8 expression protects from starvation-induced cell death; 3. Mechanistically, Nupr1/p8 inhibits apoptosis through an alternative RelB --> IER3-dependent mechanism, but not through the classical RelA-based NF-kB pathway; 4. Nupr1/p8 is required for the development of PanIN lesions in KrasG12D mice, these lesions expressing both RelB and IER3 proteins; 5. KrasG12D: RelBPapc mice, which display a pancreas-specific conditional ablation of RelB, show a significant delay in developing PanINs, which are devoid of the antiapoptotic effector IER3. Hence, Nupr1/p8, RelB and IER3 pathways play an important role in PanIN formation.

**Conclusions:** An original intracellular pathway named Nupr1/p8 -> RelB -> IER3, initiated in pancreas in response to nutrient deprivation, is critical in the formation of preneoplastic lesion, the first step towards pancreatic cancer development. Manipulation of this pathway may be of interest in both chemoprevention and therapy of pancreatic cancer.

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**O29**

Pancreatic Cancer Cells Secrete CXCL12 Which is Chemoattractive Upon Peripheral Neural Glia: Reversal of a Paradigm

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**Introduction:** Neural invasion (NI) in pancreatic cancer (PCa) results from the biological affinity of PCa cells (PCCs) to intrapancreatic nerves. However, the molecular mediators of NI, and particularly the role of chemokines in this chemotraction between nerves and PCCs, remain largely unknown.

**Objectives:** To determine the role of the chemokine CXCL12 and its receptor CXCR4 in NI in PCa.

**Material & Methods:** Expression of CXCL12 and CXCR4 was studied in normal human pancreas (NP), PCa tissues, PCC lines, intrapancreatic nerves and human Schwann cells (hSC) via immunohistochemistry, immunoblotting and enzyme-linked-immunosorbent-assay (ELISA). To identify the contribution of CXCL12/CXCR4 axis to NI, 3D-neural-migration and chemotaxis assays were performed under the influence of the CXCR4 chemical inhibitor AMD3100 and recombinant CXCL12.

**Results:** PCa tissues and PCCs demonstrated an upregulation of CXCR4 and especially of CXCL12 when compared to NP. Interestingly, intrapancreatic nerves and within these especially hSC showed prominent levels of CXCR4. When co-cultivated, hSC migrated in a strictly targeted manner towards PCCs long before these even started with their migratory activity. Pre-treatment of hSC with AMD3100 significantly reduced the cancer-targeted migration of hSC. Correspondingly, recombinant CXCL12 exerted a potent chemotactic effect upon hSC.

**Conclusion:** Chemokines like CXCL12 which are secreted by PCCs strongly attract glia cells that harbor the corresponding chemokine receptors like CXCR4. Hence, in sharp contrast with the traditional assumption, NI results from the migration of peripheral glia (hSC) towards PCCs. This “chemokine-mediated migration of nerves towards cancer” urges for a reversal in our common understanding of NI in PCa.
Reclassification of Tumour Origin in Resected Periampullary Adenocarcinomas Reveals Underrecognised Diagnosis of Distal Bile Duct Cancer

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Introduction: Primary adenocarcinomas removed by pancreatoduodenectomy originate from the duodenum (DC), ampulla (AC), distal bile duct (DBC), or pancreas (PC). Pathobiology, staging, survival, and adjuvant chemotherapy vary among these cancers. The proximity of the structures of origin renders it difficult to obtain a correct diagnosis, leading to inconsistencies in reported data and inappropriate adjuvant treatment.

Objectives: Identify changes in diagnosis of tumour origin when routine histopathology examination performed by multiple pathologists was reevaluated by one experienced pancreatic pathologist.

Patients & Methods: Records of 207 patients undergoing pancreatoduodenectomy (1998–2009) for periampullary adenocarcinoma were reviewed. Diagnosis of tumour origin was reviewed based on predetermined criteria.

Results: Slide review changed the diagnosis in 49 (24%) patients. After reclassification, final distribution was 28 (14%) DC, 61 (29%) AC, 46 (22%) DBC, and 72 (35%) PC. The diagnosis was revised in 6 (22%) DC, 10 (16%) AC, 19 (41%) DBC and 14 (20%) PC. The underestimation of DBC during routine histopathology was caused by misinterpretation as PC and AC. Misclassification of PC was mainly due to erroneous diagnosis of AC. Reassignment of tumour origin caused no significant changes in survival within each group of cancer, but resulted in a significant difference (p = 0.003) in survival between DBC and PC.

Conclusion: Specialist slide review resulted in reassignment of tumour origin in 24% of periampullary adenocarcinomas. Distal bile duct cancer was found to be most frequently misdiagnosed (41%). Correct diagnosis of tumour origin is crucial for data quality, appropriate adjuvant therapy, and patient inclusion in clinical trials.

Treatment of the Primary and Metastatic Solid-Pseudopapillary Tumors

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Background: Solid-pseudopapillary tumor (SPT) of the pancreas is a rare pancreatic tumor with positive prognosis but uncertain malignant potential.

Method: The clinical, demographic, imaging, and pathologic findings of 21 patients operated for SPT (2005 – 2010) were analyzed. Positive immunohistochemical staining for vimentin, nuclear β-catenin and e-cadherin, α -1-antitrypsin and α -1-antichymotrypsin with negative reaction for sinaptophisin and chromogranin A were the diagnostic signs.

Results: The mean age was 37.4 (15–70) years, 20 were female. The duration of follow-up after the first tumor detection varied from 0.5 to 17 years. The main symptoms were nausea, vomiting and vague abdominal pain. Tumor markers were normal in all cases. On B-US, CT and MRI tumor were solid in 7 cases. Tumors with the mean diameter of 7.2 cm (3–15 cm) were located at the head(10), body(10), and tail(1) of the pancreas. Surgical procedures included pancreatoduodenectomy(10), distal (including combined and extended) pancreatectomy(8) and segmental resection(3). One (4.75%) had had at presentation and 2(9.5%) patients developed liver and retroperitoneal metastases in 14 and 60 months after the initial operation, which required staged hepatectomies, removal of tumor nodules and repeated arterial liver chemoembolisation. All patients are alive.

Conclusions: In spite of strong believe in low grade malignant potential of SPT 14% of patient developed distal metastases. Aggressive surgery for initial and metastatic SPTs prolongs survival even in disseminated tumors. In the absence of metastases and tumor invasion in adjacent structures pathohistology is not able to distinguish a benign SPT from a malignant one, or primary SPT from metastatic tumor.

Serous Cystic Tumors of the Pancreas: Longitudinal Study of Tumor Growth Rate and of Factors Influencing Tumor Growth

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Introduction: The management of asymptomatic serous cystic tumors (SCT) of the pancreas is still under debate.

Objectives: To investigate the growth rate of SCT and the effects of different factors (sex, age, history of other tumors, radio-
logical pattern, presence of symptoms, tumor site and size) on tumor growth.

**Patients & Methods:** Patients in follow-up for a well-documented SCT and having serial magnetic resonance imaging (six studies performed on a yearly basis, for an observation period of five years) were analyzed using a multivariate generalized linear model with repeated measures.

**Results:** Study population consisted of 123 patients. Estimated mean growth rate was 0.13 cm/year. Tests for effects within subjects showed that an age <40 years, an oligo/macrocystic pattern and the history of other tumors had a significant effect on tumor growth (p=0.006, 0.001 and 0.008). Tests for contrasts within subjects (time*age, time*radiological pattern and time*history of other tumors) indicated that the effects on tumor growth become relevant after two years from the diagnosis in patients <40 years and after three years in patients with history of other tumors and oligo/macrocystic lesions.

**Conclusion:** SCT grow very slowly. Tumor growth is estimated to be more rapid in young patients (0.21 cm/year), in case of a history of other tumors (0.20 cm/year), and of an oligo/macrocystic lesion (0.22 cm/year). Initial tumor size was not a significant factor in the model and should not be used for recommending surgery. A non-operative approach is feasible in all asymptomatic SCT, the optimal imaging interval during follow-up seems to be at least 2 years from the baseline evaluation.

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**7A – New Targets for Treatment of PAC**

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**O33**

**Neoadjuvant/Preoperative Gemcitabine for Patients with Localized Pancreatic Cancers: a Meta-Analysis of Prospective Studies**

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**Introduction:** Long-term prognosis for localized pancreatic cancers remains poor.

**Objectives:** To assess the benefit of neo-adjuvant/preoperative chemo-radiotherapy.

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**O34**

**Replicative-Stress Induced Midkine Expression is Linked to Chemoresistance in Pancreatic Cancer**

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**Introduction:** Insufficient diagnostic and therapeutic options for pancreatic ductal adenocarcinoma (PDAC) still substantiate its ranking as the 4th leading cause of cancer related death. The combination of an unusual aggressiveness and early metastatic locoregional and distant spread reflects the urgent necessity of new therapeutic options for this deadly disease. This devastating prognosis is partially due to a frequent occurrence of intrinsic/acquired chemoresistance in PDAC specimens against the nucleoside analogue gemcitabine which is still the standard for chemotherapeutic treatment of locally advanced and metastatic PDAC.

**Objectives:** In this study we dealt with the evident need of identifying novel players and to further comprehend their molecular role for chemoresistance in PDAC.

**Materials & Methods:** We have established three primary pancreatic cancer lines (intrinsically chemoresistant) from patients who underwent total pancreaticoduodenectomy in our hospital. RNA expression profile were obtained using Affymetrix microarray and overexpression was validated by real-time PCR. Validation of overexpression on protein level was performed immunohistochemically and via western blot. Targeted gene knockdown experiments were
performed using small interfering RNAs (siRNA). The influence of targeted gene depletion on cancer cell chemoresistance was analyzed with MTT assay.

Results: We identified Midkine (MK) as frequently overexpressed in chemoresistant PDAC through gene-expression profiling and real-time PCR. We found that MK expression is inducible by gemcitabine in a dose-dependent manner in chemoresistant PDAC cells whereas no induction was observed in chemosensitive cells. Further, depletion of MK by RNAi correlated with a strong increase in sensitization towards gemcitabine.

Conclusion: Gemcitabine-induced MK upregulation promotes drug resistance in chemoresistant PDAC cells.

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7B – Actual Development in PAC Diagnostics

**O35**

**Circulating Tumor Cells in Resectable Pancreatic Cancer: Which Prognostic Role?**

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**Introduction:** Pancreatic adenocarcinoma in resected patients has a really poor prognosis (OS 24 months; DFS 13.5 months, with about 20% of patients relapsing within 6 months from surgery). Circulating tumor cells (CTCs) could represent a new attractive frontier in oncological decision making.

**Objectives:** to investigate the prognostic role of CTCs in patients with resectable pancreatic cancer.

**Materials & Methods:** from February 2009 to January 2010 20 patients undergoing pancreatic resection for malignancy were enrolled. Blood samples (10 mL) were collected intraoperatively both from systemic and portal circulation at the same time. Blood samples were analyzed for CTCs with J&J Veridex CellSearch® within 72 hours from collection. A strict follow-up was carried out using CT and/or PET scan once every about 3 months.

**Results:** CTCs were detected in 9 patients (45%). No correlations were found between presence or number of CTCs and tumor dimension/grading, stage, serum levels of CEA and CA 19.9.

Patients with CTCs were significant younger than the others (61.5 vs. 71 years). At 1-year follow-up both overall (OS) and disease-free survival (DFS) were not significant different in patients with or without CTCs.

Interestingly, patients who developed only local or peritoneal recurrence had no CTCs (3 patients), whereas recurrence in patients with CTCs was always systemic (4 patients).

In particular, liver metastasis were found in 50 % of patients with CTCs in portal circulation and in 20% of patients without CTCs in portal circulation.

**Conclusion:** CTCs were found in about half of our series, however their presence did not correlate with OS and DFS.

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**O36**

**The Accuracy of MDCT in Prediction of the Pancreatic Cancer Size**

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**Introduction:** Preoperative evaluation of tumor extent is crucial in determining of the treatment algorithm but the size of pancreatic ductal adenocarcinomas measured on CT and those measured during pathohistological examination are often differ.

**Objectives:** Estimation of the MDCT accuracy in assessment of the pancreatic adenocarcinoma size.

**Material & Methods:** Retrospective analysis of CT scans and pathohistological reports of 81 cases of pancreatic ductal adenocarcinoma after Whipple procedures (2005–2010). The tumor size was defined as the maximum dimension in any direction.

**Results:** In 57 patients (70%) tumor size reported by pathologist surpassed one claimed by CT study. From these 57, the difference ranged from 5% to 30% (6–21mm) in 12 cases (21%), from 31% to 60% (10–40mm) in 38 (67%), from 61% to 99% (19–62mm) in 7 (12%) cases. Only in 20 (25%) of 81 patients, tumor size specified by MDCT coincided with the morphological report (with a permissible error of 5mm). 4 patients (5%) of 81, had overestimated tumor size determined by MDCT compared with the results of morphological studies (12–31% of the actual tumor size, range 7–11mm). The difference in the estimated sizes based on the results of CT and morphology did not depend on the tumor grade.

**Conclusion:** MDCT significantly underestimates the size of pancreatic ductal adenocarcinoma when compared to morphological reports, which has to be taken in consideration by surgeons and radiologists.
O37
Risk of Pancreatic Cancer Among BRCA1 and BRCA2 Mutation Carriers from Breast Cancer Families
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Introduction: Pancreatic (PC) and breast (BC) cancer may occur in the same families and in some cases PC follows BC in the same individual. Several studies reported that mutations in the BRCA2 and BRCA1 genes increase the risk of PC.

Objectives: To assess the risk of PC in BRCA1 and BRCA2 mutation carriers from BC families.

Patients & Methods: We analyzed data from 885 families (36,280 individuals) recruited into the Breast Cancer Family Registry (BCFR) that were found to carry mutations in BRCA1 or BRCA2. Mutation carrier probabilities were imputed in untested family members. We estimated the relative risk (SIR) for PC in each of BRCA1 and BRCA2 mutation carriers, by computing the ratio between observed number of PCs and that expected assuming population PC rates.

Results: Overall, carriers of BRCA2 mutations had an increased risk of PC (SIR = 2.06, 95%CI = 1.16–3.65). BRCA1 mutation carriers had a similar risk pattern though more moderate (SIR = 1.50, 95%CI = 0.81–2.80). Both BRCA1 and BRCA2 mutation carriers appeared to have a higher PC risk at younger ages (< = 50 years) (SIR = 7.03, 95%CI = 2.13–23.24 and SIR = 9.16, 95%CI = 2.86–29.31, respectively). The relative risk estimate was higher in families with less than two reported BC (SIR = 3.89, 95%CI = 1.14–13.26, versus SIR = 1.70, 95%CI = 0.81–3.55 for families with more cases of BC). We did not observe differences in the risk of PC between males and females for carriers of mutations in either gene.

Conclusion: Our study confirmed the role of BRCA2 mutations in pancreas carcinogenesis and were suggestive of an increased risk for BRCA1 mutation carriers.

O38
Diabetes and Pancreatic Exocrine Dysfunction Due to Mutations in the Carboxyl-Ester Lipase Gene (CEL-MODY): A Protein Misfolding Disease
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Introduction and Objectives: CEL-MODY, diabetes with pancreatic lipomatosis and exocrine dysfunction, is due to dominant frame-shift mutations in the acinar cell carboxyl-ester lipase gene (CEL). As Cel knock-out mice do not express the phenotype and the mutant protein has an altered, intrinsically disordered tandem repeat domain, we hypothesized that the disease mechanism might involve a cytotoxic mutant protein.

Materials & Methods: Stably transfected HEK293 cells expressing wild-type (WT) and mutant (MUT) CEL was used as a model system to investigate secretion, degradation and intracellular localization of the two proteins using biochemical and microscopic analysis.

Results: In silico analysis showed that the pI of the tandem repeat was markedly increased from pH 3.3 in wild-type to 11.8 in mutant human CEL. By stably over-expressing CEL-WT and CEL-MUT in HEK293 cells, we found similar glycosylation, ubiquitination, constitutive secretion and quality control of the two proteins. The CEL-MUT protein demonstrated, however, a high propensity to form aggregates found intracellularly and extracellularly. Different physico-chemical properties of the intrinsically disordered tandem...
repeat domains of WT and MUT proteins contribute to different short-range and long-range interactions with the globular core domain and other macromolecules, including cell membranes.

**Conclusion:** CEL-MODY can be regarded as a protein misfolding disease due to a cytotoxic gain-of-function of the mutant protein in pancreatic tissues.

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**O39**

**Gene Copy Number Status in Patient and Cell Line Derived Pancreatic Cancer Xenografts**

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**Introduction:** Pancreatic cancer is known to show a variety of genomic alterations including mutations, chromosomal rearrangements and aneuploidy.

**Objectives:** Objective of this study was to assess copy number changes in a panel of patient derived pancreatic cancer xenografts, to identify genes frequently altered in copy number and to identify subtypes of pancreatic cancer based on copy number status.

**Material & Methods:** Tissue of pancreatic cancers of 10 patients and the pancreatic cancer cell lines MiaPaca2 and Capan2 were passaged as stable growing subcutaneous xenografts in mice (NMRI). Xenografts were harvested, DNA was isolated and SNP/CNA-analysis was performed using Affymetrix SNP 6.0 chips. After quality control of the data evaluation was performed using Genespring and Affymetrix genome browser software.

**Results:** Copy number variations were frequently seen. In nine tumours more than half of the chromosomes were heavily altered in copy number status whereas only three tumours had a lower incidence of copy number changes. Frequently altered alterations were copy number loss of 8p in combination with copy number gain of 8q (6 tumours), copy number gain of 1q (7 tumours) and copy number gain of 13q (4 tumours). Using GISTIC (Genomic Identification of Significant Targets in Cancer) analysis several genes with relevant copy number gain were identified including AKT, Erbb2, ADAM6, LBR and SIRPB1.

**Conclusion:** Genomic alterations are frequently seen in pancreatic cancer. Most tumours show a heavily altered genomic status. As some tumours have a significantly lower number of changes, they could represent a molecular subtype of pancreatic cancer. Several genes with relevant copy number gain were identified using GISTIC analysis. Evaluation on RNA and Protein-expression levels are necessary to assess the relevance of these genes in the context of pancreatic cancer.

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**O40**

**LRH1/NR5A2, a Link Between Pancreatitis and Pancreatic Cancer?**

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Chronic pancreatitis increases the risk of developing pancreatic ductal adenocarcinoma (PDAC) though the molecular links between these processes remain unknown. The liver receptor homolog-1 (LRH1/NR5A2) is an orphan nuclear receptor involved in cholesterol and bile acid homeostasis, steroidogenesis, inflammatory response and cell proliferation. Nr5a2 is highly expressed in the exocrine pancreas and is regulated by Pdx1. Recent data from a genome-wide association study of PDAC identified 5 SNPs mapping to the vicinity of NR5A2, suggesting that it plays a role in PDAC development. Here, we investigated the role of Nr5a2 in caerulein-induced acute and chronic pancreatitis using Nr5a2 heterozygous mice. Upon acute caerulein administration, Nr5a2+/- mice showed a higher inflammatory response with increased cell infiltrates, edema and double TNFα levels when compared with wild type mice. While control mice had almost completely recovered at day 8, Nr5a2+/- mice still displayed ductal metaplasia and signs of edema and inflammatory cell infiltrates. When an acute pancreatitis was induced weekly for a period of 8 weeks, Nr5a2+/- mice presented more severe acinar damage and a 2.5–5 fold decrease in Ptf1a, elastase and CEL transcript levels. Besides, 6 weeks after the last pancreatitis, Nr5a2+/- mice had only 50% of the CEL and elastase transcript levels found in control. These results demonstrate that loss of one Nr5a2 allele leads to a more severe inflammatory response in the pancreas and an impaired recovery after both acute and chronic pancreatitis. This defect may contribute to a permanent epithelial damage and an increased risk of PDAC.

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**O41**

**Smad7 Is a Major Regulator of the Fibrotic Response in an Animal Model for Chronic Pancreatitis**

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**Background:** Chronic pancreatitis (cP) represents a very difficult to treat disease and a significant risk factor for the development of pancreatic ductal adenocarcinoma (PDAC). Both, cP and PDAC are characterized by an extraordinarily strong fibrotic component, which is composed of activated pancreatic stellate cells/myofibroblasts producing large amounts of collagen fibers, fibronectin and other extracellular matrix components in response to the cytokine transforming growth factor-beta (TGF-β). Smad7 via a negative feed-
back loop primarily modulates the activity of TGF-β. We have used different genetic models, i.e. a general (all cell incl. epithelial and mesenchymal cells of the pancreas) knockout of Smad7 and a pancreas-specific (only epithelial cells) KO of Smad7 to investigate the role of increased TGF-β signaling during experimental CP in mice.

**Materials & Methods:** We have recently generated Smad7 partial knockout mice, in which the C-terminal part of Smad7 is still expressed (Li et al., J Immunol. 176, 6777–84(2006)). In addition, we have crossed a conditional knockout of Smad7 (Kleiter et al., Brain, 2010) with a mouse deleting Smad7 specifically and only in pancreas progenitor cells. The pancreas histology of these mouse strains is comparable to wildtype mouse pancreas. CP was induced by 6-hourly i.p-injections of 50mg/kg cerulein (or NaCl) in sex- and age-matched Smad7 knockout mice and corresponding wt controls for 4 weeks, twice a week. The 4th day after the last injection, tissue and blood was sampled.

**Results:** The fibrotic response/TGF-β signaling was increased in knockout mice versus wildtype mice, independent of where Smad7 function was lost, in the epithelial plus stromal the compartment or only in the epithelial compartment.

**Conclusion:** Pregabalin was superior to placebo for adjuvant treatment of pain in chronic pancreatitis.
Does Dietary Fat Intake Play a Role in the Natural History of Chronic Pancreatitis (CP)?


Although the role of diet on the etiopathogenesis of CP is unknown, a high fat diet could cause earlier and more severe symptoms of the disease.

Aim: To evaluate the effect of total fat intake and fat in different food groups on the age of diagnosis, and clinical, morphological and functional severity of CP at diagnosis.

Methods: Prospective cohort study including consecutive patients with CP. A morphologically severe disease was defined by the presence of ≥7 endoscopic ultrasound criteria of CP. Pancreatic exocrine insufficiency (PEI) was diagnosed by 13C-MTG breath test. Dietary habits before diagnosis were collected on a detailed nutritional questionnaire. A high fat diet was defined as a fat consumption >30% of daily calories. Results are shown as OR and 95% CI and analysed by logistic regression.

Results: 168 patients were included. 58.9% smoked and 57.5% consumed alcohol. 42.5% had continuous abdominal pain, 22.4% PEI and 23% a morphological or functional severity of CP at diagnosis.

Conclusions: A high fat diet increases the risk of pain leading to an earlier diagnosis of CP. Fat intake plays no role on the morphological or functional severity of CP at diagnosis.

O45
The New Treatment of Autoimmune Pancreatitis, Associated with Herpes Virus Type VI and/or Epstein-Barr Virus

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Introducción: The autoimmune pancreatitis (AIP) can be considered as viral disease that requires the development of new treatment approaches.

Objective: To develop new treatment approaches to AIP evaluating the etiological role of herpesvirus.

Materials & Methods: 58 patients (average age 56.89±3.12 years) with AIP were enrolled. The diagnosis was verified using standard clinical and laboratory examinations, ultrasound, computed tomography and IgG4 levels. In addition, PCR was applied to detect the viruses in saliva.

Results: the markers of herpes infection in saliva such as DNA of herpes virus type VI, EBV and IgG for the above mentioned viruses were identified in 77.5%, 65.5% and 100% of patients, respectively. The replication of EBV and herpes virus type VI was more prominent during relapse. When comparing the significance with a control group for DNA in saliva, the herpes virus type VI and EBV were found in 13.3% in 26.6% cases, respectively (p<0.05). Test on presence of DNA in saliva was positive during active phase of disease. The antiviral therapy (cimiven) was carried out when replication markers of herpes virus type VI were detected. Described treatment resulted in fast reduction of pain and normalization of pancreatic function.

Conclusions: Complex treatment for AIP should include antiviral and immune therapy when positive markers of herpes infection are present.

O46
“Ductitis” at Endoscopic Ultrasonography Has High Diagnosis Value in Autoimmune Pancreatitis

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Introduction: The diagnosis of autoimmune pancreatitis (AIP) remains difficult despite recent advances in diagnostic criteria. Endoscopic ultrasonography (EUS) is a key tool for the diagnosis of chronic pancreatitis and its interest for AIP diagnosis has been suggested.

Objective: To assess the interest of the EUS for positive and differential diagnosis of AIP.

Patients & Methods: EUS characteristics of 49 patients (27 M) in whom the diagnosis of type 1 AIP (n = 17) and type 2 AIP (n = 32) was made, were evaluated before corticosteroid therapy. Patients with alcoholic chronic pancreatitis (ACP, n = 32), pancreatic adenocarcinoma (PC, n = 42), pancreatic endocrine tumor (PET, n = 21) or symptomatic choledolithiasis (CL, n = 52) served as controls. The following abnormalities were systematically looked for at EUS: i- ductal signs: “ductitis” (irregular main pancreatic duct with succession of narrowed/normal or dilated segments), hypo/hyperochoic thickening of main pancreatic duct wall, cholangitis of the common bile duct; ii- parenchymal signs: hypoechoic heterogeneity of pancreatic parenchyma, calcifications. EUS findings in patients with AIP were compared with those in and control groups. The sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) of EUS abnormalities for the diagnosis of AIP were calculated.
**Results:** "Ductitis" was significantly associated with the diagnosis of AIP (present in 89.8, 0, 2.4, 0 and 0% of AIP, ACP, PC, PET and CL patients, respectively, p < 0.05). Hyperchoic thickening of the main pancreatic duct wall (32.7% in AIP vs none of the others, p < 0.05) and hypochoic thickening of the main pancreatic duct wall (61.2, 0, 2.4, 0 and 0% respectively, p < 0.05) were significantly associated with the diagnosis of AIP. Sensitivity, specificity, PPV and PPV of ductitis for the diagnosis of AIP were 89.8, 99.3, 97.8 and 96.7%, respectively. The diagnostic value of other abnormalities was lower.

**Conclusion:** "Ductitis" seen at EUS has a high diagnostic value in AIP. These data need to be confirmed in prospective studies.

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**O47**

**A Comparison of Clinical Findings Between Histologically Confirmed Type 1 and Type 2 Autoimmune Pancreatitis with Special Emphasis on Radiological Findings and Steroid Responsiveness**


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**Introduction:** Type 2 AIP has been reported mainly in Western countries and is thought to be very rare in Asia.

**Objectives:** The aim of this study was to compare the prevalence, clinical profiles, radiological findings, and response to steroids of type 1 and type 2 AIP in Korea.

**Patients & Methods:** From 120 patients diagnosed with AIP between January 2003 and August 2010, 52 patients with histologically confirmed type 1 (n = 37) or type 2 (n = 15) AIP were included.

**Results:** The type 2 AIP patients’ median age (34 years [18 – 64]) was significantly lower than that of the type 1 AIP patients (61 years [39 – 72]) (p < 0.05). At initial presentation, severe abdominal pain and presentation with acute pancreatitis were more frequent in type 2 AIP patients than in type 1 AIP patients (p < 0.05). Ulcerative colitis was associated with only type 2 AIP (33.3%), but type 2 AIP patients had no other organ involvement. On CT scan, the type of pancreatic enlargement did not differ significantly between the two groups. On ERCP/MRCP, intrapancreatic CBD narrowing, long (>1/3) narrow stricture of main pancreatic duct (MPD), lack of upstream MPD dilatation from the stricture (<5 mm), and multiple MPD strictures did not differ significantly different between the two groups. All type 2 AIP patients showed normal serum IgG and IgG4 levels. Initially steroid therapy was performed on 25 patients in type 1 AIP and 14 in type 2 AIP, all of whom improved clinically and radiologically in response. During the follow-up period, 32.4% of type 1 AIP patients experienced a relapse, but none of the type 2 AIP patients did (p < 0.05).

**Conclusion:** Type 2 AIP in all AIP cases in Korea may not be as rare as originally thought, with an estimated 12% of prevalence rate. Differences in initial clinical presentations existed between type 1 and type 2 AIP. The detailed radiological findings of type 1 and type 2 AIP were not significantly different, and both subtypes responded well to steroids.

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**O48**

**Direct Endoscopic Testing of Exocrine Pancreatic Function in CEL-MODY**

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**Introduction:** CEL-MODY is a recently described autosomal dominant disorder, characterized by abdominal pain, pancreatic lipomatosis and low fecal elastase from childhood, steatorrhea and onset of insulin dependent diabetes mellitus from young adult age.

**Objectives:** To study exocrine pancreatic function in CEL-MODY patients compared with healthy controls.

**Patients and Methods:** Patients with CEL-MODY were enrolled in the study. Healthy volunteers were recruited as controls. Samples of duodenal juice were collected through upper endoscopy in two aliquots in the period 30 till 40 minutes after intravenous administration of secretin 1 cU/kg, max 70 cU. Bicarbonate was calculated in the samples by back titration. Fecal elastase-1 was determined in each of the subjects.

**Results:** Twelve CEL-MODY patients (mean age 44.6 ± 16.7 yrs), seven (58 %) of whom had diabetes, and 25 healthy controls (mean age 39.2 ± 11.6) yrs underwent endoscopic procedure after secretin stimulation. Mean peak bicarbonate concentrations in CEL-MODY patients and controls were 43.5 ± 16.0 mEq/L and 110.2 ± 16.0 mEq/L respectively (p < 0.001). There was no significant difference in bicarbonate concentration between diabetic and non-diabetic CEL-MODY patients (p = 0.08). Mean fecal elastase-1 was 27 ± 27 μg/g CEL-MODY patients (n = 7) and 531 ± 141 μg/g in controls. In CEL-MODY patients, all bicarbonate levels were below lower reference limit of 80 mEq/L, and all fecal elastase-1 levels were below lower reference limit of 100 μg/g.

**Conclusion:** Here we, for the first time with physiological investigations, show that the fecal elastase deficiency seen in CEL-MODY is due to severe exocrine pancreatic insufficiency preceding development of diabetes.
SEM5 in Chronic Pancreatitis – An Individual Decision
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Introduction: Self expanding metal stent (SEMS) therapy is an established therapeutic concept for malignant common bile duct (CBD) stenosis, while its use in benign causes of CBD stenosis is still controversial. In exceptional cases SEMS insertion may be a valuable alternative to surgical treatment.

Objectives: Aim of our evaluation is to analyze the outcome of patients with chronic pancreatitis (CP) and CBD stenosis treated with SEMS.

Patients & Methods: 13 patients with CBD strictures due to alcoholic CP were treated with SEMS. All patients had calcifications of the pancreas. Uncovered SEMS (cSEMS) were used in 8 patients (2 females), in 5 patients (1 female) covered SEMS (uSEMS) were inserted. All patients treated with SEMS had contraindications for surgical treatment.

Results: Average follow-up was 192 (52–412) weeks for patients with uSEMS and 87 (25–233) weeks in cSEMS group. Mean stent patency was 148 (44–112) weeks in uSEMS and 50 (25–113) weeks in cSEMS. In the uSEMS group, re-intervention was necessary in 4 patients (50%) due to stent occlusion, whereas in cSEMS group 3 patients (60%) needed re-intervention (2 occlusions, 1 dislocation). In patients requiring re-intervention, the mean re-intervention rate during follow-up was 5.2 for patients with uSEMS and 2.7 for patients with cSEMS. In both groups one patient suffered from hepatic abscess as a severe complication of stent occlusion (uSEMS 12.5% / cSEMS 20%).

Conclusion: SEMS as a definitive therapeutic concept for benign CBD strictures remains an individual decision. Although early and severe complications occur in some cases, in many patients a definitive treatment with long term success can be achieved.

Diagnostic Informativity of Endoscopic Ultrasonography in the Evaluation of High Risk Pancreatic Cystic Lesions for Patients with Chronic Pancreatitis
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Introduction: Endoscopic ultrasonography (EUS) is used as a method for detection of early changes of pancreas parenchyma related to chronic pancreatitis (hyperechoic foci, hyperechoic strands, irregular gland margin, hyperechoic lobules, accentuation of lobular pattern) and malignancy (high sensitivity in the early diagnostic of malignant cystic lesions).

Objectives: Diagnostic assessment of high risk cystic lesions (multilocular cysts, with septae, solid content) in correlation with EUS detected chronic pancreatitis (CP).

Patients/Material & Methods: 390 patients with clinical or radiological (CT, MR, US) signs of CP underwent EUS examination. 182 (47%) patients from them (mean age 53.5 years) had cystic lesions of the pancreas. Cyst with high malignant potential underwent FNA. CEA level more than 500 ng/mL of EUS-FNA was used as significant.

Results: EUS structure changes of the pancreas parenchyma related to CP were observed in 133 cases, pancreatic duct changes (n=91, 50%), cystic lesions less than 20mm (n=78), lesions bigger than 20mm (n=104). EUS-FNA study of the cyst content; malignant cells (n=31, 17%), adenocarcinoma (n=24), carcinoid (n=2), neuroendocrine tumor (n=4), Non-Hodgkin lymphoma (n=1), atypical cells (n=15), inflammatory content (n=85), non-inflammatory content (n=51).

Conclusions: EUS diagnostic sensitivity in CP is increasing due to new technical modalities in EUS-FNA. Majority of included patients with CP and cystic lesions had benign structure with additional changes of the pancreatic duct. Cystic lesions more than 20mm in size had higher malignancy rate. Combined CEA and cytology studies enhanced diagnostic sensitivity up to 100%.

Radical Surgical Resections in Patients with Periampullary Cancer
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Introduction: Results of treatment of patients with periampullary cancer remain disappointing.

Materials & Methods: We have analyzed the results of 457 pancreaticoduodenectomies (PD) in patients with periampullary malignancies in the period of 1998–2010 years. In 332 patients standard Whipple procedure was performed, in 125 patients with malignancies of papilla of Vater or distal part of bile duct pylorus-preserving PD was preferred. We personalized our surgical strategy and implemented modern techniques of pylorus-preserving PD with preservation of the gastroduodenal artery (5 patients), selective ligation of right branch of the dorsal pancreatic artery (2 patients), ligation of the inferior pancreaticoduodenal artery first approach (6 patients), mesenteric artery first approach (3 patients). In 33 patients additional vascular resections were performed, including 4 artery resections. In 24 patients we implemented no-touch PD. We also analyzed the results of modified extended lymphadenectomy in patients with PD.
Results: Postoperative morbidity was 29.5%, postoperative mortality- 2.4% (11 patients). Median survival was 24, 48, 72 months in patients with pancreatic cancer, bile duct cancer and cancer of papilla of Vater correspondingly.

Conclusion: Implementation of new techniques of PD could potentially improve nearest and long-term results of PD in periampullary malignancies.

O52
Centralization of Pancreaticoduodenectomy in the Netherlands

Introduction: Hospitals performing higher volumes of pancreaticoduodenectomy (PD) have lower mortality rates. In The Netherlands, the first initiative to centralize PD dates back to 1997. Evaluation of this process in 1999 and 2005 showed no change in referral patterns or a decrease in mortality.


Methods: Hospital volume and mortality of PD were retrieved from the independent, nationwide registry (KiwaPrismant Utrecht) for ICD-9 code 5-526 (pancreaticoduodenectomy, including Whipple) for the period 2004–2009. Based on previously established cut-off points of PDs performed annually, hospitals were categorized as very-low- (<5), low- (5–10), medium- (11–19), or high-volume (≥20).

Results: Overall, 2,157 PDs were included. The number of hospitals performing PD decreased from 48 in 2004 to 30 in 2009 (P = 0.01). During these years the percentage of patients undergoing PD in a medium-high-volume center increased from 52.9% to 91.2% (P = 0.0001). PD associated mortality decreased from 10.1% in 2004 to 5.3% in 2009 (P = 0.04). The mortality during the six-year period for hospitals categorized by volume (<5, 5–10, 11–19 or ≥20 PDs) was respectively 14.7%, 9.8%, 6.2% and 3.5% (P = 0.0001). The two centers with the highest annual volumes of PDs had the lowest overall mortality, respectively 1.7% (N = 356) and 2.0% (N = 199).

Conclusion: Centralization of PD in The Netherlands is succeeding and PD-associated mortality has decreased. Current measures to further improve outcome include a governmental enforced minimum of 20 PDs per hospital and the establishment of the Dutch Pancreatic Cancer Group.

O53
Advanced Age Should Not Exclude Patients from Pancreaticoduodenectomy
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Introduction: The dismal prognosis of pancreatic cancer (PC) make it life time limiting also in patients of old age. However, sometimes advanced age is considered a contraindication to pancreaticoduodenectomy (PD) due to fear of a worse outcome.

Objectives: To analyze peri-operative outcome and costs after PD in patients of old age (O) compared to younger (Y) individuals.

Methods & Patients: From our prospective registry at Karolinska all patients undergoing PD between 2004 and 2010 were included. The cohort was divided by age into O ≥ 75 yrs and Y < 75 yrs). Pre-operative anesthesiologic risk (ASA), perioperative outcome, length-of-stay (LOS days) and costs were calculated.

Results: In total 367 patients were analyzed. Comparing O (n = 65, mean age 78.7 yrs) and Y (n = 302, mean age 61.5 yrs), O had higher ASA class (ASA1–2: O 49.0% vs Y: 65.4%, ASA 3–4: O 51% vs Y 34.8%, P = 0.022). No differences between O and Y were observed in total post-operative morbidity (O 55.3% vs Y 56.6%), severe (Clavien score ≥ 3b) complications (O 16.9% vs Y 16.5%), re-operation rate (O 6.1% vs Y 7.9%), mortality (O 1.5% vs Y 3.3%), LOS (O 16.0 vs Y 16.7) or costs (€ 30570 vs € 32176).

Conclusions: In our experience patients of advanced age have the same peri-operative outcome and costs after PD. Thus, by careful patient selection, PD is sensible in the elderly patients and should never exclude them from the only potentially curative therapy.
Ghrelin Regulates Heat Shock Protein in Pancreatic Acinar Cells

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Introduction: Ghrelin, is 28-amino acid polypeptide, originally isolated from the stomach. Experimental studies have shown that ghrelin protects the gastric mucosa and the pancreas from the acute damage, but the involvement of heat shock protein (HSP) in the protective effect of ghrelin on acute pancreatitis is unclear.

Objectives: This study was undertaken to investigate the effect of ghrelin on gene expression of pro-apoptotic HSP60 and Bax or anti-apoptotic HSP27 and Bcl-2 in the pancreatic acinar cells.

Material & Methods: Wistar rats (250 g) were injected with ghrelin (12.5; 25.0 or 50.0 μg/kg i. p.). Control animals received injections of physiological saline. 48 h later pancreatic acinar cells were isolated from all groups of rats and subjected to caerulein stimulation (10−10M - 10−8M) for: 0 h, 20 min, 1, 3 or 5 h at 37°C. For RT-PCR analysis the most gene expression, spectacular experimental point (3h of incubation in the presence of ghrelin (50,0 μg/kg) and caerulein (10−8M)) was chosen.

Results: In culture the pancreatic acini subjected to basal conditions high level of HSP60 or Bax gene expression contrary to low level of HSP27 and Bcl-2 in the pancreatic acinar cells. Pretreatment of rats with ghrelin failed to affect gene expression of these markers. Caerulein stimulation upregulated the levels of HSP27 and Bcl-2 and downregulated the HSP60 or Bax. Pretreatment of rats with ghrelin reversed described above caerulein – induced suppression of proapoptotic and inhibited antiapoptotic related genes in the pancreatic acini.

Conclusions: Ghrelin presumably promotes apoptosis and take part in the protection of the pancreatic acinar cells against acute damage.

Disordering of Lysosomal Membrane Proteins in Models of Pancreatitis

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Introduction & Objective: LAMPs and LIMPs are major lysosomal integral membrane proteins critical for lysosomal function and autophagy. Here, we examined the effects of experimental pancreatitis on these proteins as well as the role of LAMP deficiency in pancreatitis.

Methods: Acute pancreatitis was induced in rats by administration of cerulein or L-arginine, and in mice, by feeding them choline-deficient ethionine supplemented (CDE) diet. Acinar cells stimulated with supraphysiologic dose of CCK-8 were used as in vitro model of pancreatitis. The effects of LAMP-2 were assessed using LAMP-2 deficient mice.

Results: LAMP-1, -2, and LIMP-2 pancreatic levels dramatically decreased in experimental pancreatitis tested. The magnitudes of the decreases were LAMP- and model- specific. For example, LAMP-1 decreased by 50–80% in all models of pancreatitis tested, whereas decreases in LAMP-2a and LIMP-2 were only detected in cerulein models of pancreatitis. LAMPs decrease was already evident at 30 min after cerulein administration and progressed with time. In pancreas from animals with cerulein pancreatitis LAMP-1 and -2 showed vesicular staining, although of much lesser intensity than in control pancreas. CCK-induced decrease in LAMPs was largely prevented by the inhibitor of proteasomal degradation MG-132. LAMP-2 deficient mice time-dependently developed pancreatitis-like changes manifest by acinar cell vacuolization, which was already prominent at 2 month after the birth; necrosis, macrophage and neutrophil infiltration at 5 month after birth.

Conclusion: Pancreatitis causes profound pathologic alterations in lysosomal membrane proteins, which mediate acinar cells vacuolization, necrosis and inflammation.
**O56**

**Autophagic Process in Pancreatic Tissue of Rats During Experimental Acute and Chronic Pancreatitis**

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**Introduction:** there are several pathways to the death of acinar cells in inflammation of pancreatic tissue.

**Objectives:** to establish the relationship between autolysis and apoptosis in the damage of pancreatic tissue.

**Patients & Methods:** reproduced acute (AP) and chronic pancreatitis (CP) in albino rats (33, weight 220 grams). Experimental observations were carried out in a humane attitude towards animals. Morphological and biochemical (serotonin – 5-HT, proteolytic activity at pH 6.0 and 4.5) studies were performed.

**Results:** In extracts of pancreatic tissue in stage of AP level of proteolytic activity at pH 6.0 was reduced by 16%, with slightly acidic pH 4.5 increased by 27%. The concentration of 5-HT increased from 0.8±0.07 to 1.64±0.23 mg/g of tissue (p<0.05). According on morphological study, mechanism for destruction of acinar cells was autolysis. Acinar cells in a state of apoptosis were absent. In stage of CP level of proteolytic activity at pH 4.5–5.0 remains high. Morphologically we founded focus of acute and chronic inflammation.

**Conclusion:** Both in AP and CP dominated process of death of acinar cells was autolysis.

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**O57**

**Does Tobacco Induce Intracellular Trypsinogen Activation and Acinar Cell Necrosis? A Dose-Dependent In-vitro Study Compared to Alcohol**

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Premature intracellular activation of zymogens is an early event in chronic pancreatitis (CP). Tobacco is a risk factor for CP, but whether it is able to activate intracellular trypsinogen and to induce acinar cell necrosis is unknown.

**Aim:** To analyze the effect of different concentrations of tobacco compared to alcohol in the intracellular activation of trypsinogen and induction of acinar cell necrosis.

**Methods:** Pancreatic acinar cells were isolated from Swiss mouse pancreas by enzymatic degradation (collagenase) and mechanic degradation, filtration and centrifugation. Intracellular trypsin activity and acinar cell necrosis in response to six different concentrations of tobacco (from 0.001 to 0.5 mg/ml) and alcohol (from 10 to 100 mM) were measured at 20 minute-intervals for one hour by fluorescence assay. CCK at supramaximal dose (10^{-10}M) was used as positive control. Data were analyzed by Anova.

**Results:** Trypsinogen was significantly activated by CCK, but not by alcohol and tobacco. Tobacco at 0.4 and 0.5 mg/ml induced 13% and 14% cell necrosis, respectively, after 40 minutes (p<0.05 compared to negative control), similar to that obtained by supramaximal dose of CCK. Percentage of necrosis increases linearly with the concentration of tobacco (r=0.92, p=0.04). Alcohol induced no significant cell necrosis.

**Conclusion:** Tobacco, but not alcohol, induces acinar cell necrosis. This effect is not mediated by intracellular trypsinogen activation.

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**O58**

**Trypsinogen, But Not Chymotrypsinogen, is Activated in Autophagolysosomes During Experimental Pancreatitis**

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Premature zymogen activation is an early event for acute pancreatitis. Recently we found that trypsinogen is activated in distinct vesicular compartments of pancreatic acinar cells which can be separated by density gradient centrifugation. At later time points in caerulein pancreatitis, trypsin activity occurs in autophagolysosomes. Because trypsin can activate chymotrypsinogen we tested whether chymotrypsin activity appears in that compartment in which trypsin activity is present.

**Methods:** Acute pancreatitis was induced in wild-type and cathepsin B-deficient mice by 7 hourly injections of caerulein (50 μg/kg i.p.). Control mice received saline. Subcellular pancreatic fractions were prepared by Percoll gradient centrifugation. Activities of trypsin (trypsinogen after activation by entero/kinese) and chymotrypsin (chymotrypsinogen after activation by trypsin) were fluorometrically measured using the substrates Boc-QAR-MCA and Suc-AAPF-AMC, respectively. Subcellular compartments were identified by Western blots for organelle markers or by marker enzyme activities.

**Results:** In the early time course of pancreatitis (up to 3 h) trypsin and chymotrypsin activity appear in different vesicles which show a much higher density than autophagosomes. Chymotrypsinogen activation occurred independently of cathepsin B or trypsin activity. In the later course (8 h) trypsin activity increasingly appeared in autophagolysosomes. Although, both proteases were sufficiently present in autophagolysosomes, only trypsin activity could be measured in this compartment.

**Conclusion:** Zymogen activation in experimental pancreatitis represents a complex process that is strongly compartmentalized in vesicular structures of acinar cells.
**O61**

**WNT5A Mediates Resistance to Apoptosis in Pancreatic Cancer via NFAT1**

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**Introduction:** WNT5A belongs to the Wnt family of secreted signalling molecules. Using transcriptional profiling, we previously identified WNT5A as target of the anti-apoptotic transcription factor CUX1 and demonstrated high expression levels in pancreatic cancer. However, the impact of WNT5A on drug resistance and the signalling pathways employed by WNT5A remain to be elucidated.

**Objectives:** This project aims to decipher the impact of WNT5A on resistance to apoptosis and the signalling pathways employed by WNT5A in pancreatic cancer.

**Methods:** WNT5A levels were modulated by knock-down, overexpression and addition of the recombinant protein. Apoptosis was induced by TRAIL and different chemotherapeutic agents. The effect of WNT5A on drug-induced apoptosis was measured in vitro using FACS, DNA fragmentation assays, PARP cleavage and caspase activation assays. In vivo, the impact of WNT5A was studied using xenograft models and in vivo imaging strategies.

**Results:** Knock-down of WNT5A results in a significant increase in TRAIL- and chemotherapy-induced apoptosis. In contrast, overexpression of WNT5A or addition of recombinant WNT5A confers resistance to apoptosis. In our attempt to search for downstream effectors of WNT5A, we identified the transcription factor NFAT1 as transcriptionally upregulated by WNT5A signalling. NFAT1 also confers a strong antiapoptotic phenotype mediating at least in part the effects of WNT5A on drug resistance and tumor cell survival. In vivo, WNT5A expression leads to resistance to gemcitabine-induced apoptosis in a xenograft model which is paralleled by upregulation of NFAT1.

**Conclusion:** We identified the WNT5A – NFAT1 axis as important mediator of drug-resistance in pancreatic cancer.

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**O62**

**c-myc Directs Apoptosis of Pancreatic Cancer Cells via Activation of the NOXA Gene**

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**Introduction:** The impaired balance of pro- and antiapoptotic proteins is a crucial hallmark of cancer. Activation of BH3-only proteins is one of the apical pro-apoptotic events in vertebrates. Recently we identified the BH3-only NOXA as a potent pro-death protein in pancreatic cancer cells. Disclosure of the molecular mechanisms of NOXA's activation is essential for understanding pro-death signaling in pancreatic cancer.

**Objectives:** Analysis of NOXA's impact on apoptosis and investigation of the transcriptional regulation of the NOXA gene.

**Materials & Methods:** We used human pancreatic cancer cell lines and genetically defined mouse embryonic fibroblast (MEF wildtype, MEFNOXA-/-, MEFc-myc/Mycfl/fl-CreER). c-myc and NOXA was targeted by chemical inhibitors, siRNAs and shRNAs. qPCR served for mRNA expression analysis. Protein expression was analyzed by Western blot. DNA-protein interactions were determined by Avidin biotin complex DNA binding assays and endogenous promoter scanning by Chromatinimmunoprecipitations (ChIP). Viability and apoptosis was measured by MTT, Hoechst-stains, Caspase 3/7 assay and AnnexinV/PI-FACS analysis.

**Results:** Proteasome inhibition by bortezomib induces NOXA protein and mRNA expression in pancreatic cancer cells and murine embryonic fibroblasts. This effect was abrogated in the absence of the c-myc protein and therefore, inhibition of c-myc circumvents bortezomib-induced apoptosis. Upon bortezomib treatment, c-myc binds to the NOXA gene promoter leading to the acetylation of histones and transcriptional activation.

**Conclusion:** c-myc is an essential transcription factor for the activation of the NOXA gene in pancreatic cancer cells.

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**O63**

**VMP1 Triggers Autophagy and Cancer Cell Death Through the Interaction with BH3 Domain of Beclin1**

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1: Autophagy has recently elicited significant attention as a mechanism that either protects cells or promotes cancer cell death. However, different pathways that could explain autophagy function in cancer remain to be elucidated. We recently showed that VMP1-mediated autophagy leads to cell death in MIAPaCa2 and Panc1 pancreatic cancer cells.
2: Here we report a thorough cellular and biochemical characterization of VMP1 mediated autophagosome formation and cell death in human pancreatic cancer cells. We demonstrate that VMP1 triggers autophagy and cell death interacting with the tumor suppressor protein Beclin1.

3-4: Using recombinant Beclin1 peptides and mutated peptides, co-immunoprecipitation assays show that VMP1 interacts with the BH3 domain of Beclin1, which is essential for VMP1-Beclin1 interaction. FRET analyses confirm the VMP1-Beclin1 in vivo direct interaction. Moreover, VMP1-Beclin1 interaction enhances PI3K activity recruiting Beclin1-hVsp34 complex to the autophagosomal membrane. Also, VMP1 deficient mutant, (VMP1ΔAM), which is not able to interact with Beclin1, fails to recruit PI3K complex to the autophagosome. Finally, we found that VMP1-Beclin1 interaction displaces Bcl2 from the BH3 domain of Beclin1, favoring autophagy and leading to pancreatic cancer cell death. Also, VMP1ΔAM expression does not alter cell survival.

5. These data characterize the VMP1-Beclin1 interaction and reveal the molecular pathway by which VMP1 expression leads to autophagic cell death in human pancreatic cancer cells. Our findings provide further understanding of the VMP1-autophagy molecular mechanism and are potentially relevant to therapeutic strategies in pancreatic cancer.

O64
TP53INP1 Interacts with LC3 and LC3-Like Proteins Through the LC3-Interacting Region (LIR) and Promotes Autophagic Degradation of Oxidized Proteins in Pancreatic Cancer
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Introduction: TP53INP1 is a proapoptotic stress-induced p53 target gene whose expression is dramatically reduced in early steps of PDAC. TP53INP1-deficient mice are more susceptible to develop tumors in an oxidative stress context. Based on these observations TP53INP1 is considered as a tumor suppressor gene. Its expression is induced by reactive oxidative species such as the ones that accumulate in PDAC and that are able to damage cellular molecules promoting cancer. Cells have developed sophisticated strategies to detoxify these oxidized metabolites. Principally two cellular mechanisms are considered candidates for removing oxidized proteins: the proteasome-dependent proteolytic system and autophagy.

Objective: Our aim is to investigate the role of TP53INP1 in the autophagic degradation of oxidized proteins.

Methods: Two hybrid system and co-immunoprecipitation was used to detect TP53INP1 interactors; Western blot and immunocyto-fluorescence to study TP53INP1 implications in autophagy; BRET to evidence the p62/LC3 interaction shift to TP53INP1/LC3. Oxidized proteins were estimated by 2,4-DNPH staining followed by western blot.

Results: We showed that TP53INP1 interacts with three major molecules implicated in autophagy: LC3 and two LC3-like proteins. This interaction occurs via a LIR domain present in TP53INP1. TP53INP1 co-localize with LC3 in autophagosomes and when over-expressed, is able to shift p62 from its interaction with LC3. This shift facilitates the degradation of oxidized proteins.

Conclusion: TP53INP1 could exert its tumour suppressor function in pancreatic pre-tumoral lesions by eliminating toxic oxidized proteins.

O65
The Pro-Survival Effect of PHLPP1 in Pancreatic Cancer is Mediated Through Overexpression of Akt2
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Background & Aims: Akt kinase is a potent pro-survival factor in pancreatic cancer and its activity is regulated by phosphorylation. We have recently shown that the phosphatases PHLPP1 and 2 regulate Akt phosphorylation and cell death.

Here, we investigate the specificity of PHLPP1 and 2 towards the Akt isoforms in pancreatic cancer, and the Akt isoform expression pattern in pancreatic cancer.

Methods: PHLPP1 or 2 were either overexpressed or silenced with siRNA in MIA PaCa-2 and PANC-1 cells. Akt and PHLPP co-immunoprecipitations, pAkt and Akt targets were analyzed by western blot. Human pancreatic adenocarcinoma samples were stained for western blot. Human pancreatic adenocarcinoma samples were stained for western blot. Human pancreatic adenocarcinoma samples were stained for western blot.

Results: In IPs Akt1 was associated with PHLPP2 but not PHLPP1 and Akt 2 with PHLPP1 but not PHLPP2. Furthermore, PHLPP1 knock-down increased Akt 2 phosphorylation whereas PHLPP2 knock-down increase phosphorylation of Akt1. Similarly, PHLPP isoforms affected Akt downstream targets like GSK-3α or β. PHLPP overexpression had no effect on ERK or PKC phosphorylation.

Staining of human pancreatic cancer tissues revealed a significantly decreased expression of PHLPP-1/2 in human and mouse pancreatic tumours, but only a low PHLPP-1 expression correlated significantly with poor survival. Nearly 90% of the Tumours overexpressed Akt2, the target of PHLPP1 but only 20% showed an increase in Akt1.

Conclusion: PHLPP1 specifically binds and dephosphorylates Akt2 and PHLPP2 is specific for Akt1 in pancreatic cancer. The high overexpression of Akt2 but not Akt1 in pancreatic ductal adenocarcinoma may explain the strong pro-survival effect of PHLPP1 expression.
Autophagy in Pancreatic Cancer Cells
Signals via the Non-Canonical hVps34 Dependent Pathway
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Background & Aims: Autophagy can play a dual role in cancer development. Recent data indicate that autophagy is oncosuppressive. On the other hand, autophagy has been proposed as a prosurvival mechanism, and its inhibition may increase cancer cell death. The complex of Beclin-1 and the class III PI3K hVps34 is necessary for autophagosome formation in non-transformed cells.

We investigated the role of hVps34 and Beclin1 for autophagy and apoptosis in pancreatic cancer cells.

Methods: PANC-1, and CAPAN-2 cells were subjected to amino-acid (AA) and growth factor (GF) depletion, or treated with an Akt 1/2 inhibitor, all known to be strong inducers of autophagy. hVps34 and Beclin1 were depleted by siRNA. Autophagy was assessed by LC3-II formation, p62 degradation and by quantification of autophagic vesicles (IF). Apoptosis was measured by DNA fragmentation and necrosis via LDH release.

Results: AA and GF depletion increased LC3-II formation and decreased p62 level, indicating that autophagic degradation was stimulated. Akt 1/2-inhibition increased LC3 II and p62 dramatically, pointing to an increase in autophagy induction but a decrease in autophagy progression, whereas hVps34 siRNA knock-down also decreased autophagy induction and abolished autophagosome formation. Silencing of hVps 34 had no effect on apoptosis or necrosis. Knock down of Beclin-1 or Atg5 had no effect on autophagy induction, apoptosis or necrosis.

Conclusions: AA depletion and FBS withdrawal activates autophagy in pancreatic cancer cells. Induction of autophagy in pancreatic cancer cells requires hVps 34, but is independent of Beclin1 or Atg5. This non-canonical pathway of autophagy does not affect apoptosis or necrosis.

Pancreatic Exocrine Function Measured Post Major Upper Gastrointestinal Resections
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Introduction: Major upper gastrointestinal resectional surgery can result in nutritional difficulties which may in part be associated with reduced pancreatic exocrine function. The Carbon 13 labeled mixed triglyceride breath test (C13-MTG-BT) is one test which can indirectly measure pancreatic exocrine function.

Objectives: The aim of this study was to calculate normal levels of pancreatic exocrine function using the C13-MTG-BT and to measure the levels in patients post oesophagectomy, gastrectomy and pancreato-duodenectomy.

Patients & Methods: 30 normal subjects, 15 post-oesophagectomy patients, 15 post-gastrectomy patients and 10 post-pancreateoduodenectomy patients were recruited to undertake the C13-MTG-BT at Box Hill Hospital, Melbourne, Australia, between August 2009 and January 2011. The C13-MTG-BT was performed using 200mg of C13-MTG substrate. The cumulative percentage of ingested C13 exhaled after 6 hours (cum.%C13–6hr) and the time at peak rate of C13 excretion (peak-%C13/hr) were measured in all subjects and compared between groups.

Results: The mean cum.%C13–6hr of the control group was 28.6% with a standard deviation of 8.8%. The cum.%C13–6hr in each post-operative group compared with the control group was not significantly different. The time of peak-%C13/hr was earlier in the post-operative groups compared with the control group.

Conclusion: This study has not found a large percentage of patients post major upper gastrointestinal resections with measurable reduction in pancreatic exocrine function using the C13-MTG-BT. The finding of earlier times of peak rate of excretion imply the post-operative patients tend to have more rapid gut transit.
**P01**

**Thioredoxin 1 in Acute Pancreatitis Patients**

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**Introduction:** Recent research suggests that reactive oxygen species (ROS) are a critical factor in the pathophysiology of AP and that the oxidative stress caused by ROS is related to disease severity. Thioredoxin-1 (TRX-1) is an endogenous redox-active multifunctional protein and has anti-inflammatory and antiapoptotic effects, as well as antioxidative effects. TRX-1 has potent antioxidant and anti-inflammatory actions in experimental acute pancreatitis. Serum TRX-1 levels are recognized as an oxidative stress marker.

**Objectives:** Role of thioredoxin 1 in pathophysiology of acute pancreatitis

**Materials and Methods:** Thioredoxin 1 levels were determined on admission in 12 patients with severe AP and 18 patients with mild AP. Serum TRX-1 levels were measured using sandwich sandwich enzyme-linked immunosorbent assay (ELISA) kit (Abfrontier Co., Ltd., Korea).

**Results:** Thioredoxin 1 levels in patients with AP were highly elevated within 24 hours of the onset of AP. TRX-1 levels in patients with AP were significantly higher than those in control subjects, in patients with severe AP were significantly higher than those in patients with mild AP. A significant positive correlation was observed between serum TRX-1 levels and Ranson scores, between serum TRX-1 levels and the highest serum CRP levels. A significant positive correlation was observed between serum TRX-1 levels and Ranson scores, between serum TRX-1 levels and the highest serum CRP levels. The sensitivity of TRX-1 was much greater than that of the Ranson score; the specificity of TRX-1 were higher than the corresponding values for CRP.

**Conclusion:** Serum TRX-1 levels significantly correlate with AP severity. TRX-1 measurements had a high diagnostic value in predicting of AP severity. TRX-1 might be a new therapeutic strategy to improve the prognosis of severe acute pancreatitis.

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**P02**

**Value of Three-Dimensional Reconstructions in Pancreatic Necrosis Using Contrast-Enhanced CT Data: Initial Results**

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**Introduction:** Pancreas segmentation and three-dimensional reconstruction in CT images is desirable for computer-aided diagnostics and operation planning.

**Objectives:** To evaluate the use of three-dimensional imaging of pancreatic and peripancreatic necrosis using contrast-enhanced computed tomography (CT) in a prospective study.

**Material & Methods:** Thirty five patients with severe acute pancreatitis were examined prospectively using contrast-enhanced CT. The images were evaluated for the presence of a pancreatic necrosis and the spread of the peripancreatic tissue and the relationship of surrounding organs and vessels. Using the isotropic CT data sets, a three-dimensional image was created with semi-automatic segmentation of the pancreatic necrosis and surrounding organs and automatic vascular analysis by a radiologist. The CT examinations and the three-dimensional images were presented to the surgeon directly before and during the patient’s operation. Immediately after surgery, the value of the all images was judged by the surgeon.

**Results:** Twenty patients had an infected pancreatic necrosis, and fifteen patients had a sterile pancreatic necrosis with acute peripancreatic fluid collections. Twenty patients with infected pancreatic necrosis underwent an open necrosectomy. Fifteen patients with a sterile pancreatic necrosis had ultrasound guided percutaneous catheter drainage of acute peripancreatic fluid collections. In comparison to the CT image with axial and coronal reconstructions, the three-dimensional image was judged by the surgeons as better for operation planning and consistently described as useful.

**Conclusion:** A 3D-image of the pancreatic and peripancreatic necrosis represents an invaluable aid to the surgeon. However, the 3D-software must be further developed in order to be integrated into daily clinical routine.
Role of C-Reactive Protein, APACHE II and Glasgow Score in Early Prediction of Severity of Acute Pancreatitis

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Introduction: The early prediction of the severity of an acute attack of acute pancreatitis (AP) has important implications for management and timely intervention.

Objectives: The aim of this study was to compare the accuracy of Glasgow and Apache II scores and C-reactive protein (CRP) level in prediction of severity of acute pancreatitis.

Patients/Material & Methods: Ninety one consecutive patients with acute pancreatitis primarily admitted were prospectively studied. APACHE II score was recorded on admission, while Glasgow score and CRP levels were determined 48 hours later. Severity of AP was defined according to Atlanta classification system. Two study groups comprising 33 patients with mild AP (MAP) and 58 patients with severe AP (SAP) were compared.

Results: Mean values of Glasgow and Apache II scores and CRP were 79% and 81%, 72.7% and 100%, 90.9% and 150 mg/l, respectively (derived from ROC curves), were calculated. The sensitivity and specificity of Glasgow and Apache II scores and C-reactive protein were 4 and 10 points and 331 mg/L, respectively in SAP group, while in MAP group it were 1 and 4 points and 62 mg/L, respectively. CRP offers little, if any, advantage over the Glasgow and APACHE II score. CRP level and Glasgow score proved to be powerful prognostic model as the more complicated APACHE II scoring systems, but with the disadvantage of a 24-hour delay.

Conclusions: This is the first description of the use of TE in the assessment of coagulation in AP. Contrary to other publications; these data suggest that patients with AP are not procoagulant but in fact have impaired coagulation that is not attributable to heparin therapy. The clinical significance of this is unknown and requires further research.

A Novel Technique for the Assessment of Coagulation in Acute Pancreatitis

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Introduction: Local complications of acute pancreatitis (AP) are associated with the development of pancreatic necrosis. It has been postulated that necrosis is related to a disease-related coagulopathy.

Objectives: To assess coagulation in AP using thromboelastometry (TE).

Materials & Methods: 86 patients (serum amylase greater than 300U/L) were recruited within 6 hours of admission. Median age 62 years, male:female ratio 63:37. Venepuncture was performed at 0, 6, 12, 24 and 48 hours from admission. TE was performed on kaolin activated and heparinised samples using the TEG®5000 system (Haemoscope UK). The reaction time (R-time) is the time taken from onset of reaction to fibrin formation. Maximum amplitude (MA) is used to assess clot quality.

Results: 13% of patients had APACHE scores predictive of severe disease. 9% developed severe disease according to the Atlanta classification. 62% had evidence of prolonged coagulation according to R-time. There was a trend towards increased R-time across the time points assessed. No significant difference in MA was observed in patients over the time points measured or compared to normal range. No differences in TEG parameters were seen between patients with severe and uncomplicated disease or between heparinised and non-heparinised samples.

Conclusions: This is the first description of the use of TE in the assessment of coagulation in AP. Contrary to other publications; these data suggest that patients with AP are not procoagulant but in fact have impaired coagulation that is not attributable to heparin therapy. The clinical significance of this is unknown and requires further research.

Is Pancreatic Gland Affected in Patients with Septic Shock?

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Introduction: Hyperamylasemia has been reported anecdotally in severe sepsis or in septic shock (SSh).

Objective: To investigate the pancreatic involvement in SSh patients using serum pancreatic amylase (AMY) and lipase (LIP) determination and imaging techniques.

Patients & Methods: Twenty-one consecutive SSh patients and 21 healthy subjects were enrolled in the study. The serum activity of AMY and LIP were assayed initially in all subjects and 24 and 48 hours after the initial observation in SSh patients. AMY and LIP serum activities did not significantly changed throughout the study period in SSh patients. Two patients (9.5%), one with upper gastrointestinal tract injury due to the ingestion of caustic substances and the other with infection of an aortic prosthesis, had serum activity of AMY more than three times the upper reference limit, while none of the patients studied had serum LIP activity more than three times the upper reference limit. Patients who died during hospitalization and the survivors had no significant differences in the serum activity of AMY and LIP in the three days of the study. None of the patients with pancreatic hyperenzymemia had
clinical signs or morphological alterations compatible with acute pancreatitis.

Conclusions: The presence of pancreatic hyperenzymemia in SSH patients is not a biochemical manifestation of acute pancreatic damage, and the management of these patients should be guided by the clinical situation and not merely by evaluation of the biochemical results.

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**P06**

**CECT Differentiation of Collections in Acute Pancreatitis**

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**Introduction:** There is a lack of information regarding CT differentiation of collections in acute pancreatitis also is of great value for choosing of treatment modality.

**Objectives:** To evaluate the ability of contrast-enhanced computerized tomography (CECT) to differentiate peripancreatic collections.

**Patients & Methods:** Retrospective observation double centre study: 4 radiologists revised all CT images, performed to our patients with AP admitted in Gomel Regional Clinical and Mozyr City Hospitals in 2010. We concentrated our efforts on definition of acute peripancreatic collection (APC – a collection not associated with peri/pancreatic necrosis) and acute post-necrotic collection (APNC – a collection associated with peri/pancreatic necrosis). Collections were described in terms of volume, location, number, heterogeneity, fluid attenuation, wall perceptibility, wall enhancement, presence of extraluminal gas and predominantly with the emphasis on densitometric (Hounsfield units) data.

**Results:** We included 159 consecutive episodes of AP. Collections were present in 46 (28.9%) of them. 35 (76.1%) out of abdominal collections were APC and 11 (23.9%) were APNC. APC were detected around the head (n–9), body (n–7), around the tail (n–10), body – tail of the pancreas (n–9); vs APNC body (n–5), tail (n–4) and body – tail (n–2).

The Hounsfield units' analysis of CT images (Me [25%-75%]): APC HU=11 [10–13]; APNC HU=27 [14–39]. According to Mann-Whitney analysis, the U-test for the HU APNC-APC was 33.5 (p<0.001).

**Conclusion:**

1. The Hounsfield units was statistically significantly lower in APC, than in APNC (11 [10–13] vs 27 [14–39] (Me [25%-75%])) respectively (p<0.001).
2. The data obtained can be used for differentiating APC and APNC.

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**P07**

**Predictive Factors for Severe Evolution in Acute Pancreatitis**

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**Introduction:** Acute pancreatitis (AP) is an acute inflammation of the pancreas with an unpredictable evolution.

**Aim:** To assess the factors associated with severe evolution of AP and to create a new score for predicting severe outcome of AP.

**Material & Method:** The initial group included 422 patients hospitalized in our Department during 2006–2009. According to Atlanta criteria we classified AP as mild our severe. The validation group included 144 patients admitted in 2010.

**Results:** The initial group (422 patients) included 60.9% cases of mild AP ans 39.1% cases of severe AP. The validation group (144 patients) included 32.6% cases of severe AP and 67.4% cases of mild AP. The overall mortality rate was 4.9%. The following factors were correlated with severe evolution of AP: CRP (r = 0.67; p < 0.001), creatinine (r = 0.36; p < 0.001), white blood count (r = 0.31; p < 0.001), BMI (r = 0.16; p = 0.002), age (r = 0.11; p = 0.02); and the following factors were not correlated with severe AP: etiology (alcoholic r = 0.02, p = 0.92; biliary r = 0.03, p = 0.35; nonA-nonB r = 0.07, p = 0.20), hematocrit (r = -0.11, p = 0.17), serum lipase (r = 0.09, p = 0.06). Using only parameters available in emergency, by multiple regression analysis we obtained the following score for predicting severe evolution of AP in the initial group: -0.699+0.138x creatinine (mg/dl)+0.011xBMI (kg/m²)+0.0318 x white blood count/1000 (cel/mm³)+0.004x age (years). For a cut-off value >0.41, the new score had 61.1% Se, 84.4%Sp, 70.4% PPV, 78.1% NPV, 75.6% accuracy (AUROC = 0.80) for predicting severe evolution of AP. In the validation group we obtained 47.6% Se, 84.1% Sp, 58.8% PPV, 77.1% NPV, 72.3% accuracy.

**Conclusions:** The new score calculated based on parameters available at admission had a good accuracy in predicting the severe evolution of AP.

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**P08**

**Fatty Acid Composition of Erythrocyte Membrane in Acute Pancreatitis Patients**

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**Introduction:** It is suggested that oxidative stress (OS) may play a role in the development of pancreatic injury and systemic complications during acute pancreatitis (AP). Moreover, free radical spe-
cies can react with membrane lipid fatty acids (FA) and participate in lipid peroxidation, but the role of this process in the development of AP is poorly described.

**Objectives:** We evaluated the change of FA composition in erythrocyte membrane in AP patients comparing with the healthy control.

**Patients & Methods:** Blood samples were collected from patients with mild (n=22) and severe (n=15) AP, and a group of healthy individuals (n=26). The fatty acids were extracted from erythrocyte phospholipids and expressed as percentage of the total fatty acids present in the chromatogram.

**Results:** Erythrocyte membranes of acute pancreatitis patients had significantly higher percentage of saturated fatty acid expressed as mean± SD (44.1±1.4 versus 43.2±1.0, p<0.01) and monounsaturated fatty acid (20.4±1.8 vs 19.2±1.3, p<0.01) than controls. Furthermore, fatty acid profiles of AP patients showed a decreased percent of total polyunsaturated fatty acid (PUFA) (35.5±1.7 vs 37.5±1.5, p<0.01), PUFA n-3 (8.1±1.9 vs 9.2±1.1, p<0.01) and a tendency of decrease of n-6 PUFA (27.0±2.0 vs 28.0±1.6, p=0.052). We also found the significant decrease of peroxidation index (133±12.3 vs 145.2±7.2, p<0.001) and unsaturation index (152.4±8.4 vs 161.4±5.1, p<0.001) in AP patients.

**Conclusion:** The difference of fatty acid composition of erythrocyte membranes between AP patients and healthy controls is likely to be associated with increased lipid peroxidation and OS.

**P10**

Peripheral Blood Polymorphonuclear Leucocytes (PMNLs) of Patients with Acute Pancreatitis (AP) Complicated by Organ Dysfunction (OD) and Immune Suppression (IS) Show Abnormal Intracellular Signaling Assessed by Phospho-Specific Flow Cytometry

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**Introduction:** Circulating PMNLs are considered to contribute to development of OD in patients with AP.

**Objectives:** To outline signaling profiles of PMNLs of AP patients with OD and IS.

**Materials & Methods:** Thirteen patients participated, 12 needed mechanical ventilation, five dialysis, each had proportion of HLA-DR-positive monocytes <80%. Thirteen healthy volunteers served as reference subjects. Phosphorylation of PMNL NFκB, p38, ERK1/2 and STAT-3,-5,-6 was determined using whole blood flow cytometry. Formyl-methionyl-leucyl-phenylalanine (FMLP)-induced transmigration of separated PMNLs was studied using Transwell inserts covered with EA-HY cells.

**Results:** The proportions of pNFκB-positive PMNLs were lower in patients in presence of TNF (7.5 ± 1.7% vs 11.5 ± 1.7%, p = 0.014), E. coli (7.4 ± 1.4% vs 11.5 ± 1.7%, p = 0.053) or S. aureus (7.1 ± 2.3% vs 10.9 ± 3.3%, p = 0.073). p38 phosphorylation was normal while ERK1/2 phosphorylation, induced by calcium ionophore and phorbol 12-myristate-13-acetate, was decreased (8.7 ± 1.6% vs 15.0 ± 2.4%, p = 0.027). STAT-3 was constitutively activated in five patients. Proportions of pSTAT-3-positive PMNLs, induced by IL-6, were higher in patients (38.1 ± 8.4% vs 10.7 ± 2.2%, p = 0.016). Proportions of pSTAT-6-positive cells, induced by IL-4, were comparable (20.0 ± 3.9% vs 21.8 ± 3.3%, p = 0.05) while fluorescence intensity of such cells was lower in patients (7.7±0.3 RFU vs 9.1±0.4 RFU, p = 0.011). STAT-5 phosphorylation, induced by granulocyte-macrophage colony stimulating factor, was normal. Proportions of transmigrated PMNLs were comparable.

**Conclusions:** In patients with AP complicated by OD and IS, increased STAT-3 activation and normal transmigration capacity of PMNLs may exaggerate OD. Decreased proportion of pNFκB-posi-
tive PMNLs may increase risk of secondary infections. Impaired PMNL STAT-6 activation may alleviate or exaggerate of OD.

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**P11**

**Early Changes in Serum Creatinine Level (SCL) and in Estimated Glomerular Filtration Rate (eGFR) Predict Mortality in Acute Pancreatitis (AP)**

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**Introduction:** Simple laboratory tests that reflect severe intravascular volume depletion can play an important role in the early assessment of AP.

**Objectives:** The aim of this study was to evaluate accuracy of SCL and eGFR, measured on admission, for prediction of fatal AP.

**Patients & Methods:** A cohort of 147 patients with AP was retrospectively enrolled in the study. SCL and eGFR (calculated by the abbreviated MDRD equation) on admission were analyzed for each patient. Utility of SCL and eGFR for the prediction of fatal AP was evaluated by receiver operator characteristic curve analysis and comparison of average values of these parameters.

**Results:** Of the 147 patients 7 died. Mortality rate was 4.8%. SCL and eGFR turned out to be good predictors of fatal AP with AUC respectively 0.879 and 0.787.

CRP measured on admission was not able to predict fatal outcome (AUC 0.505).

In the group with fatal AP, patients had significantly higher average value of SCL (1.52 mg/dL) and lower average eGFR (60.4 mL/min) in comparison with survival group (0.96 mg/dL and 95.4 mL/min, respectively). These differences are statistically significant (p = 0.001 and p = 0.01, respectively).

**Conclusion:** We assume that limited visceral blood flow which results from severe intravascular volume depletion and the associated stress response, could lead to fatal outcome of AP. As a single parameter, SCL and eGFR were most useful for predicting death in AP.

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**P12**

**TNFα Polymorphism in Patients with Acute Pancreatitis (AP) in Association with Cytokine Level and Disease Severity in Polish Population**

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**Introduction:** Severe AP may lead to complications and multiorgan failure (MOF). Polymorphism in the regulatory regions of cytokine genes can affect the level of cytokine production, and may be associated with predisposition to AP as well as different clinical outcomes.

**Objectives:** The aim of this study was to evaluate the association of polymorphisms of TNFα and it’s serum level in the AP.

**Patients/Material & Methods:** We investigated, in a prospective manner, 299 patients with AP and 106 healthy controls. The severity of AP was stratified according to Ranson and Balthazar scale, CRP level and Atlanta criteria. Genomic DNA was isolated from the whole blood in investigated and control group. Polymorphisms of TNFα (G-308A) were genotyped using polymerase chain reaction followed by restriction fragment length polymorphism (PCR-RFLP). Quantitative detection of human TNFα was measured with enzyme-linked immunoabsorbent assay (ELISA) for in vitro diagnostic use. Statistical analysis was done with Chi square and Fisher tests for polymorphism frequency and Wilcoxon test as appropriate. P value less than 0.05 were considered statistically significant.

**Results:** Unexpectedly we found significantly lower TNFα 308A (GA) genotype in AP patients compared to control. There was no statistic significancy in frequency of TNFα 308A (AA) in both groups. Serum level of TNFα (day 1, 3, 7) were higher in AP group, P<0.001. No difference in genotypes frequency and serum level between mild and severe AP was observed.

**Conclusion:** Significantly lower frequency of TNFα 308A (GA) polymorphism did not influence cytokine level and disease severity. Additional studies on a larger group of patients will be required to confirm these findings and to associate the polymorphism frequency and risk of AP.
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P13
The Probability of Drug-Induced Pancreatitis (DIP) Development in Patients with Pulmonary Tuberculosis

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Pancreatoxocity of modern anti-TB drugs hasn’t been studied enough.

Objective: to study the frequency of drug-induced lesion of the pancreas in patients with pulmonary tuberculosis.

Materials & Methods: The study included 280 patients with pulmonary tuberculosis. For DIP detection we investigated alpha-amylase, pancreatic isoenzyme, lipase of blood. Sonography of pancreas was performed. The study included only those patients who didn’t abuse alcohol. 30 healthy were examined.

Results: On the background of anti-TB therapy the frequency of alpha-amylase increased in 2.5–3.0 times amounted to 18.2%; in more than 3 times – 6.8%; the frequency of increase of pancreatic isoenzyme –20.7%; lipase activity was increased in 18.9%. At sonography the symptoms of pancreatitis were found in 25.4% of cases. The frequency of drug-induced lesion of the pancreas was dependent on which antibacterial agents have been prescribed. At the prescription of the first stage of therapy with the use of kanamycin, streptomycin, isoniazid in schemes, the incidence of DIP was higher in comparison with treatment regimens of the second stage (rifampicin, Avelox, etc.). In particular, the activity of alpha-amylase in blood in the first case was increased 2.31 times more frequently than in the second one.

Conclusion: In patients with pulmonary tuberculosis at the prescription of the second and especially the first step of therapy it’s necessary to monitor the biochemical parameters, to perform sonography for early diagnosis of pancreatitis.

P14
Analysis of Anisotropy CT Imaging in the Diagnosis of Infected Pancreatic Necrosis

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Introduction: The standard analysis of CT images may not accurately differentiate between sterile and infected pancreatic necrosis. One of the new techniques of computer medical imaging is the method of verification of the anisotropy of tissues.

Objectives: To develop and evaluate the diagnostic possibilities of a new method of computer analysis of CT images for verification of infectious complications of severe acute pancreatitis.

Material & Methods: We calculated the following anisotropy parameters: extreme anisotropy factor (F1); integral anisotropy factor (F2); coefficient of the spatial inhomogeneity of the anisotropy (F3); grain texture (G) (the program «Texture prober v2.0», UIIP, Belarus). We used the CT images of 16 patients with proven infected pancreatic necrosis, 23 patients with sterile pancreatic necrosis.

Results: When sterile pancreatic necrosis was observed pattern of unidirectional anisotropy, which has one clear direction of orientation: F1 = 2.40 [2.36–2.58], F2 = 4.35 [3.98–4.59], F3 = 7.71 [7.27–8.08], G = 34.5 [27.5–43.0] (Me [25%–75%]). Histogram of the anisotropy of pancreatic tissue with infected pancreatic necrosis was mainly unidirectional view: F1 = 3.71 [3.32–4.47], p = 0.0001; F2 = 5.99 [5.68–6.99], p = 0.0001; F3 = 8.74 [8.32–10.19], p = 0.0004; G = 39.5 [38.0–48.0], p = 0.006. Area under curve (AUC) are F1 = 0.980, F2 = 0.978, F3 = 0.842, G = 0.755. Cut off values of anisotropy parameters for the diagnosis of pancreatic infection are F1>3.27 (87.5% sensitivity and 100% specificity), F2>4.73 (sensitivity-100%, specificity-97.3%), F3>8.46 (68.6% and 95.7%) and G>36.0 (100% and 56.5% respectively).

Conclusion: Comparison of the anisotropy of the CT images of the pancreas revealed a significant difference in the groups of patients with sterile and infected pancreatic necrosis.

P15
Differential Step-by-Step Techniques in Surgical Treatment of Acute Necrotizing Pancreatitis

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Introduction: Acute necrotizing pancreatitis (ANP) is a dangerous disease that could cause serious complications and death.

Patients & Methods: We have analyzed the results of treatment of 569 patients with ANP; treated in the period of 1997–2008 years. Main group comprised of 387 patients, treated during 2002–2008 years. Control group comprised of 182 patients, treated during 1997–2001 years. Aseptic forms were diagnosed in 260 (67.18%) patients of the main group and in 107 (58.79%) of the control group. Infected necrosis with septic complications were diagnosed in 127 (32.82%) patients of the main group and in 75 (41.21%) of the control group.

Results: Conservative treatment made it possible to treat successfully 150 (38.76%) patients of the main group with aseptic forms of ANP. Ultrasound controlled interventions were performed in 193 (49.87%) patients of the main group and 44 (24.18%) of the control group. Percutaneous interventions made it possible to stabilize general state of the patient in 181 (46.77%) cases. In 8 patients with septic forms of ANP percutaneous retroperitoneal necrosectomy with nephroscope was used. Open surgical procedures were done in 128 (33.07%) patients of the main group and in 104 (57.14%) of the control group. Mortality was 6.78% (8.15% postoperative) in the main
Late Onset Pancreatic Necrosis in Acute Pancreatitis

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Introduction: The full extent of necrosis in acute pancreatitis usually occurs within 96 hours of symptom onset, with guidelines recommending contrast enhanced CT (CE-CT) two to 10 days after admission to assess extent.

Objectives: To determine whether late onset necrosis is a significant clinical problem potentially requiring guideline modification.

Patients/Materials & Methods: Patients who had minimal or no pancreatic necrosis on an initial CE-CT seven or more days after symptom onset (6 days after admission) were identified from a prospectively maintained database of patients who had pancreatic necrosectomy between 2005 and 2010. All their serial CE-CTs were assessed for necrosis blindly by two independent investigators by a novel morphometric method.

Results: Eight patients (6 males, 2 females, median 72 y) were included. Aetiology was gallstones (5; one underwent sphincterotomy and stone extraction), alcohol (1) and idiopathic (2). New or progressive pancreatic necrosis (median 62%, range 36–80%; median 4.3-fold increase; P = 0.01) was found at a median of 15 (6–36) days after admission. There were significant increases of necrosis in all parts of the pancreas (head P = 0.01, body P = 0.01, tail P = 0.02). Head or body necrosis significantly increased total necrosis (head P < 0.001, body P = 0.003). Six patients underwent minimal access necrosectomy (median 3 procedures, range 1–7), two open. Median ITU/HDU stay was 7.2 (0–28) and hospital stay 93 (77–171) days, with no mortality.

Conclusion: Clinically significant late onset necrosis in acute pancreatitis requires particular consideration that may mandate additional CE-CT later than previously recommended.

Early Collections in Acute Pancreatitis

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Introduction: The distinction between the different types of peripancreatic collections facilitates the choice of the treatment.

Objectives: To study the incidence and natural history of early peripancreatic collections associated with AP.

Patients and Methods: Retrospective cohort study: we revised every patient with AP admitted to our hospital in 2010 who developed acute peripancreatic collection (APC) or Acute post-necrotic collection (APNC). We defined: 1. APC as fluid collection lasting less then 4 weeks, lack a defined wall, not associated with pancreatic necrosis; 2. APNC as a collection occurs at the same time as APC, also lack of defined wall but associated with pancreatic necrosis.

Results: We included 61 patient with AP, 21 (34.4%) of them developed local complication. 16 (76.2%) out of 21 abdominal collections were APC and 5 (23.8%) were APNC. There were 11 male (mean age 54 years) and 5 female (mean age 46 years) in APC group. APC were definable by CT on 13th day after onset of AP. Location of APC regarding to anatomy of pancreas: head – 5 cases, body – 5, tail – 6. Two patients (13%) were operated: lumbotomy performed on day 10. Mean hospital stay in operated patients with APC was 53 (range 41–62), in non-operated patients – 18 (range 9–40).

In APNC group there were only 1 male (40 years) and 4 female (mean age 53 years). APNC become definable by CT on 16th day, located 4 around the tale and 1 in the head of the gland. All of them were operated on an average 23 day: open necrosectomy – 2, lumbotomy – 2 and PCD – 1. Mean hospital stay was 48 (range 28–88).

Conclusion: both types of collections develop at the same period of time, but the treatment approach differs significantly.

Efficacy of Percutaneous Catheter Drainage in Severe Acute Pancreatitis

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Introduction: The traditional approach to the treatment of Severe Acute Pancreatitis (SAP) is conservative management followed by open surgery.

Objectives: To evaluate the efficacy of percutaneous catheter drainage (PSD) under sonography in treatment of various form of SAP.

Methods: 52 patients with SAP requiring PSD from May 2008 to December 2010 were retrospectively analyzed. Drainage technique was the trocar method using an 9-F and 12-F multiside pigtail catheter.

Conclusion: Implementation of step-by-step procedures with individualized treatment protocols could significantly increase the results of treatment in patients with ANP.
Results: 10 patients underwent PSD for pancreatic fluid collection – all patients recovered completely after one drainage (volume 150–550 ml).

Drainage therapy was performed in 11 patients for acute pseudocysts with compression of bile duct (5), duodenum (2) and splenic vein (1). In 7 patients culture was negative. Surgery was performed in one case.

15 patients underwent PSD for pancreatic abscess, total number of catheter – 18. In addition to PSD surgical drainage required in 2 patients. 16 patients with infected pancreatic necrosis underwent 28 PSD (CT severity index – median 7 (4–9), multiorgan failure – 5 patients, monorgan failure -7). Surgical necrosectomy was performed in all patients. Four patients died because of multigorgan failure (12, 20, 37, 40 days after admission).

Conclusion: PSD is a safe and efficient component of treatment of pancreatic acute pseudocyst and abscesses. Percutaneous drainage as a part of minimally invasive step-up approach is a effective technique in the management of infected pancreatic necrosis.

P20
The Surgical Tactic for Prevention of Acute Pancreatitis in Patients with Difficult ERCP Cannulation

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Introduction: ERCP is widely used procedure. But in up to 10% cases it is difficult to perform. The main reason for the failure of ERCP is papillary or juxtapapillary diverticula and edema or deformation of the duodenum. From other hand the pancreatitis often occurs of patients who undergo ERCP after precut EPST with or without a guide wire. This study tested the tactic which makes possible to avoid post-ERCP pancreatitis.

Patients & Methods: research in the period from January 2008 to December 2010 was conducted. The design of study was built as case – result. Patients with mechanical jaundice who was ERC undertaken were included.

Results: 970 patients was performed ERCP. In 85 (8,76%) cases bile duct cannulation was not successful. In 37 (44%) of them it was completely unsuccessful procedure. In 48 (56%) ERCP was performed without precision cannulation of bile duct. We didn’t use precut EPST or guide wire cannulation. After unsuccessful attempts we used MRCP. Depending on the results we used mini-access laparotomy for the removal of stones in the common bile duct or elimination of other reasons of a mechanical jaundice. No case of acute pancreatitis and lethal outcomes was detected in the given group.

Conclusions: the offered tactics prevents complications and makes possible to avoid unreasonable EPST.

P21
Effect of Modified Da-Cheng-Qi Decoction on Severe Acute Pancreatitis Complicated with Intra-Abdominal Hypertension: A Pilot Study

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Introduction: Severe acute pancreatitis (SAP) complicated with continued intra-abdominal hypertension (IAH) leads to acute compartment syndrome and organ dysfunction, causing significant mortality. Our early experiment has shown that Da-Cheng-Qi Decoction (DCQD) relieves IAH and improves acute lung injury simultaneously in experimental acute pancreatitis.
Objectives: To evaluate effect of modified DCQD on IAH in patients with SAP.

Patients & Methods: We conducted a randomised, placebo controlled trial of modified DCQD therapy in patients with predicted SAP. Forty-two patients were enrolled from West China Hospital over the period January to December 2008. Randomisation stratified for APATCH-II score, treatment group and placebo group were similar at baseline. Intra-abdominal pressure was expressed indirectly by measuring intra-cystic pressure.

Results: Modified DCQD treatment significantly decreased intra-abdominal pressure (Day 4–8), APATCH II score (Day 6–8), CRP (Day 8) and the length of hospitalization, while improved oxygenation index (Day 4–8) compared to placebo group. However, there was no statistically significant difference in Balthazar CT score, rate of ICU transfer, and mortality between two groups.

Conclusion: This study provides the evidence that modified DCQD can effectively relieve IAH, therefore improve clinical outcome of patients with SAP. However, larger sample size clinical trials with double blinded design are still needed to justify our findings.

P22
Correlation Between Pancreatic Necrosis and Organ Failure in Patients with Severe Acute Pancreatitis

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Introduction: Developments of pancreatic necrosis and organ failure have a serious influence on the course of severe acute pancreatitis (SAP).

Objectives: The aim was to evaluate the relation between pancreatic infection, extent of necrosis and organ failure in patients with SAP.

Patients/Methods: This prospective study included 71 patients with diagnosis of NP admitted to Center for Emergency Surgery between 1996 – 2000. Diagnosis of SAP was established by contrast enhanced computed tomography (CCT) (66 patients) and/or by intraoperative findings (41 patients). Sonographically guided fine-needle punction with Gram stain was done in 43 patients with clinically suspected infection. During the course of disease 41 patients were surgically managed.

Results: In twenty nine (41%) patients infected necrosis were intraoperatively proved. According to CCT and intraoperative findings 33 (46%) patients had less than 50% of gland necrosis. There were statistically significant differences in development of organ failure and MOF among the patients with infected and sterile necrosis. Organ failure occurred more frequently in patients with more than 50% of gland necrosis than in those with less than 50% of necrosis. Statistically significant difference in development of infected necrosis was found between the patients with more than 50% of necrosis and those with less than 50%.

Conclusion: Bacterial infection and extend of necrosis has a strong impact on the occurrence of organ failure in SAP. Future therapeutic strategies should be reduction of systemic complications by decreasing the rate of infected pancreatic necrosis or by impact on pathophysiological pathways responsible for development of organ failure.

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P23
Changes in Pancreas Structure in Patients with Chronic Abdominal Ischemia

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It’s known that at the elderly age there exists an atrophy of pancreatic parenchyma and pancreatic fibrosis. But frequency and intensity of these changes haven’t been studied.

Objective: to study sonographic pancreatic changes in elderly patients with atherosclerosis of abdominal aorta.

Materials & Methods: 120 patients with chronic abdominal ischemia with atherosclerosis of abdominal aorta and its branches were included into the study. Diagnosis was confirmed by dopplerography. The age of the patients was over 60. Pancreatic US with histography was performed. 30 healthy were examined.

Results: Frequency of pancreas enlargement was 8,3%. Hyperechogenicity was observed in 90,0% of cases, hypoechogenicity — in 5,0%, heterogeneity of pancreatic structure — in 95,0%, irregularity of its margins — in 10,0% of cases. 13,3% of patients had calcifications in pancreatic tissue, 10,0% — calcifications in its ducts, 3,3% — dilatation of main pancreatic duct. In one-fifth of all cases there was observed a dimension of pancreas, in 23,3% of cases — pseudocysts.

Value of index L of US histography was significantly increased in comparison with control (respectively 36,9 ± 0,7 and 17,3 ± 0,5; p<0,05).

Conclusions: Patients of the elderly and old age with chronic abdominal ischemia frequently have structural changes of pancreas. They may lead to pancreatic insufficiency. Therefore, patients with atherosclerosis of abdominal aorta and its branches should undergo pancreatic US.
P24
Chronic Pancreatitis – Significance of C-Reactive Protein
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Introduction: C-reactive protein has many-sided functional activity and provides different variants of systemic inflammation syndrome in case of chronic recurrent pancreatitis (CRP) and chronic pancreatitis (CP).

Objectives: Research purpose is to investigate the results of C-reactive protein in the diagnostic of the chronic inflammation of CP.

Patients & Methods: The level of C-reactive protein was determined by the quantitative method with help of DAI (USA) reagent on the of immune-enzyme analyzer «Uniplan». 43 patients with CRP and CP aged 32–64 were examined.

Results: Three groups of patients were formed. The results of middle line in group I (7 patients) was 34.18 mg/ml. The percentile interval was 15,8–42.9 mg/ml. Main complaints were pain, dyspepsia both with gastroduodenitis, biliary system disorders, dysbiosis stage II–III. The result of middle line in group II (11 patients) was 6 mg/ml. The percentile interval was 3.1–8.97 mg/ml. The majority had rising of the weight, dyspeptic syndrome, dysbiosis stage II, accompany with anxiety dream, irritability. The result of C-reactive protein in group III (n=25) was the lowest. The results of middle line was 1.2 mg/ml. The percentile interval was 0.3–2.5 mg/ml.

Conclusions: Different forms of C-reactive protein (monomers, pentamers) can be estimated as trigger mechanism of the certain stage of the inflammation, reparation and angiogenesis that determine the acute or latent periods of the CRP and CP and variants of the treatment.

P25
The Frequency of Infection with Different Serotypes of Helicobacter Pylori in Chronic Pancreatitis
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It’s proved that Helicobacter pylori (Hp) infection is important in pathogenesis of chronic pancreatitis (CP), however Hp genotyping wasn’t carried out.

Objective: To study the frequency of infection in CP patients by different Hp serotypes.

Materials & Methods: 136 patients with CP were examined. In 79 (58,1%) patients Hp infection was diagnosed. In these patients biopsy of stomach mucosa to determine the genotype of Hp was performed. The polymerase chain reaction was made for detection of cagA, vacA, babA, iceA genes. Depending on identifying combinations of genes the strains of Hp were divided into 4 serotypes. 30 patients with Hp infection without CP were examined.

Results: The detection rate of various Hp genes was the following. CagA was found in 56 (70,9%), vacA — in 65 (82,3%), babA — in 10 (12,7%), iceA — in 12 (15,2%) Hp-infected patients.

Serotype I (cagA +, vacA +) Hp was detected in 47 (59,5%), serotype Ia (cagA +, vacA-) — in 9 (11,4%), serotype Ib (cagA-, vacA +) — in 18 (22,8%), serotype II (cagA-, vacA-) — in 5 (6,3%) patients. In 10 (12,7%) patients babA gene was identified, in 12 (15,2%) — iceA gene. These results differed from the data of patients with Hp but without CP.

Conclusion: In CP patients it’s necessary to diagnose Hp infection and in case of its detection to make its genotyping. The data in the future should be considered for further therapy decision.

P26
The Influence of the “Essentiale forte N” on the Indicators of the Endothelial Function in Patients with Chronic Obstructive Pulmonary Disease and Concomitant Chronic Pancreatitis
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Introduction: Currently there is no information about endothelial dysfunction in patients with chronic obstructive pulmonary disease (COPD) and concomitant chronic pancreatitis (CP).

Objectives: of our research was to study the influence of the essential phospholipids (“Essentiale forte N”, Sanofi Aventis, Germany) on endothelial function parameters in patients with COPD with concomitant CP.

Patients & Methods: We examined 20 patients with COPD with concomitant CP (group I) and 10 healthy persons (group II). Patients of the group I were divided into subgroups IA and IB. Patients of the IA group received basic therapy, IB – additionally received Essentiale forte N in a dose of 2 caps. three times a day during 1 month. Functional condition of endothelium was studied by using color duplex scanning of the right brachial artery with the use of samples with shorttime compression.

Results: The reduction of the reactive hyperemia and flowdependent vasodilatation in patients group I compared with a group ІІ. After the received treatment the parameters of the endothelial function significantly improved in patients who received additional medication that contains essential phospholipids.

Conclusion: Thus, in patients with COPD with concomitant CP the signs of the endothelial damage were discovered, such as the violation of the vascularregulating activity of the vascular wall, which can be adjusted by an additional appointment to the basic treatment Essentiale forte N.
Lipid distress syndrome develops in patients with obesity. It manifests with fatty infiltration and inflammatory changes of internal organs.

**Objective:** to study the frequency of fatty infiltration of the pancreas and the incidence of CP on the background of this infiltration in patients with obesity.

**Materials & Methods:** The study included 164 patients with obesity. Re-search of alpha-amylase activity, pancreatic isoamylase, lipase of blood, sonography with hystography of the pancreas, computer tomography were carried out. 30 healthy were examined.

**Results:** Fatty infiltration of the pancreas was detected by means of computer tomography in 123 (75,0%) patients. At sonography fatty infiltration of the pancreas was reflected in the increase of its echogenicity and it was difficult to differentiate fatty infiltration from CP. The increase of ultrasonic histogram index L gave evidence of fatty infiltration and it was detected in 119 (72,6%) patients. Marked correlation between the index L and Hounsfield index (r=−0,68) was revealed. The activity of alpha-amylase of blood was increased in 58 (35,4%), of pancreatic isoamylase of blood — in 64 (39,0%), of lipase of blood — in 62 (37,8%) patients. Clinical manifestations of CP occurred in 52 (31,7%) patients.

**Conclusion:** In obesity fatty infiltration of pancreas develops in 75.0% of cases and CP on the background of this fatty infiltration — in 39.0% of cases.

Pathogenesis of duodenal ulcers in chronic pancreatitis is diverse and not completely studied.

**Objective:** to study the frequency of pancreatic insufficiency in patients with combined pathology.

**Materials & Methods:** The study included 136 patients with chronic pancreatitis in combination with duodenal ulcers. The diagnosis was confirmed in presence of typical clinical symptoms, as well as taking into account data of pancreatic enzymes of blood and urine tests, the results of sonography and endoscopy. Fecal elastase test had been performed; and after treatment – in case of ulcer healing duodenal intubation with the detection of bicarbonates debit-hour was also carried out. 30 healthy were examined.

**Results:** The frequency of reduction of fecal pancreatic elastase-1 results was 79.4%, the rates below 100 mcg/g (severe pancreatic insufficiency) were recorded in 30.9% of cases. According to the results of duodenal intubation the decrease of bicarbonate production was observed in 38.2% of cases. Hypoenzymatic type of pancreatic secretion was detected in 32.4% of cases. Clinical manifestations of exocrine pancreatic insufficiency (weight loss, diarreya, hypovitaminosis) occurred in 35 (25.7%) patients.
Abstracts

**Conclusion:** in the majority of cases the pancreatic insufficiency takes part in pathogenesis of duodenal ulcers in patients with chronic pancreatitis. The decrease of bicarbonate production, which is registered in 38.2% of cases, is particularly important.

**P30**

**Portal Vein Thrombosis in Chronic Pancreatitis – Prevalence and Risk Factors**

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**Introduction:** Portal vein thrombosis (PVT) is an uncommon, well-recognized complication of chronic pancreatitis (CP).

**Purpose:** to assess PVT incidence and outcome in CP patients, and find possible risk factors.

**Material & Methods:** 170 CP patients operated between 2001 and 2010 were included in the study. Average CP duration was 12.33 years. PVT prevalence was calculated. Clinical data, treatment and outcome of PVT were described. PVT statistical correlations to potential risk factors were calculated.

**Results:** PVT prevalence was 3.53%. Six males (CP etiology: 5 alcoholic and 1 hypertrigliceridaemic) developed PVT (mean age = 54 years, mean CP duration = 11.51 years). Symptoms included low protein ascites (2), weight loss (5), splenomegaly (4), segmental hepatic necrosis (1). Mesenteric vein was not involved by thrombus, while splenic vein thrombosis was associated in all patients. Infected fluid collections, present in 5 patients were treated by percutaneous drainage. One patient died due to severe sepsis. During evolution, 4 patients suffered surgery addressing chronic pancreatitis (2 = distal spleno-pancreatectomy, 2 = Frey procedure). None of the patients had bleeding from eso-gastric varices during 3.7 years mean follow-up. Statistical analysis found as PVT risk factors: alcoholic etiology, CP duration > 10 years, recent acute episodes, infected fluid collections and previous splenic vein thrombosis.

**Conclusion:** PVT usually occurs after >10 years CP evolution, in patients with advanced morphological changes, infected fluid collections and preexistent splenic vein thrombosis. Less frequent, PVT develops early in younger patients, after severe acute episodes. PVT usually evolves to cavernoma, which makes surgery more difficult and risky.

**P31**

**Lipid Profile of Blood in Patients with Chronic Pancreatitis on the Background of Chronic Abdominal Ischemic Syndrome**

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Disorders of lipid blood spectrum take place as a rule in patients with chronic abdominal ischemic syndrome because of atherosclerosis. The type of these disorders should be taken into account in treatment administration.

**Objective:** to study indices of blood lipids in patients with chronic pancreatitis, developed on the background of abdominal ischemic syndrome.

**Materials & Methods:** 82 patients and 30 healthy persons were examined. The diagnosis of abdominal ischemia was confirmed by results of dopplerography of abdominal aorta and its branches. Indices of cholesterol, alpha-cholesterol, lipoproteins of high, low and very low density, triglycerides were analyzed with the help of kits Coultronics (France) on biochemical analyzer Vitalab Flexor (Netherlands).

**Results:** Significant increase of indices of cholesterol, lipoproteins of low and very low density, blood triglycerides, atherogenic index were revealed in patients. At the same time level of lipoproteins of high density and alpha-cholesterol were essentially lowered. It is important that negative correlation connections between degree of lipid disorders and intensity of changes of blood flow in abdominal aorta and its unpaired branches were found.

**Conclusion:** Atherogenic lipid blood profile presents in patients with chronic pancreatitis on the background of chronic abdominal ischemia that it is necessary to take into account in treatment administration.

**P32**

**The Relationship Between the Function of External Respiration and Vascular Endothelial Growth Factor in Patients with Chronic Obstructive Pulmonary Disease with Concomitant Chronic Pancreatitis**

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**Introduction:** Important role in the development of chronic obstructive pulmonary disease (COPD) and chronic pancreatitis (CP) belongs to hypoxic component.

**Objectives:** To study the relationship between lung function parameters and vascular endothelial growth factor (VEGF) in patients with chronic obstructive pulmonary disease with concomitant chronic pancreatitis.
P33

Violation of Evacuation Terms from the Stomach in Chronic Pancreatitis (CP)

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Gastroduodenal dysmotility in chronic pancreatitis is not well examined.

Objective: to study the velocity of evacuation from the stomach in chronic pancreatitis.

Materials & Methods: 32 patients with CP were examined. Faecal elastase test was carried out (kits Schebo, Germany). The rate of gastric emptying was determined using 13C-octanoic breath test (infrared gas analyzer IRIS, Germany). The study included 20 healthy persons.

Results: In healthy the gastric emptying index was more than 3.1, and half-life of the stomach contents — at least 130 min. In patients with CP in 65.6% of cases there was a moderate decrease in the rate of gastric emptying (emptying rate 3.1–2.5); in 18.8% of cases there was an expressed reduction in the velocity of stomach emptying (emptying coefficient<2.5); only in 15.6% of cases the velocity of emptying was normal. Results of the study of gastric contents half-life time in patients were related. Thus, the half-life of less than 130 min was determined in 5 healthy, moderate decrease of half-life — in 21 patients, marked reduction — in 4 patients.

It’s important that the half-life period of the test breakfast from stomach was inversely correlated with indices of fecal elastase-1.

Conclusions: In CP in the predominant majority of patients there is a delayed evacuation from the stomach and these changes are connected with reduced exocrine pancreatic function. These findings point to the necessity of gastroduodenal motility correction in CP.

P34

Influence of Concomitant Chronic Pancreatitis on the Endothelial Functional State in Patients with Chronic Obstructive Pulmonary Disease

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Introduction: The specificity of pathogenesis of endothelial dysfunction in a large circle of blood circulation in patients with chronic obstructive pulmonary disease (COPD) is the development of chronic inflammatory reaction that leads to the emergence and progression of both COPD and chronic pancreatitis (CP).

Objectives: To study the effect of concomitant CP on the functional state of endothelium in patients with COPD.

Material & Methods: 32 patients with COPD, including 16 COPD patients with concomitant CP and 7 healthy subjects (HS) were examined. Functional state of endothelium was assessed by endothelial content in plasma of stable metabolites of nitrogen monoxide – NO (nitrites, nitrates) and endothelin-1 using a set to determine endothelin (1–21) produced Biomedica (Austria).

Results: The content of nitrogen monoxide metabolite (NO) in patients with COPD decreased in 1.4 times, in patients with concomitant pathology similar index decreased in 1.8 times (p<0.05) compared to the HS. Analysis of the results showed excessed levels of endothelin-1 in patients with COPD in 2.02 times (p<0.05) and in 4.5 times (p<0.05) in patients with a concomitant CP.

Conclusion: Thus, in patients with COPD with concomitant CP there are signs of more extensive endothelial dysfunction due to increased synthesis of ET-1 and reduced synthesis of NO, which may cause the development of fibrous changes in pancreas and lungs.

P35

Slowed EEG Rhythmicity in Patients with Chronic Pancreatitis: Evidence of Abnormal Cerebral Pain Processing?

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Introduction: Intractable pain usually dominates the clinical presentation of chronic pancreatitis (CP). Slowing of electroencephalogram (EEG) rhythmicity has been associated with abnormal cortical pain processing in other chronic pain disorders.

Objective: The aim of this study was to investigate the spectral distribution of EEG rhythmicity in patients with CP.

Patients & Methods: Thirty-one patients with painful CP (mean age 52 years, 19 males) and 15 healthy volunteers (mean age 49, 9 males) were included. A multichannel EEG was recorded from
62 surface electrodes. Amplitude strengths of the resting EEG were retrieved based on wavelet frequency analysis and summarised in frequency bands with corresponding topographic mapping.

**Results:** Patients with CP had slowed EEG rhythmicity compared to healthy volunteers. This was evident as increased activity in the lower frequency bands delta [1–3.5 Hz] ($P<0.05$), theta [3.5–7.5 Hz] ($P<0.001$) and alpha [7.5–13.5 Hz] ($P<0.001$). Due to normalisation a reciprocal relationship was observed for the high frequency band beta [13.5–32 Hz]. In a sub-analysis, delta band activity was modified by diabetes, opioid treatment and alcohol aetiology of CP. However, no effect modification was seen for the theta or alpha bands. Differences in theta activity were located over centro-frontal brain regions, while differences in delta, alpha and beta band activity were located in frontal regions.

**Conclusion:** Slowed EEG rhythmicity was evident in patients with CP. This possibly mirrors abnormal central pain processing and may serve as a clinically useful biomarker.

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**Clinical Science – Chronic Pancreatitis IV**

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**P36**

**Erythrocytic Deformability Index and Relative Viscosity of Erythrocytic Suspension in Patients with Chronic Pancreatitis and Concomitant Heart Insufficiency**

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**Introduction:** The diagnostic sign of hypoxia is a disturbance of the morphofunctional properties of erythrocytes.

**Objectives:** to investigate the index of deformability of erythrocytes (IDE) and relative viscosity of Erythrocytic suspension (RVES) in patients with chronic pancreatitis (CP) and heart insufficiency (HI).

**Patients & Methods:** 32 patients have been examined, 10 of them being afflicted with CP underlying HI, 12 persons -with CP and 10- with HI and 10 – apparently healthy persons. The morphofunctional state of erythrocytes was evaluated by means of the method of Z.D. Fedorova, M.O. Kotovshchikova (1989).

**Results:** It has been established that the IDE indices ($p<0.05$) decrease reliably in patients with coronary disease (CD) with underlying HI as compared with the indices of the apparently healthy persons. As far as RVES is concerned, they augment reliably in the groups of patients with CP with underlying HI and CD with underlying HI in relation to the group of the apparently healthy persons.

**Conclusion:** The findings obtained are indicative of an increase of the index of the viscosity of erythrocytic suspension and a decrease of their capability towards deformity, the latter being a sign of hypercoagulation in the vessels and tissue hypoxia in the presence of the syndrome of heart insufficiency both in the CP patients and those with CD.

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**P37**

**Autoimmune Pancreatitis and IgG4 Positive Mastitis**

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**Introduction:** Autoimmune pancreatitis (AIP) is frequently combined with simultaneous involvement of extrapancreatic organs. This applies particularly to the lymphoplasmacytic sclerosing pancreatitis (LPSP), also referred to as AIP type 1. This type of autoimmune pancreatitis is often accompanied by concurrent sclerosing cholangitis, sialadenitis, retroperitoneal fibrosis, sicca syndrome and other extrapancreatic lesions. High levels of IgG4 immunoglobulin in blood serum and affected tissues are typical for this diagnostic entity.

**Objectives:** To present a case report of AIP patient with multisystem involvement.

**Patients & Methods & Results:** We describe a 52 year old female with findings of AIP (according to Asian criteria), IgG positive mastitis and histologically verified Mikulicz syndrome. The effects of corticoid therapy supported the diagnosis of AIP and simultaneously led to the eradication of recurrent mastitis.

**Conclusion:** To our best knowledge, this is a first reported case of concurrent findings of AIP and IgG4 mastitis. By adding next organ affected with IgG4 derived inflammation, our findings support a concept of systemic IgG4 syndrome with multisystem involvement. Timely diagnosis and appropriate therapy can be effective in a high percentage of patients.

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**P38**

**Interconnection Between the Proteolytic and Apoptotic Activity of Blood Plasma in Patients with Chronic Pancreatitis and Concomitant Ischemic Heart Disease**

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**Introduction:** Features of pancreatic blood flow, the influence of proteolytic enzymes on kininogenesis and hemostasis system determine the importance of microcirculatory and hemoreological disorders in the pathogenesis of chronic pancreatitis (CP) and coronary heart disease (CHD).

**Objectives:** To investigate the relationship between apoptotic indices and proteolytic activity of blood plasma in patients with CP and concomitant CHD.

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Abstracts
Material and Methods: 114 patients with CP and concomitant coronary heart disease from 60 to 74 years, 28 patients with coronary heart disease and 25 healthy individuals were examined.

Results: Plasma activation of proteolysis determined by azoalbumin, azokazeine and azokol lysis in all groups of patients, with a maximum increase of intensity of macromolecular proteins proteolytic degradation. Activation of proteolysis may lead to increased apoptotic activity in the pancreas tissue, proved by direct correlations between the level of CD 95, azokazeine lysis (r=0.8, p<0.05) and azoalbumine lysis (r=0.69, p<0.05).

Conclusion: The growth of proteolytic activity creates the conditions to increase the viscosity of the wall surface of plasma layer in small capillaries and concentration of substances that enhance the aggregation function of blood elements.

P39 Clinical Manifestation of Hereditary Pancreatitis in Children

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Introduction: Hereditary Pancreatitis (HP) is a rare inherited condition. The reported pediatric experience with HP is small. We reviewed our experience over the past 20 years.

Objectives: The aim of our study was to evaluate the clinical aspects of HP in children.

Methods: 171 children with CP, hospitalized since 1990 to 2010, were enrolled into the study. The medical records of these patients were reviewed for data on the presentation, diagnostic findings and endoscopic treatment. All children were screened for the PRSS1 gene mutations.

Results: PRSS1 gene mutations were found in 19 patients (11%) (11 girls and 8 boys). We detected R122H- in 11, R122C- in 5, N29I/- in 2 and E79K/- in 1 patient. In one patient we found SPINK1 mutation (N34S/-). Family history was positive in all children with HP except one. There was no difference in age of the disease onset between HP group and non-HP group (8.03 vs. 9.08 years; NS). In children with PRSS1 mutation ERCP had mean 2.6 Cambridge grade, vs. 1.6, p<0.05. 13 patients with HP had calcifications in the imaginary stones (72% vs. 31%, p<0.05). Therapeutic intervention, including both surgical and endoscopic intervention, was more frequent in the HP group (78% vs. 35%; p<0.05). Pancreatic duct stenting was done in 11 children with HP (61% vs. 26%; p<0.05). ESWL was performed more frequent in HP group (28% vs. 3%; p<0.05).

Conclusions: Hereditary pancreatitis in children has worse clinical course than CP in children without PRSS1 mutations.
Abstracts

P42

Immunological Markers for Diagnosis of Autoimmune Pancreatitis

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Introduction: Nowadays, the immunological markers of AIP are showed to be of great importance.

Objective: To study some immune markers of AIP.

Materials and Methods: 58 patients diagnosed with AIP. The immunity, thyroglobulin antibodies, thyroid peroxidase, gastric parietal cells were investigated in patients as well.

Results: In patients, specific immune indexes were higher than normal values in general population. In these patients, the numbers of lymphocytes expressing CD25, activated T-lymphocytes (CD3+ HLA DR+), activated NK-cells [CD (16+56) + HLA DR+] were increased. Number of double-positive T-lymphocytes, was close to the upper limit of the population norm. Number of auto-reactive B-1 B lymphocytes (CD19+CD5+) exceeded the limits of population norms that accompanied high levels of spontaneous production of interleukin-6 and serum IFN-γ. These values were significantly higher than those in healthy individuals. The levels of secretory immunoglobulin A in blood exceeded the upper limit of norm more than 2 times and confirmed that exacerbation of chronic pancreatitis occurred. The concentration of autoantibodies to gastric parietal cells in patients with AIP was higher than 3 times norm. Increased antibodies to thyroid peroxidase and to thyroglobulin were revealed in 20.7% and 8.6% of cases, respectively.

Conclusions: 1. AIP is accompanied by multi-organ lesions, including autoimmune gastritis, autoimmune thyroiditis. 2. Increased severity of AIP manifested with higher specific immune indexes and the level of secretory immunoglobulin A in blood.
**P44**

*Cystic Duodenal Dystrophy in a Young Patient with Early-Onset Idiopathic Pancreatitis: A Case Report*

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**Introduction:** Cystic duodenal wall dystrophy, first described as a separate entity by in 1970, is a rare complication of chronic pancreatitis.

**Objectives:** We report a case of a large duodenal wall cyst in a patient with severe chronic calcifying pancreatitis, successfully treated with a Whipple procedure.

**Materials & Methods:** A 29-years old Caucasian male has been referred to our Department with complaints on constant abdominal pain and weight loss of about 15 kg in 6 months. Recurrent attacks of pancreatic pain began at the age of 18. Despite enzyme therapy the symptoms gradually became intolerable. No history of alcohol consumption, smoking or genetic predisposition was found. The patient's symptoms gradually became intolerable. No history of alcohol consumption, smoking or genetic predisposition was found. The patient's Body Mass Index was 22.1 kg/m². Laboratory tests revealed no abnormalities.

**MRI:** hugely dilated and distorted pancreatic ducts with distal flow obstruction and a 4 cm cystic lesion laterally to the head of the pancreas. CT: chronic calcifying pancreatitis with multiple intraductal and intrapancreathous stones. Endoscopic US: a cystic lesion in the submucosal layer of the duodenum, partly obstructing duodenal lumen.

A Whipple procedure with termino-lateral pancreato-jejunostomy was performed. The patient was discharged 17 days after.

**Results:** Histology revealed a submucosal duodenal cyst without epithelial lining or ectopic pancreatic tissue as well as complete obstruction of both major and accessory pancreatic ducts. One year after the procedure the patient is free of symptoms, gained 10 kg and has normal glucose levels.

**Conclusion:** Cystic duodenal dystrophy is a seldom complication of chronic pancreatitis. A formal Whipple procedure seems beneficial in these special settings.

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**P47**

*Course of Chronic Pancreatitis in the Northeast of Germany*

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**Introduction:** Data regarding the course of chronic pancreatitis (CP) were published many years ago. New studies are necessary.

**Objectives:** Here, we aimed to characterize the course of CP in the Northeast of Germany.

**Patients & methods:** In this retrospective study 118 patients with CP could be included. Pathogenesis, gender, age, nicotine abuse, alcohol abuse, pain, calcification, pseudocysts and venous occlusion were analyzed.

**Results:** Characterizing the disease patients had alcoholic CP (71.2%), idiopathic CP (24.6%), hereditary CP (2.5%), and autoimmune CP (1.7). Only 11% of the patients had acute necrotizing pancreatitis before the manifestation of CP. 28% of patients developed diabetes mellitus (82% treated with insulin). In one patient pancreatic carcinoma was detected. 30% of patients had surgery, 74% within 5 years after diagnosis. Manifestation of alcoholic CP was significant earlier than in patients with idiopathic CP (age 42.4 vs 49.8 years). Occlusions of veins were observed more often in patients with alcoholic CP than in idiopathic CP (38% vs 17%). Other evaluated parameters differed not in comparison to the literature.

**Conclusion:** In CP occlusion of veins has been observed more often than in published literature and need to be detected during diagnostic procedures.

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**P45**

*Correlation Between Exocrine Pancreatic Insufficiency as Determined by Fecal Elastase 1 Concentrations and Neuropathy in Patients with Diabetes Mellitus*

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**Introduction:** Exocrine pancreatic insufficiency (PEI) is present in 30–50% of patients with diabetes mellitus. Several hypothesis have been raised to explain these findings. One hypothesis dating back to the 1960ies suggested that PEI might be due to a dysregulation of exocrine function by autonomous neuropathy. However, no data comparing exocrine function and neuropathy have been published until now except for a few case reports.

**Objectives:** Comparison of neuropathy findings with studies on exocrine function in patients with diabetes mellitus.

**Patients & Methods:** The registry of our university hospital was searched for patients with completed neuropathy status and data on exocrine pancreatic function (fecal elastase 1 concentrations (FEC)). If both informations could be obtained, data on gender, age, disease duration, diabetes type and complications were collected with a standard form.

**Results:** 416 patients met the inclusion criteria (34% type 1, 59% type 2, 7% type 3c), mean age 55 years (15–88). The mean diabetes duration was 12 years, HbA1c 8.6% (4.6–17.3). Neuropathy (DN) was present in 48.5%. PEI was present in 29.3%. There was an inverse correlation between diabetes duration and PEI (p < 0.001) as well as a positive correlation between the presence of neuropathy and PEI (p = 0.01). There was no correlation between HbA1c and PEI.

**Conclusion:** The data confirm recent reports on a correlation between diabetes duration and the presence of PEI suggesting that PEI could in fact be a diabetic complication. For the first time it is demonstrated that the degree of PEI is correlated significantly with the presence of diabetic neuropathy.
**Abstracts**

**Basic Science – Chronic Pancreatitis/Genetic Disorders**

**P48**

**The Impact of Urethral Reconstructive Surgery and Pancreatic Recurrence of Disorder**

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**Purpose:** Our project conducted a study which reflects many years of intra and postoperative complications following urethral reconstructive surgery, and the impact of these complications at the pancreatic disorders formation.

**Materials & Methods:** Me being a practical example in 1988 and many others from then through 2005, 153 consecutive urethral reconstructive procedures were performed on 130 patients by one surgeon (CMG). Complication rates were determined, and subgroups were categorized based on stricture etiology, patient age, length of stricture, location of stricture, type of repair, and presence of various co-morbid conditions.

**Results:** Overall, 23 of 153 cases had an intra or postoperative complication. The most common complications were related to infection (n=9). Other complications included repair breakdown (n=4), bleeding (n=4), fistulae (n=3), thromboembolic (n=2), positioning-related (n=2), and Foley catheter malfunction (n=1). The number of patients with at least one year of follow-up who had a complication and eventual stricture recurrence was 20% (4/20), while only 7.4% (7/95) of those who did not have a complication recurred (p = 0.08).

**Conclusions:** Complications following reconstructive surgery for urethral stricture disease were mostly related to infection or repair breakdown in pancreatic disorder and system. It does not appear that an intra or postoperative complication following urethral reconstructive surgery impacts the chance of eventual stricture recurrence at intermediate follow-up.

**P49**

**The Evidence for the Pancreatic Oxide Injuries Induced by the Chronic High-Fat Diets in Rat**

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**Introduction:** The pathogenesis of CP has improved in recent years, which mainly due to the identification of Pancreatic stellate cells (PSC) and its pivotal role in the fibrotic process of chronic pancreatitis. Accumulated evidence suggests that oxidative stress involved in the pathogenesis of CP and therapeutic approaches target-ing oxidative stress have been carried out in the clinical setting. However, the efficacy of antioxidant therapy is limited perhaps due to lack of the exact target.

**Objective:** To provide more evidence of lipid peroxidation in the pathogenesis of chronic pancreatitis; 2) to find some clues of the antioxidant therapy target.

**Methods:** Rats of HFD groups (n=12) were fed with an HFD for 2, 4, 6, 10, and 16 weeks respectively. Histopathologic changes were observed by HE and Sirias Red staining for fibrosis. Immunohistochemistry of desmin and α-smooth muscle actin (α-SMA) was performed to identify the PSC in the pancreatic tissues. The expression of the lipid peroxidation were detected by the immunostaining of 4-Hydroxy-2-Nonenal (4-HEN, one of the major toxic products generated from lipid peroxides) and Thromboxane A2 receptor (TXA2 r, a receptor of F2-isoprostanes which be considered the most reliable markers of oxidative stress). The colocalization of α-SMA and HNE or -SMA and TXA2 Receptor on PSC was detected by double immunofluorescent staining.

**Results:** The number of PSCs significantly increased in all the HFD groups. The levels of pancreatic 4-HEN and TXA2 r increased in rats of HFD groups. HNE and TXA2 r can colocalize with activated PSC respectively. These enhancements were accompanied with sequential histopathology alterations resulted from acute inflammatory response in the early stages of secondary pancreatic fibrosis.

**Conclusion:** The results indicate that chronic HFD increased lipid peroxidation associated with pancreatic injuries and collagen synthesis by activated PSC in rats.

**P50**

**Serotonin Plays a Key Role in the Pathogenesis of Pancreatitis**

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**Introduction:** Inflammation of the pancreas results in pancreatitis, a severe and incapacitating disease characterized by pain, intestinal malabsorption and endocrine dysfunction. The etiologic factors involved in the initiation and aggravation of pancreatitis have not been well defined, and the treatment of the disease is still to be established.

**Objectives:** To gain more insights into the pathophysiology of pancreatitis, we investigated whether serotonin, a monoamine with several and still not completely characterized physiological functions, plays a role in the progression of the disease.

**Materials & Methods:** Pancreatitis was induced by repetitive injections of cerulein in wild type and tryptophan hydroxylase 1-deficient (TPH1-/-) mice, which have markedly reduced peripheral levels of serotonin. The progression of the disease in the two mouse strains was evaluated over a period of two weeks by serum enzyme analyses, immunohistochemistry and qRT-PCR of known genes coding for inflammatory mediators and profibrotic proteins.

**Results:** We found that the absence of serotonin delayed the onset of pancreatitis, attenuated the cerulein-induced hyperenzymia and reduced the levels of immune cell infiltration. However, the protection conferred by low levels of serotonin was temporary and
reverted at two weeks of cerulein treatment, leading to increased leukocyte infiltration and fibrotic lesions. In addition, by using in vivo and in vitro models, we revealed that serotonin modulates amylase secretion in acinar cells.

**Conclusion:** Our results demonstrate that serotonin plays an important role in the onset and progression of cerulein-induced pancreatitis and in the physiology of the exocrine pancreas.

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**P52**

**Violation of Adaptive Mechanisms in Chronic Pancreatitis**

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**Introduction:** exocrine function of pancreas is under composite neurohumoral regulation

**Objectives:** to establish violation of adaptive mechanisms in regulation of pancreatic secretory activity depending on the clinical stage of chronic pancreatitis by M-ANNHEIM classification.

**Patients & Methods:** study involved 68 patients with chronic pancreatitis (CP) and a control group – 15 healthy volunteers. Concentration of serotonin (5-HT) and acetylcholine (Ach) were counted in blood samples at baseline and after a standard breakfast (SB).

**Results:** In control group concentration of 5-HT initially and after SB were the same (0.19±0.02 vs. 0.23±0.019 mg/ml; p>0.05), but concentration of Ach were increased (0.8±0.06 vs. 1.0±0.05 mmol/l; p<0.05). In patients with CP stage I was the same dynamics. On the contrary in patients with CP stage II concentration of 5-HT increased after SB, but Ach didn’t change. In CP stage III-IV we founded high baseline level of 5-HT which was increasing after SB (0.40±0.07 vs. 0.55±0.05 mg / ml; p<0.05) and high baseline level of Ach which didn’t change after SB (1.7±0.3 to 1.6±0.3 mmol/l; p>0.05).

**Conclusion:** We founded different types of neurohormonal regulation depending on the clinical stage of chronic pancreatitis. In stage I regulation is carried out by parasympathetic nervous system, but then its significance reducing. In last stages of CP are growing complex of compensatory reactions, one of markers of which is 5-HT.

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**P53**

**Genetic Analysis of Hemoxygenase-1 in Chronic Pancreatitis**

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**Introduction:** Hemoxygenase-1 (HO-1) is the rate limiting enzyme in the catalabolism to form biliverdin, free iron and carbon monoxide. Activity of HO-1 is induced by heme itself and by various other substances. By activation of HO-1 anti-inflammatory processes are upregulated, that contribute to a milder disease course in animal models of acute pancreatitis. A (GT)₃-repeat in the HO-1 promoter influences HO-1 expression and might therefore be of importance in chronic pancreatitis (CP).

**Methods:** We analysed the (GT)₃-repeat in 170 patients with alcoholic CP (ACP), 148 patients with alcoholic liver cirrhosis (ALC), 150 patients with idiopathic CP (ICP) and in 289 healthy controls. Additionally, sequencing of the coding exons and exon-intron junctions was performed in 146 ACP patients, 148 ALC patients, 150 ICP patients and in 153 healthy controls.

**Results:** (GT)₃-repeat numbers were classified in 3 categories: S = <25 GTs, M = 25–30 GTs and L = >30 GTs. Distribution of (GT)₃-repeat groups was similar in the different groups: ACP: S = 42.1 %, M = 53.2 %, L = 4.7 %; ALC: M = 42.2 %, M = 54.4 %, L = 3.4 %; ICP: S = 33.8 %, M = 59.7 %, L = 6.5 %; Controls: S = 37.7 %, M = 56.7 %, L = 5.7 %. Sequence analysis detected non-synonymous variants in the ACP (p.P193S), the ICP (p.R136H) and in the control group (p. M34T).

**Conclusions:** HO-1 promoter (GT)₃-repeat is not associated with ACP, ICP or ALC. Rare non-synonymous variants were detected in different groups and most probably have no influence on the development of the diverse disease entities most of all in ICP and ACP.

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**P54**

**Mucosal-Associated Invariant T Cells Infiltrate Pancreatic Tissue in Chronic Pancreatitis**

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**Introduction:** Mucosal-Associated Invariant T-cells (MAIT) are recently described human T lymphocytes with possible functions...
in mucosal antibacterial host defence. It is suggested that T lymphocytes play a role in the pathogenesis of chronic pancreatitis (CP), but little is known about the composition of T cell subsets in this disease.

**Objectives:** Intestinal bacterial overgrowth is common in CP patients. We hypothesised that this antigenic load may promote MAIT infiltration into the pancreas and therefore aimed to investigate this in pancreatic tissue and blood.

**Methods:** Fresh resected pancreatic tissue from 5 patients with CP (5 male, aged 35–62, median age 43) and 4 controls (2M/2F, aged 62–75, median age 70) was enzymatically and mechanically digested. Lymphocytes were then isolated using density gradient centrifugation. Peripheral blood mononuclear cells (PBMCs) were also isolated from the blood of all patients. Tissue lymphocytes and PBMCs were analysed with fluorochrome conjugated antibodies (anti-CD3; CD4; CD8; CD161; T cell receptor (TCR) Va7.2) and a live/dead stain according to standard techniques using a FACSAria.

**Results:** Double negative (DN) and CD8+ MAIT (TCR Va7.2+ / CD161+) were identified in pancreatic tissue and blood in all CP patients. A significantly higher number of CD8+ and DN MAIT were seen in the tissue of patients with CP compared to controls: 9.6±0.2%, p<0.007; and 20.9±0.2%, p<0.04 respectively. The proportion of DN MAIT was significantly higher in pancreatic tissue compared to blood in patients with CP: 20.9% (5.7–41.1%) vs 8.6% (4.4–19.1%), p<0.04.

**Conclusion:** These preliminary data demonstrate that MAIT infiltrate pancreatic tissue in CP. Furthermore DN MAIT are enriched in tissue of patients with CP suggesting a specific role in local immune responses. Future analysis using a larger patient cohort and functional studies to assess the possible role of these cells in the regulation of pancreatic inflammation is required.

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**P55**

**The Impact of MFG-E8 in Chronic Pancreatitis: Potential for Future Immunotherapy?**


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The glycoprotein MFG-E8 mediates phagocytic clearance of apoptotic cells and influences the pathogenesis and progression of inflammatory diseases. MFG-E8 was shown to attenuate the progression of inflammation and survival in sepsis. Accumulating evidence suggests an immunomodulatory link between MFG-E8 and the pro-inflammatory chemokine fractalkine, which is determining the severity of pain and inflammation in chronic pancreatitis (CP).

To determine the potential impact of MFG-E8 in CP, the expression and localization of MFG-E8 was investigated in CP (n=65), and normal pancreas (NP) (n=34) by QRT-PCR, western blot and immunohistochemistry. Results were correlated with the mRNA expression of fractalkine and with the degree of pain and fibrosis.

MFG-E8-mRNA was significantly overexpressed in CP when compared to NP. Western blot and immunohistochemistry analysis confirmed the accumulation of MFG-E8 in chronic pancreatitis tissues where MFG-E8 immunoreactivity was noticeably increased in tubular complexes and inflammatory cells. MFG-E8 expression correlated significantly with fractalkine expression, the degree of fibrosis, and the severity of pain.

In the present study, we demonstrated that MFG-E8 is significantly up-regulated in CP patients and together with Fractalkine correlated significantly with the degree of fibrosis and the severity of pain. These results are in contrast to previous reports of MFG-E8 in inflammatory diseases where it is rather down-regulated in the acute phase and administration of recombinant MFG-E8 was reported to be beneficial. Taken together, these novel findings demonstrate that MFG-E8 blockade seems to be a promising tool for future therapy in CP to attenuate the severity of fibrosis and pain.

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**P56**

**Genetic Polymorphisms and Gene Expression in Pancreatic Ductal Adenocarcinoma, Chronic Pancreatitis and Normal Pancreatic Tissue**


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**Introduction:** Little is known about etiology of pancreatic cancer, particularly regarding inherited risk. In addition to tobacco smoking, obesity, diabetes and chronic pancreatitis, family history is an established risk factor, and pancreatic cancer has been reported in some rare genetic cancer syndromes. In 2009 the PanScan project, a genome-wide association study, identified several common polymorphisms affecting pancreatic cancer susceptibility.

**Objectives:** The aim of the present study was to investigate possible effects of inter-individual genetic variation in 19 risk loci identified by PanScan on the expression of genes mapping to the same genomic regions.

**Materials & Methods:** Nineteen SNPs mapping to six regions identified by PanScan were genotyped in samples of 154 cases of pancreatic ductal adenocarcinoma (PDAC), 63 cases of chronic pancreatitis and 35 normal subjects (organ donors). For all these subjects, genome-wide gene expression data were collected with an Illumina array. Genotyping was performed using TaqMan. We evaluated associations between SNP alleles and gene expression.

**Results:** We found that several SNPs were associated with differential expression of various genes, among them the strongest correlation was observed between SNP rs657152, mapping to ABO, and the ABO gene expression (p=0.001) in PDAC, and between SNP
rs8176720, mapping to ABO, and the TNF gene expression (p = 0.001) in normal pancreatic tissue.

**Conclusion:** This study clearly indicates that the better understanding of the interplay between genetic variation in PC risk loci and gene expression could be an important step to shed light to the genetic predisposition to this deadly disease.

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**P57**

**PanGen-EU: European Multicentre Study of Pancreatic Cancer and Genetics**

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**Introduction:** A large European multidisciplinary study of pancreatic cancer (PC) and genetics (PanGen-EU) was launched in 2009 in 30 centres from 7 countries. The study follows a case-control design aiming to assess gene*environment interaction. It will include 2000 cases and 2000 controls. The project integrates epidemiological, genetic, clinical, and molecular objectives and also studies familial PC.

**Objectives:** To describe the PanGen-EU study and provide an update on its present status to the research community.

**Patients & Methods:** Newly diagnosed patients with PC are rapidly ascertained by trained monitors and invited to participate in the study. Age, gender, and area-matched controls from the same hospitals are included if their primary diagnosis is not related to any known/possible risk factor for PC. In Sweden and Ireland, population controls are included. All subjects are personally interviewed and data are uploaded to a single database in real-time using web-based questionnaire (EPIQuest); biological samples (blood, saliva, urine, and toenails) are collected and stored. The study also registers detailed pathological and clinical data, as well as patient follow-up (progression and death). Fresh tissue is collected when possible.

**Results:** The participation rate is 82% for cases and hospital controls. At present, 1567 cases and 610 controls have given informed consent to participate in the study. Overall, >90% of subjects provided epidemiological information and blood/saliva samples.

**Conclusion:** This is the largest European study to apply homogeneous methods covering a broad range of pancreas cancer research objectives; thus, it represents a long-term investment for the scientific community in the post-GWAS era.

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**P232**

**Pancreatic Acinar Cell Ultrastructure and Death in Mice Expressing Human PRSS1**

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**Introduction:** Hereditary pancreatitis is caused by human cationic trypsinogen gene (PRSS1) mutations. We generated transgenic mice expressing and secreting wild type (wt) PRSS1 or one of two mutant forms (R122H and N29I) driven by the pancreatic-specific elastase promoter.

**Objectives:** We sought to evaluate ultrastructural characteristics and cell death pathway activation of pancreatic acinar cells from these animals.

**Materials & Methods/Results:** Electron microscopy of transgenic mouse pancreas (n = 4 of each line) revealed disrupted acinar cell architecture, decondensing zymogen granules, intracellular membrane disruption, swollen endoplasmic reticulum, as well as surrounding inflammatory cell infiltration, rarely observed in wt mice (n = 6).

In vivo immunohistochemistry revealed a statistically significant increase in apoptosis activation in all transgenic lines (vs wt, PRSS1 p = 0.029; R122H p = 0.0014; N29I p = 0.0041). An in vitro cell death assay exposing isolated acinar cells to the bile acid taurolithocholic acid sulphate (TLC-S) demonstrated significant increases in apoptosis but not necrosis activation in all transgenic lines (vs wt, apoptosis with TLC-S: PRSS1 p = 0.0249; R122H p = 0.0483; N29I p = 0.0186; without TLC-S: PRSS1 p = 0.0016; R122H p = 0.0253; N29I p = 0.00002).

**Conclusions:** This study demonstrates that in vivo transgenic expression of human PRSS1 in mouse pancreatic acinar cells induces ultrastructural abnormalities with increased apoptotic pathway activation, highlighting the potential importance of apoptosis in hereditary and chronic pancreatitis.
P58
Molecular Analysis of Pancreatic Cyst Fluid in Pancreatic Malignancy Diagnosis
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Introduction: Analysis of cyst fluid may be useful in distinguishing between benign and malignant cysts which has significant impact on their management.

Objectives: The aim of our study was to assess the concentration of carcinoembryonic antigen (CEA), CA19-9 and K-ras mutations presence in pancreatic cyst fluid.

Methods: The study included 41 patients (27 men and 14 women) with pancreatic cystic lesions, with cystic fluid collected for analysis. Based on surgical histopathology and/or imaging follow up of at least 12 months cysts were classified as benign (pseudocysts, serous cystadenoma) – 32 patients or premalignant/malignant (mucinous cystadenoma, cystadenocarcinoma) – 9 patients. The cytology and fluid concentrations of CEA, CA19-9 and K-ras mutation were analysed.

Results: The mean diameter of pancreatic cyst was 4.2 cm (1.5–9.5 cm). Cytology was diagnostic only in 2 of 9 pancreatic malignant lesions (22.2%). CEA and CA19-9 fluid levels were available in 36 patients (28 with benign and 8 with malignant lesions) and were elevated in patient with malignant cysts (respectively 167±14.5 ng/ml and 624±43.5 U/mL) compared to benign lesions (19.8±3.4 ng/ml and 36.3±2.5 U/mL; p<0.05). K-ras mutation was assessed in all cases and was detected in 7 patients, 6 with malignant cysts and 1 in benign lesions (the sensitivity 66.7% and the specificity 96.8%).

Conclusion: Molecular analysis of pancreatic cyst fluid adds diagnostic value to the preoperative diagnosis and should be considered when cyst cytologic examination is negative for malignancy.

P59
Preoperative F-18 Fluorodeoxyglucose-positron Emission Tomography Predicts Survival After Pancreatic Cancer Resection
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Introduction: The identification of prognostic factors useful in selecting patients with pancreatic cancer who will benefit from surgery or other treatments, is still debating.

Objective: The aim of this study is to evaluate the role of 18-Fluorodeoxyglucose Positron Emission Tomography (18-FDG PET) as a prognostic factor for patients who underwent resection for pancreatic cancer.

Materials & Methods: From January 2003 to July 2009, a total of 90 patients who underwent resection for pancreatic cancer, were examined with 18-FDG PET (with-CT acquisition) in their preoperative work-up. The standardized uptake value (SUV) of 18 FDG was calculated and the patients were divided into high (> 3.8) and low (≤ 3.8) SUV groups. They were also evaluated according to the tumor node metastases, stage (TNM), tumor grade and radicality of resection.

Results: Forty-six cancers showed low and 44 high SUVs. Disease free survival (DFS) was significantly influenced by tumor stage (p=0.009), nodal status (p=0.03), radicality of resection (p=0.01), SUV (p=0.02) and grading (p=0.0004). Multivariate analysis showed that only grading (p=0.01) and radicality (p=0.02) were independent predictors of DFS. Overall survival was significantly influenced by node status (p=0.02), radicality of resection (p=0.007), stage and SUV (p=0.002) and grading (p=0.0001). Multivariate analysis showed that grading (p=0.009), stage and radicality (p=0.01) were independent predictors of survival. When patients analyzed for SUV were stratified according to stage, FDG uptake was related to DFS (p=0.02) and overall survival (p=0.001) in tumor stage I-II. In these patients, multivariate analysis confirmed that SUV was independent predictor of survival.

Conclusion: This study confirms that tumor grading is the strongest independent factor influencing disease-free and overall survival after resection for pancreatic cancer. The SUV, calculated with 18 FDG PET, is an important prognostic parameter in stage I-II pancreatic carcinoma and may be useful in selecting patients for neo-adjuvant therapy.
**P60**

**Clinical Relevance of Circulating and Splenic Immature Myeloid Cells in Pancreatic Diseases**

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**Introduction:** The expansion in blood and spleen of immature myeloid cells contributes to the failure of immune response to cancer enabling tumor outgrowth and metastasis.

**Objectives:** To study the pattern of circulating and splenic lymphocyte subsets and immature myeloid cells in patients with pancreatic benign and malignant diseases.

**Patients & Methods:** We enrolled patients undergoing pancreatic and/or splenic surgery [52 ductal adenocarcinoma (PaCa), 10 NETs, 10 IPMNs, 9 SCA, 9 non-pancreatic tumors and 13 control cases (chronic pancreatitis, splenic non neoplastic lesions)]. In blood and splenic samples, lymphoid (CD4+, CD8+, CD4+CD25+ T cells) and myeloid cells (CD33+CD14+HLA-DR+, CD33+CD14+HLA-DR-, CD33+CD14-HLA-DR+ and CD33+CD14-HLA-DR-) were FACS analysed. In 30 splenic samples the inhibitory molecules PDL-1 and CTLA4 molecules.

**Results:** In PaCa circulating cytotoxic CD8+ (p = 0.015) and CD33+CD14-HLA-DR+ dendritic cells (p = 0.01) were significantly reduced. In spleen the latter were increased in both exocrine and endocrine malignant pancreatic tumors (p = 0.077), but in PaCa they had a higher expression of PDL-1 (p = 0.028). CTLA4 expression was reduced among CD33+CD14+HLA-DR- cells in PaCa with respect to the other diseases (p = 0.029). In PaCa circulating lymphocytes/monocytes ratio was lower (p = 0.002) while CD33+CD14+HLA-DR-cells were higher (p = 0.0023) in patients who developed disease recurrence or died after surgery.

**Conclusion:** Among exocrine and endocrine benign or malignant pancreatic tumors, PaCa is that which mainly imbalances immune cells pattern. Reduced circulating dendritic and cytotoxic T cells might favour PaCa growth, while the expansion of CD33+CD14+HLA-DR-cells, potentially immunosuppressive, might favour tumor progression. PaCa might affect immune cells by targeting PDL-1 and CTLA4 molecules.

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**P61**

**Discovery of New Serum Biomarkers for Pancreatic Cancer Diagnosis by MALDI-TOF Analysis**

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**Introduction:** The discovery of serum biomarkers is desirable to achieve a correct classification among patients with suspected pancreatic cancer (PaCa).

**Objectives:** To identify new serum biomarkers of PaCa by MALDI-TOF analysis.

**Patients & Methods:** 51 PaCa, 38 chronic pancreatitis (ChrPa), 48 controls (24 with type II diabetes mellitus, DM) were studied. Fasting sera were purified by Sep-Pak C18 before MALDI-TOF anchorchip analysis.

**Results:** Features present in at least 3% of all MALDI-TOF spectra were selected (n = 176, m/z range = 1206.6–5373.7). At univariate analysis seven features were highly correlated (p ≤ 0.0001) with disease: two (m/z 3182 and 4009) correlated with PaCa, one (m/z 2049) correlated with ChrPa, four (m/z 1530, 1778, 2006, 2602) were less represented in PaCa and/or ChrPa as compared to controls. Ten-fold cross validation binary recursive partitioning trees for patients classification were obtained. The first tree, which included CA19-9, age, m/z 2006, 2599, 2602, allowed to well discriminate controls from PaCa (AUC=0.974) and to obtain a correct classification in 90.5% of the cases. The second tree (CA19-9, age, m/z 2006, 2599, 2753, 4997), built considering only patients and controls with DM, allowed to distinguish DM (AUC=0.997) from ChrPa (AUC=0.968) and PaCa (AUC=0.980) with an overall correct classification rate of 90.1%. While CA19-9 alone did not discriminate localized from advanced PaCa (AUC=0.685), the tree including CA19-9, 1550 and 2937 m/z features, achieved an AUC=0.970.

**Conclusion:** We demonstrated that new serum biomarkers identified using a proteomic approach, significantly enhance the diagnostic performance of CA19-9.
Circulating Metalloproteinase-3 and Tissue Inhibitor of Metalloproteinase-2 in Patients with Ductal Pancreatic Neoplasms

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Introduction: There is increasing evidence regarding the involvement of inflammation in patients with intraductal papillary mucinous neoplasms (IPMNs) of the pancreas.

Objectives: To evaluate the circulating concentrations of MMP-3 and TIMP-2 in patients with IPMNs and in those with ductal adenocarcinomas (ADAC).

Patients: Sixty patients (32 males, 28 females, mean age 69.3 ± 11.3 years) were enrolled: 31 (51.7%) had IPMNs and 29 (48.3%) had histologically confirmed ADAC. Thirty blood donors were also studied as controls.

Materials & Methods: The serum concentrations of MMP-3 and TIMP-2 were determined in all study subjects using commercially available kits.

Results: Serum concentrations of MMP-3 were significantly higher both in patients with ADAC (14.8 ± 11.3 ng/mL) and in those with IPMNs (18.2 ± 19.8 ng/mL) as compared to the healthy subjects (5.9 ± 2.9 ng/mL, P = 0.001) whereas serum levels of TIMP-2 were significantly lower both in IPMN patients (91.3 ± 23.5 ng/mL) and in patients with ADAC (84.7 ± 18.2 ng/mL) than in those of the healthy subjects (141.3 ± 47.9 ng/mL, P < 0.001). No significant differences in the serum levels of both MMP-3 and TIMP-2 were found between patients with IPMNs and those with ADAC as well as in the patients with branch type IPMN (MMP-3: 20.0 ± 16.5 ng/mL; TIMP-2: 94.7 ± 24.4 ng/mL) as compared to those with main duct IPMN (MMP-3: 16.2 ± 23.3 ng/mL, P = 0.220; TIMP-2: 87.7 ± 22.7 ng/mL, P = 0.607).

Conclusions: IPMNs have a pattern of extracellular matrix factors and their inhibitors are similar to those of ADAC; MMP-3 and TIMP-2 cannot be utilized to routinely differentiate IPMNs from ductal adenocarcinomas.

Tumour Origin of Adenocarcinomas in the Pancreatic Head – Impact on Survival and Prognostic Factors

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Introduction: Three different groups of adenocarcinomas arise in the pancreatic head, ampullary (AC), distal bile duct (DBC), and pancreatic cancer (PC). These tumours differ significantly in pathobiology, clinical features and prognosis. The reported relative frequency of these cancers in pancreatoduodenectomy series varies considerably: 33% – 75% for PC, 10% – 39% for DBC and 16% – 42% for AC. Hence, comparison of results in terms of survival and prognostic factors is difficult.

Objectives: To compare overall survival and independent prognostic factors for survival between the three cancer groups after slide review for accurate determination of tumour origin within the pancreatic head.


Results: The distribution of tumour origin was 72 (40%) PC, 46 (26%) DBC, and 61 (34%) AC. Five-year actuarial survival was 11%, 43%, and 48% for PC, DBC and AC, respectively. Multivariate analysis revealed significant differences in prognostic factors between the tumour groups. For AC, lymph node status (p = 0.003), lymph node ratio (LNR) (p = 0.004), grading (p = 0.006) and R-status (p = 0.014) were significant independent prognostic factors. For DBC, vascular invasion (p = 0.026), and for PC, LNR (p = 0.004) were the only independent predictors of poor outcome.

Conclusion: Accurate diagnosis of tumour origin resulted in a lower frequency of PC (40%) and a higher frequency of DBC (26%) than usually observed. It also revealed patterns of independent adverse prognostic factors that were distinctly different for the three cancers. For PC, LNR was the only independent prognostic factor.
P64

Can the New RCP R0/R1 Classification Predict the Clinical Outcome in Ductal Adenocarcinoma of the Pancreatic Head?

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Introduction: According to the International Union Against Cancer (UICC), R1 is defined as the microscopic presence of tumor cells at the surface of the RM. In contrast, the Royal College of Pathologists (RCP) suggested to declare R1 already when tumor cells are found within 1 mm of the RM. The aim of this study was to determine the significance of the resection margin (RM) concerning the prognosis of pancreatic ductal adenocarcinoma (PDAC).

Method: From 2007 to 2009, 62 patients underwent a curative operation for PDAC of the pancreatic head. The relevance of R status on cumulative overall survival (OS) was assessed on univariate and multivariate analysis for both, the classic R classification (UICC) and the suggestion of the RCP.

Results: Following the UICC criteria, a positive RM was detected in 8%. Along with N stage, grading and lymph node ratio, R status revealed a significant impact on OS on univariate analysis. Applying the suggestion of the RCP, R1 rate rose to 26% resulting in no significant impact on OS in univariate analysis. On multivariate analysis only grading and lymph node ratio achieved significance.

Conclusions: Our study has shown that the RCP suggestion for R status has no impact on the prognosis of PDAC. In contrast, our data confirmed the UICC R classification of RM as well as N category, grading and lymph node ratio as significant prognostic factors. In conclusion, the UICC R classification of the RM should be maintained and a new concept of circumferential resection margins should be discussed.

P65

Quality of Life After Pancreas Resection

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The Quality of Life (QoL) after pancreatic resection was investigated using QLQc-30 questionnaire. Final assessment was investigated in scales, including function, symptoms and global health status QoL. After surgical pancreatic resection we observed improvement in quality of life in comparison to the pre operative period. QoL in patients with carcinoma is improving until one year after operation and then decrease gradually (relapse of malignancy). In patients with chronic pancreatitis QoL falls suddenly 3 month after the operation and then reached the level higher in comparison to preoperative status.

P66

Preoperative Chemotherapy Does Not Adversely Affect Short-Term Outcome After Pancreatic Resection

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Introduction: PCHT has recently been suggested also in patients with resectable disease. No comparative study is available at present on the impact of PCHT on short-term postoperative outcome after pancreatic resection.

Objective: To assess the impact of preoperative chemotherapy (PCHT) on short-term postoperative outcome after pancreatic resection.

Methods: Between 2003 and 2010, 40 patients with locally advanced pancreatic cancer received gemcitabine-based chemotherapy and successfully underwent resection. Each patient was matched with two control patients with pancreatic adenocarcinoma selected from our prospective electronic database. Match criteria were age (+/- 3 years), gender, ASA score, type of resection, pancreatic duct diameter (+/- 1 mm), and tumour size (+/- 5 mm). Primary endpoint was mortality rate. Secondary endpoints were mortality rate and length of hospital stay (LOS).

Results: Overall morbidity rate was 45.0% in the PCHT group vs. 50.0% in the control group (p=0.62). Pancreatic fistula rate was 17.5% in the PCHT group vs. 25.0% in the control group (p=0.49). Mortality rate was 5.0% in the PCHT group and 2.5% in the control group (p=0.60). Mean LOS (days) was 11.8 in the PCHT group vs. 12.8 in the control group (p=0.31). There was no difference in resection margin status, while the rate of patients without nodal involvement (N0) was higher in the PCHT group (47.5% vs. 18.8%, p=0.001).

Conclusion: PCHT did not adversely affect short-term outcome after pancreatic resection and was associated with a higher rate of N0.

P67

Cystic Masses of the Pancreas: How Useful is Cyst Fluid Analysis in the Diagnosis?

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Objective: Evaluation of the cystic masses of the pancreas is a challenge in the routine daily practice. Pancreatic cyst fluid analysis seems to have an added value in the differential diagnosis, but the utility in the daily practice is questioned.

Method: The objective of this study was to investigate the accuracy and value of cyst fluid analysis in the differentiation of benign from (pre-)malignant masses of the pancreas in our center.

Results: The diagnostic accuracy of preoperative cyst fluid analysis was 83% in our center. The sensitivity and specificity were 90% and 71%, respectively. The diagnostic accuracy of preoperative cyst fluid analysis was higher in the setting of (pre-)malignant masses (93%) than in the setting of benign masses (75%).

Conclusion: Cyst fluid analysis has a high diagnostic accuracy in the differentiation of benign from (pre-)malignant masses of the pancreas in our center.

P68

Preoperative Chemotherapy Does Not Affect Overall Survival After Pancreatic Resection

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Introduction: The Royal College of Pathologists (RCP) suggested that applying their criteria, R1 rate rose to 26% resulting in no significant impact on OS in univariate analysis. On multivariate analysis R1 status revealed a significant impact on OS on univariate analysis. In contrast, our data confirmed the UICC R classification of RM as well as N category, grading and lymph node ratio as significant prognostic factors.

Method: From 2007 to 2009, 62 patients underwent a curative operation for PDAC of the pancreatic head. The relevance of R status on cumulative overall survival (OS) was assessed on univariate and multivariate analysis for both, the classic R classification (UICC) and the suggestion of the RCP.

Results: Following the UICC criteria, a positive RM was detected in 8%. Along with N stage, grading and lymph node ratio, R status revealed a significant impact on OS on univariate analysis. Applying the suggestion of the RCP, R1 rate rose to 26% resulting in no significant impact on OS in univariate analysis. On multivariate analysis only grading and lymph node ratio achieved significance.

Conclusions: Our study has shown that the RCP suggestion for R status has no impact on the prognosis of PDAC. In contrast, our data confirmed the UICC R classification of RM as well as N category, grading and lymph node ratio as significant prognostic factors. In conclusion, the UICC R classification of the RM should be maintained and a new concept of circumferential resection margins should be discussed.
Patients/Material & Methods: Patients who underwent EUS FNA with cyst fluid aspiration between 2007 and 2010 were reviewed. CEA192 ng/ml was considered as a premalignant or malignant cystic lesion. Amylase>5000 U/L with low CEA was diagnostic for a pseudocyst.

Results: We performed cyst fluid analysis in 54 patients. In 20 patients we had a definitive pathological diagnosis: benign pathology in 7 patients, potential malignant in 2 patient and malignant pathology in 11 patients. Cyst fluid analysis predicted benign pathology in 6/7 patients and non-benign pathology in 11/13 patients (sens: 84%, spec: 85%, accuracy: 85%). In patients with cystic malignant lesions we found high CEA levels with a mean of 3472 ng/ml (range: 446–10652). 7/11 patients had a CEA> 1000 ng/ml. 2/11 patients in this group had a normal CEA. In 17/19 pseudocysts (4 operated and 15 typical cases), the cyst fluid analysis confirmed the diagnosis.

Conclusion: Cyst fluid analysis helps to differentiate benign from non-benign pancreatic masses in our center. Results of cyst fluid analysis are very accurate in differentiating pseudocysts from other cystic pancreatic lesions. In possible malignant cysts, a high CEA value in the cyst fluid can be helpful in the diagnosis if cytology and imaging are inconclusive.

P68
Disseminated Tumor Cells in Pancreatic Cancer – An Independent Prognosticator of Disease Progression and Survival
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Introduction: Pancreatic cancer is one of the most devastating cancers with a 6-month median survival and a 5-year survival rate of 3–5%. Still important aspects of its aggressive biology remain elusive and advanced therapeutic regimens have not been substantially successful.

Objectives: We investigated the prognostic role of disseminated tumor cells (DTC) in bone marrow, a reservoir for early DTC potentially contributing to metastatic progression, of pancreatic cancer patients.

Patients & Methods: We enrolled 215 patients undergoing surgery for pancreatic cancer. One-hundred-and-nineteen patients were male and 96 female with a median age of 67 years. Twenty-two patients were excluded due to different post-surgery diagnosis. Bone marrow aspirates taken at primary surgery was analyzed for DTC by an immunocytochemical cytokeratin assay and their presence correlated to survival data.

Results: Overall 13.7% of evaluable patient samples (24/175) harbored DTC in their bone marrow. Histopathological parameters did not correlate significantly. Univariate survival analysis revealed a borderline significant correlation between DTC and decreased progression-free survival (p = .069), and was significant for overall survival (p = .036). Regarding patients with resected tumors (n = 106), the respective p-values were .058 for progression-free and .016 for overall survival. Importantly, the prognostic influence was independent from other risk factors as shown by multivariate analyses for progression-free (p = .022, HR: 2.171; CI (95%): 1.116–4.224) and overall survival (p = 0.005, HR: 2.408; CI (95%): 1.312–4.421).

Conclusion: The presence of DTC in bone marrow is a strong and independent prognostic factor of survival in patients with pancreatic cancer. Thus, bone-targeting may be a new future therapeutic option for DTC-positive patients.

P69
Survival in Patients with Ductal Adenocarcinoma of the Pancreas
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Introduction: In the last years surgical and chemotherapeutical management of pancreatic carcinoma was developed. Therefore, retrospective analyses of the survival to this time are needed.

Objectives: Here, we evaluated patients with pancreatic carcinoma regarding their survival and the influence of different factors on this.

Patients & Methods: In this study data from 137 patients with pancreatic ductal adenocarcinoma were included. Survival, age, surgery, tumour localization, alcohol and nicotine abuse, body mass index, metastases, chemotherapy, were analyzed.

Results: Mean age of patients was 68.2% (range 45 – 94). The mean survival was no different comparing females and males (12.7 vs 12.1 months). Survival was shorter in relation to higher age. 28.5% of patients had surgery with significant longer survival. Only 4 patients were in stage T1 and T2 at the diagnosis. Patients with inappetence, drop in performance, and tumour in the cauda of pancreas had a significant lower survival. 35.8% of the patients had Diabetes mellitus without relation to the survival. Alcohol and body mass index had no influence on survival. 51% of patients had metastasis with a significant lower survival. Longer survival was observed in patients with chemotherapy (16.3 months versus 4.5 months).

Conclusion: Mean survival was elevated to 12 months comparing with 6 to 8 months in older studies. Surgery and chemotherapy are able to induce longer survival.
Basic Science – Pancreatic Cancer I

P70
In Vivo Resistance of Mutant Mitochondrial DNA Pancreatic Cancer Cybrids to Anticancer Drugs

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Introduction: In the previous conference we showed that mutations in mitochondrial DNA (mtDNA) are responsible for anticancer drug tolerance in vitro with trans-mitochondrial hybrids (cybrids) technique.

Objectives: This time, we addressed whether mutant cybrids transplanted into mice also exhibit chemoresistance to anticancer drugs.

Materials & Methods: We used trans-mitochondrial hybrid cells (cybrids) to reveal the role of mutations in mtDNA in the pancreatic cancer by excluding any effects of the nuclear background. Cybrids were constructed by repopulating HeLa devoid of mtDNA with mtDNA derived from enucleated the pancreatic cancer cells (CFPAC-1, CAPAN-2) harboring mtDNA mutations. We constructed several cybrids with mutations derived from the cancer cells as well as those with wild mtDNA derived healthy individuals, and transplanted mutant and wild type cybrids into nude mice to generate tumors. We compared tumor growth and massive apoptosis of mutant cybrid tumors to wild cybrid tumors administrated of 5FU, CDDP. All experiments were performed in accordance with the guidelines of the Animal Use Ethics Committee of Nippon Medical School.

Result: Tumors derived from mutant cybrids were more resistant than those from wild-type cybrids in suppressing tumor growth and inducing massive apoptosis when 5FU and CDDP were administrated.

Conclusion: Our results demonstrate that mtDNA mutations can confer chemoresistance on cancer cells both in vitro and in vivo.

P71
Next Generation Mouse Models for Sequential and Host Specific Genetic Manipulation of Pancreatic Carcinogenesis

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Introduction: Genetically engineered Cre-loxP based mouse models have dramatically improved our understanding of pancreatic carcinogenesis. However, manipulating pancreatic cancer stem cells, modelling sequential multi-step carcinogenesis and selective targeting of host factors is impossible in these models.

Objectives: We aimed to generate a conditional mouse model for sequential gene (in)activation and targeting of different pancreatic compartments by combining two different recombination-systems, Flp-frit and Cre-loxP.

Materials & Methods: To achieve Flp-dependent expression of oncogenic KrasG12D, a G12D mutation and a 5' frt-flanked stop cassette (FSF) were knocked into the endogenous Kras locus. Transgenic mice with Pdx1 promoter-driven Flp-expression were generated to activate oncogenic KrasG12D in the pancreas. For site and time-specific Cre-activation, two FSF silenced knock-in strains were generated, which express a Tamoxifen-inducible CreERT2 fusion protein in the Flp-lineage under the control of the ubiquitous CAG promoter or the proliferation marker PCNA.

Results: Pancreas-specific expression of Flp-recombinase was shown by a conditional alkaline phosphatase reporter strain (FSF-APF). Pdx1-Flp; FSF-KrasG12D/+ double-transgenic animals develop PanIN lesions and pancreatic cancer similar to the Pdx1-Cre; LSL-KrasG12D/+ model. Flp-mediated recombination of the FSF cassette results in CreER2 expression selectively in KrasG12D positive pancreatic cells. Tamoxifen treatment allows sequential and site specific genetic manipulation of recombined cells in vitro and in vivo as shown by conditional activation of reporter genes (EGFP) or mutant p53.

Conclusion: By means of this novel model we are for the first time able to 1) sequentially (in)activate genes in the pancreas, 2) manipulate pancreatic cancer subpopulations and, 3) target different pancreatic compartments and the host.

P72
Inactivation of Brcal2 Cooperates with Trp53R172H to Induce Invasive Pancreatic Ductal Adenocarcinomas in Mice: A Mouse Model of Familial Pancreatic Cancer

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Introduction: An inactivating germline mutation in BRCA2 is the most common known genetic basis for familial pancreatic cancer (FPC), accounting for 5–10% of inherited cases. A genetically engi-
neered mouse model of pancreatic ductal adenocarcinoma (PDAC) arising on the backdrop of Brca2 deficiency is likely to elucidate valuable diagnostic and therapeutic insights for FPC.

**Methods:** Both Brca2 alleles were conditionally deleted during development within the pancreatic epithelium by generating Pdx1-Cre; Brca2<sup>fl/fl;</sup> LSL-Trp53<sup>172C</sup> mice; in addition, triple transgenic Pdx1-Cre; Brca2<sup>fl/fl;</sup> LSL-Trp53<sup>172C</sup> mice were generated, in order to determine the impact of p53 deregulation on Brca2-deficient carcinogenesis.

**Results:** Both “CB” and “CBP” mice developed non-invasive ductal precursor lesions (murine pancreatic intraepithelial neoplasia or mPanIN), although these were observed at an earlier time point (5 versus 8 months) and with higher prevalence in “CBP” mice. A minority of “CB” mice (15%) developed invasive and metastatic PDAC at a latency of 15 months or greater; in contrast, “CBP” mice of comparable age uniformly developed PDAC with variable histological features. Mortality in the absence of neoplasia in CB and CBP mice was associated with profound loss of pancreatic parenchyma, consistent with progressive elimination of Brca2-deficient cells.

**Conclusion:** Loss of Brca2 function predisposes the exocrine pancreas to profound DNA damage, and the frequency of invasive neoplasia is accentuated by the concomitant deregulation of p53.

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**P73**

Gemcitabine Resistance in Pancreatic Cancer is Linked to Side-Population/Tumor Initiating Cells

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**Introduction:** The role of tumor initiating cells in chemotherapy resistance of pancreatic cancer has not been analysed yet.

**Objectives:** In the present study, we identified and characterized putative cancer stem cells within sensitive and chemotherapy-resistant variants of the human pancreatic cancer cell line L3.6pl.

**Material & Methods:** Cancer stem cells were isolated using high-speed flow cell sorting following Hoechst 33342 dye staining. Isolated side-population- (SP) and non-side-population-cells (NSP), as well as unsorted L3.6pl cells, were orthotopically xenografted into the pancreas of nude mice. In vitro analysis of SP- and NSP-cells was performed using microarray hybridization and protein analysis.

**Results:** Flow cytometry identified a distinct proportion of SP-cells versus a large subpopulation of NSP-cells. Microarray hybridization showed up-regulation of genes associated with tumorigenesis, differentiation and metastasis in SP-cells. In vivo SP-cells presented as highly tumorigenic and metastatic as compared to NSP-cells. SP-cells revealed a CD133 negative and ABCG2 positive phenotype. With increasing concentration of gemcitabine the amount of SP-, CD24- and ABCG2-positive cells was significantly enriched whereas with escalating doses of 5-FU the percentage of SP-cells was significantly reduced. ABCG2 content unaltered, nd CD24 positive cells increasing. Expression of AKR1B10, up-regulated in SP-cells, was highly enriched in gemcitabine-resistant cells but diminished in 5-FU-resistant cells.

**Conclusion:** SP-cells represent a cellular subpopulation with stem cell properties associated to gemcitabine resistance in pancreatic cancer. AKR1B10 and ABCG2 are two relevant genes preferentially up-regulated in SP-cells. AKR1B10 could display a potential predictor for gemcitabine resistance to support individualized chemotherapy approaches as treatment for pancreatic cancer in the clinic.

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**P74**

GSK-3b Modulates an Oncogenic Transcriptional Network in Pancreatic Cancer

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**Introduction:** GSK-3b is a constitutive active kinase originally described due to its tumor suppressive properties. Numerous studies however highlight its oncogenic role in pancreatic cancer, which is partially mediated by nuclear stabilization of NFATc2. The tumorigenic transcription factors NFATc2 and STAT3 display main regulatory functions in pancreatic cancer, and mutual associations have already been described.

**Objectives:** The aim of the study was to characterize a putative oncogenic GSK-3b/NFATc2/STAT3 axis in pancreatic cancer and to confirm the relevance of GSK-3b as a therapeutic target.

**Methods:** Immunohistological stainings of human pancreatic cancer tissues were performed to detect the localization of GSK-3b, NFATc2 and STAT3. The impact on cell proliferation was examined by thymidine incorporation assays and detection of cell cycle genes on protein and mRNA level. Co-IP, reporter gene assays, immunoblot analyses and site-directed mutagenesis were used to identify and characterize (GSK-3b-dependent) NFATc2/STAT3 interactions and involved target genes. The effect of a pharmacologic GSK-3b inhibition on tumor growth was verified in xenograft mouse models.

**Results:** NFATc2, STAT3 and GSK-3b co-localize in the nucleus of pancreatic cancer tissues. The modulation of GSK-3b and STAT3 expression regulates NFATc2 activity and expression, and subsequently cell proliferation. The GSK-3b-dependent interaction of NFATc2 and STAT3 is induced by mitogenic stimulation and supports tumor growth. The administration of GSK-3b inhibitors retards xenograft tumor growth.

**Conclusion:** A new GSK-3b-dependent mechanism in pancreatic cancer reveals an oncogenic cooperation between NFATc2 and STAT3 which is essential for tumor growth and supports the rationale for GSK-3b inhibition as a therapeutic intervention.
### P75

**The Combination of Gemcitabine with the Dual PI3K/mTOR-Inhibitor NVP-BEZ235**

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**Introduction:** Pancreatic ductal adenocarcinoma (PDAC) is one of the most common malignant tumor with poor prognosis. Currently, gemcitabine still remains the chemotherapeutic agent of choice for the treatment of PDAC. However, treatment with gemcitabine has a response rate of less than 20%.

**Objectives:** Combining two compounds acting via different ways of action may result in a better effectiveness.

**Material & Methods:** To analyze the outcome of a combination therapy, we have incubated four human pancreatic cancer cell lines (Panc-1, BxPC-3, MiaPaCa-2 and AsPC-1) with Gemcitabine (20, 50 and 100μM) and 500nM, 1μM or 5μM NVP-BEZ235 (Novartis Pharma, Basel, Switzerland). The cells were analyzed with MTT assay for cell viability, FACScan for cell cycle distribution and Real-time RT-PCR for Survivin mRNA expression.

**Results:** Stand alone application of NVP-BEZ235 and Gemcitabine influenced cell viability in a concentration-independent manner. Combined treatment of Gemcitabine and NVP-BEZ235 lead to a synergistic effect on cell viability of all pancreatic cancer cell lines tested. This effect was enforced by time-delayed usage of these compounds. In these cases, the strongest effect was achieved by a pretreatment with Gemcitabine followed by administration of NVP-BEZ235 24 hours later. Cell cycle analysis revealed, that pretreatment with Gemcitabine before NVP-BEZ235 administration maintained a part of the cells at the S-phase (15–20%), where gemcitabine acts preferentially. An increased gene expression of Survivin mRNA (2–4 fold increase) was observed after treatment with Gemcitabine. While treatment with NVP-BEZ235 decreased the expression of Survivin mRNA. Survivin is involved in DNA strand break repairing so down-regulation of Survivin by NVP-BEZ235 may prolong the time of repairing leading to a decrease of cell viability.

**Conclusions:** Combining Gemcitabine with dual PI3K/mTOR inhibitors like NVP-BEZ2235 may improve the efficacy of PDAC treatment.

### P76

**Pancreatic Cancer: Stromal S100A8/S100A9 Signalling**

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**Introduction:** The pancreatic tumour microenvironment plays an important role in modulating tumour progression. We have shown that S100A8- and S100A9-expressing myeloid-derived cells form a significant component of pancreatic stroma. S100A8 and S100A9 have been associated with inflammation and cancer metastasis by promoting homing of tumour cells to pre-metastatic niches. The mechanisms of S100A8/A9 signaling however, remains relatively poorly understood. The aim of the current study is to elucidate the signaling pathways activated in response to S100A8/A9 in pancreatic cancer.

**Methods:** The levels of inflammatory cytokines and chemokines were detected using a multiplex bioassay (27-plex, BioRad). Conditioned media were isolated from pancreatic cancer cells, Panc1. MAPK signaling assays were performed, following treatment of cells with GST-S100 recombinant proteins, using a Cell Signaling kit (Cell Signaling Technology). NF-κB activation in S100A8/A9 treated cells was also characterised.

**Results:** We observed that recombinant S100A8/S100A9 proteins induced increased cytokine levels of FGF, TNF-α and IL-8 in Panc-1 culture medium. This effect was partially mediated via RAGE. S100A8/A9 caused a significant rise in phosphorylation of p38 and p44/42 MAPK and enhanced NF-kB activation.

**Conclusion:** These findings show that stromal S100A8 and S100A9-expressing myeloid cells communicate with pancreatic cancer cells leading to the activation of cytokines which, in turn, may promote tumour progression. Targeting the S100A8/A9 receptors and signalling pathways represent a potential therapeutic avenue for inhibition of pancreatic cancer progression.
Disruption of the NFATc2 repressor complex by genetic depletion or pharmacological inhibition results in de-repression of the p15\(^{ink4b}\) tumor suppressor pathway.

**Conclusion:** Our results propose a new model in which NFATc2 works as a transcriptional repressor and promotes carcinogenesis through promoter restricted silencing of the p15\(^{ink4b}\) tumor suppressor. Additionally, our results provide evidence that inactivation of NFATc2 might be an attractive strategy to reactivate cellular defence mechanisms in pancreatic cancer.

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**P78**

**Dissection of the Metastatic Process in Pancreatic Ductal Adenocarcinoma**

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**Introduction:** Early metastasis is the main cause for poor prognosis of pancreatic ductal adenocarcinoma (PDAC). However, molecular and cellular mechanisms of the metastatic process have not been investigated in detail.

**Objectives:** We aimed to dissect the metastatic cascade by analyzing metastatic and non-metastatic primary tumors, disseminated tumor cells (blood, bone marrow) and metastases (liver, lung, lymph node, peritoneum) on a molecular and functional level in a genetically engineered mouse model of PDAC.

**Material & Methods:** Global gene-expression profiles, CGH arrays, transplantation studies and FACS analysis were applied to analyze the metastatic process.

**Results:** Gene-expression profiling of metastatic versus non-metastatic primary tumors revealed no differences. In contrast, primary tumors differed significantly from metastases. Interestingly, liver and lung metastases showed identical gene expression profiles, but differed from lymphatic metastases. Lineage-tracing of the metastatic process by CGH analysis showed that metastases harbor the same genomic alterations as the primary tumor, but display additional amplifications and deletions which are identical in metastases from liver and lung. Transplantation and cell culture studies using disseminated tumor cells from blood and bone marrow show that only cells from the blood are transplantable into syngenic animals and can be cultivated in vitro.

**Conclusion:** These results indicate that gene-expression profiling of primary PDAC cannot predict metastasis risk. Liver and lung metastases seem to arise from the same metastatic clone arguing for a linear progression model of PDAC. Disseminated tumor cells in the blood, but not in the bone marrow, are the cells of origin of distant organ metastasis.

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**P79**

**Neutrophil Granulocyte Derived MMP-9 Is a VEGF Independent Functional Component of the Angiogenic Switch in Pancreatic Ductal Adenocarcinoma**

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**Introduction:** Tumor cell derived vascular endothelial growth factor (VEGF) plays a key role in angiogenesis. Matrix metalloproteinase 9 (MMP-9) is produced by stromal granulocytes (PMN), remodels the extracellular matrix and promotes angiogenesis indirectly by interacting with VEGF.

**Objectives:** The aim of this study was to determine the role of PMN-derived MMP-9, its interaction with VEGF, and the efficacy of anti-angiogenic therapy targeting MMP-9 with oral Doxycycline and VEGF with Bevacizumab in pancreatic cancer (PDAC).

**Materials & Methods:** Inhibitors to MMP-9 (Doxycycline) and VEGF (Bevacizumab) were used alone or in combination in an in vitro angiogenesis assay to test their effect on angiogenesis caused by MMP-9, VEGF, PMN and PDAC cells. In an in vivo model of xenografted PDAC, treatment effects after 14 days under monotherapy with oral Doxycycline or Bevacizumab and a combination of both were evaluated.

**Results:** In vitro, PMN-derived MMP-9 had a direct and strong proangiogenic effect that was independent and additive to PDAC-derived VEGF. Complete inhibition of angiogenesis required the inhibition of VEGF and MMP-9. In vivo, co-localization of MMP-9, PMN and vasculature was observed. MMP inhibition with oral Doxycycline alone resulted in a significant decrease in PDAC growth and mean vascular density comparable to VEGF inhibition alone.

**Conclusion:** PMN derived MMP-9 acts as a potent, direct and VEGF independent angiogenic factor in the context of PDAC. MMP-9 inhibition is as effective as VEGF inhibition. Targeting MMP-9 in addition to VEGF is therefore likely to be important for successful anti-angiogenic treatment in pancreatic cancer.
Stat3/Socs3 Activation by IL-6 Transsignaling Promotes Progression of Pancreatic Intraepithelial Neoplasia and Development of Pancreatic Cancer

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Introduction: Physiological levels of KrasG12D are sufficient to induce pancreatic intraepithelial neoplasias (PanINs). The mechanisms that drive PanIN progression, however, are unknown. Although constitutive activation of Stat3 in pancreatic cancer has been shown in various cell lines as well as in human samples, its in vivo role remained unelucidated so far.

Objectives: In the present study, we aimed to identify the role of the Stat3 signaling pathway in pancreatic cancer.

Material & Methods: We generated compound mutants KrasG12D mice that lacked phosphorylatable Stat3Y705 and the endogenous inhibitor of Stat3 Socs3 specifically in the pancreas. Pancreata were investigated histologically and biochemically. To examine the mechanism of Stat3 activation in vitro, we further isolated nontransformed acinar cells, generated cell lines from tumors and immunophenotyped the infiltrates.

Results: Our data provide clear evidence for a critical role of Stat3 on PanIN progression. Stat3 activation in vivo depends on the microenvironment. We identified macrophages as a relevant component of the cellular infiltrates and the source of IL-6 during pancreatic oncogenesis. Moreover, we specified IL-6 transsignaling as the relevant mode of Stat3 activation. Levels of IL-6 dependent Stat3 phosphorylation determine the PanIN progression.

Conclusion: Our study is the first to show that KrasG12D-induced pancreatic oncogenesis depends on the microenvironment. Through IL-6 transsignaling and downstream effector Stat3, IL-6 from myeloid cells promotes tumor development in the pancreas.

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P81

Palliative Pancreaticoduodenectomy in Pancreatic and Periampullary Adenocarcinomas

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Introduction: The major concerns for undergoing a palliative pancreaticoduodenectomy are the surgical risks and the survival benefits.

Objectives: This study aims to clarify the role of a palliative pancreaticoduodenectomy in both pancreatic and periampullary adenocarcinomas.

Methods: Data on patients with periampullary adenocarcinoma who underwent surgery between January, 1997 and December, 2009 were analyzed. Survival outcomes were compared between resections and bypass operations, and between curative (R0) and palliative resections, with a microscopically (R1) and a grossly (R2) positive resection margin.

Results: There were 595 surgical patients, including 207 undergoing bypass operations and 388 undergoing pancreaticoduodenectomies, with 48.4% curative resections (R0) and 17.8% palliative resections (R1 + R2). The overall positive margin rate after a pancreaticoduodenectomy was 27.3%, with 8.0% for an R1 resection and 19.3% for an R2. The palliative resection rate was highest, 50.9%, in the patients with pancreatic head adenocarcinoma (15.3% R1 and 35.6% R2). For periampullary adenocarcinomas, there was a significant survival difference between the R0, palliative, and no resection groups. However, there was no significant survival difference between the R0 curative resections and the palliative pancreaticoduodenectomies for pancreatic head adenocarcinoma. Note that the survival outcome after either a curative or a palliative pancreaticoduodenectomy was still better than the survival outcome of a bypass operation.

Conclusion: There was a survival benefit after a pancreaticoduodenectomy regardless of the resection margin or primary origin of the periampullary adenocarcinoma, as compared to a bypass operation. The resection margin after a pancreaticoduodenectomy did not play a role in the survival outcome in pancreatic adenocarcinoma. Therefore, we recommend that pancreaticoduodenectomies should be attempted whenever possible.
P82
Resection After Radiofrequency Ablation of Stage III Pancreatic Cancer
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Introduction: Stage III pancreatic cancer (PC) is a very aggressive entity with poor prognosis. Experiences of radiofrequency ablation (RFA) in pancreatic cancer are limited and the effects on PC tissue are still unknown.

Objectives: We report our findings on resected PC specimens after RFA.

Patients: Pts with stage III PC were consecutively treated with RFA and different association of chemo-radiotherapy.

Results: Between February 2007 and April 2010, 125 patients with stage III PC underwent RFA. Four pts underwent radical resection after combined treatment of RFA+CT-R. Tumor was located in the head-uncinate process in 3 pts and body-tail in 1. One pts underwent resection because of duodenal necrosis RFA related. In 3 pts resection was performed for downstaging after combined treatment of RFA and CT-RT. Two pts received RFA as up front treatment, the other underwent RFA because of stable disease after neoadjuvant CT. All patients received CT-RT after RFA. Histopathology shows the presence of different degrees of fibrosis (related to different timing of resections) with some isolated neoplastic aggregate. In one case no residual tumor was found at histopathology. Two patients are alive without progression at 42 and 25 months, respectively. One patient is alive at 42 months with hepatic progression. One patient died of progressive disease after combined treatment of RFA+CT-R. Tumor was located in the head-uncinate process in 3 pts and body-tail in 1. One pts underwent resection after combined treatment of RFA and CT-RT. Two pts received RFA as up front treatment, the other underwent RFA because of stable disease after neoadjuvant CT. All patients received CT-RT after RFA. Histopathology shows the presence of different degrees of fibrosis (related to different timing of resections) with some isolated neoplastic aggregate. In one case no residual tumor was found at histopathology. Two patients are alive without progression at 42 and 25 months, respectively. One patient is alive at 42 months with hepatic progression. One patient died of progression after 28 months.

Conclusion: RFA does not impair a radical resection and, in some cases, seems to provide an early downstaging. In our experience for the first time we were able to achieve an histological specimen of an ablated pancreatic tumor. The impact on survival and the histopathological effects of RFA are currently being studied.

P83
Laparoscopic vs. Open Resection of Pancreatic Endocrine Neoplasms: A Review
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Introduction: Laparoscopic techniques are used to treat vast range of surgical diseases, but reports on laparoscopic resection of pancreatic endocrine neoplasms (PET) remain limited to small series.

Objective: of the study was to compare the laparoscopic resection of PET with the open approach and to investigate the feasibility and safety of this technique by reviewing the available data.

Materials & Methods: Medline search was performed for the words laparoscopic resection and pancreatic endocrine neoplasms. 51 relevant papers from 2000 till 2010 were identified and studied.

Results: Three non-randomised studies compared laparoscopic and open approach for resection of PET (insulinoma) comprising totally 64 patients – 35 laparoscopic and 29 open. There were no cases of postoperative mortality. Mean operative time was estimated in two studies where there has been a significant difference (p<0.5) in favor of open technique (121 min. vs 92 min) in one study and in favor of laparoscopic technique in the other study (188 min. vs 305 min.). Mean hospital stay was estimated in all three studies, where it reached a significant difference (p<0.05) in one study in favor of laparoscopic group (11 days vs. 14 days). Rate of postoperative pancreatic fistula was significantly higher in open group in only one study reaching up to 100% in comparison to 14% in laparoscopic group (p<0.015).

Results from all other retrieved studies showed the feasibility and safety of laparoscopic approach for PET, as shown in results and cited by authors.

Conclusion: Laparoscopic resection for PET is feasible and safe technique with comparable or better operative time, length of stay and rate of pancreatic fistula.

P84
Long Term Survival of Patients Undergoing Pancreatectomy with Vein Resection and Suffering Postoperative Complications
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Introduction: Today there are no detailed information on the oncologic outcome of patients developing complications after pancreatectomy plus superior mesenteric/portal vein (SM/PV) resection.

Objectives: To evaluate the impact of post-operative complications on the long term survival of patients undergoing pancreatectomy plus resection of SM/PV.

Methods: A retrospective analysis, including all consecutive patients undergoing pancreatectomy plus resection of SM/PV, was carried out. Survival was calculated for the entire cohort, for patients without vs patients with post-operative complications, and for patients undergoing medical therapies vs patients undergoing surgery alone.

Results: Overall, 241 patients were included. The overall morbidity and mortality rates were 47.3% and 5.3% respectively. According to the Clavien scale, 27.4% of patients developed grade 1–2 complications, 5.8% grade 3a complications, 5.4% grade 3b complications, 2.5% grade 4 complications and 5.3% grade 5 complications. A significant survival advantage at 1, 3 and 5 yrs was found in patients with non-PDAC (51 pts) compared to PDAC (187 pts) (94.9%, 73.7% and 52% vs 74.3%, 19.4% and 13.7%; p<0.0001). In patients diagnosed with PDAC the occurrence of post-operative complications was not associated with worse prognosis as compared to patients undergoing an uneventful post-operative course. A significant difference in 1, 3 and 5 yrs survival was found in patients treated with adjuvant treatments as compared to those undergoing surgery alone (p=0.03).

Abstracts

Pancreatology 2011;11:99–227
Conclusions: Major post-operative complications develop in some 13% of patients, but do not worse long-term survival. This observation underscores the central role of surgery in the treatment of PDAC infiltrating the SM/PV.

P85
Pancreatic and Periampullary Mixed Tumors
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Introduction: There is no data regarding the tumor incidence by histological type and biological behavior in terms of number of malignancy inside the mixed tumors, tumor location, and histopathology.

Objectives: With analysis of the pooled data, we tried to clarify the characteristics and survival outcomes of the pancreatic and periampullary mixed tumors.

Methods: Data of mixed tumors in the pancreas and periampullary region from our prospectively-collected computer database and cases reported in the English literature were included for analysis together.

Results: There were 43 mixed tumors. The mixed tumor composed of adenocarcinoma and neuroendocrine neoplasm was most common (42%). Thirty-two (74%) mixed tumors were malignant, and 28% were composed of double malignancies. The most common histopathological diagnosis was neuroendocrine neoplasm (43%) including 36% neuroendocrine tumor and 7% neuroendocrine carcinoma. The median tumor size was 3 cm, and larger in the benign group (6.3 vs. 2.5 cm, \( P = 0.038 \)). There was no significant survival difference between malignant mixed tumors with double vs. single malignancy, pancreatic vs. non-pancreatic origin, and adenocarcinoma vs. non-adenocarcinoma.

Conclusions: Neuroendocrine neoplasms are the most common histopathological diagnosis in pancreatic and periampullary mixed tumors. There is no significant survival difference in terms of number of malignancy, tumor location and histopathology.

P86
Simple Technique for Pancreaticogastric Anastomosis
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Introduction: The leakage of pancreatic juice is a serious and fatal complication after pancreatoduodenectomy. To lessen this complication, we have performed pancreaticogastric as the reconstruction. We have developed a simple technique for this anastomosis with transgastric approach.

Objectives: We show the operation process with a series of photo during the surgery and suggest the technique of transgastric pancreaticogastric anastomosis.

Patient & Methods: A case of 55 year-old male with intraductal papillary mucinous tumor of the pancreas is described. A standard Pancreatoduodenectomy is performed. Ultrasonic scalpel is used to divide the pancreas in order to lessen the bleeding from the cut end. A small tube is inserted into the main pancreatic duct and secured lightly with an absorbable suture line. Pancreas body is detached from splenic vein until it stands up more than 3 cm. An incision is made in the posterior wall of the stomach and the pancreatic remnant is invaginated. An incision is made in the anterior wall of the stomach and interrupted sutures are placed between the full thickness of the gastric wall and pancreatic parenchyma through inside of the stomach. After the anastomosis is accomplished, a gastrostomy tube is placed to reduce the internal pressure and drain gastric juice.

Results: Since 2002 we have performed this procedure for 21 patients. One patient showed major leakage of the anastomosis, however, recovered with conservative treatment. Other 20 cases did not show any fetal complications.

Conclusion: This technique is a simple and safe method for pancreaticogastric anastomosis.

P87
Patterns of Recurrence After Curative Resection of Pancreatic Ductal Adenocarcinoma
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Introduction & Objectives: Despite curative surgery for pancreatic ductal adenocarcinoma (PDAC), most patients develop cancer recurrence. The aim of the present study is to describe the patterns of failure after curative resection of PDAC.

Patients & Methods: A retrospective analysis of 411 consecutive radical resections (R0/R1) for PDAC between 1998 and 2008 was performed. The location of the first recurrence, and the time to recurrence after surgical resection were considered. First recurrences were defined as local (LR), hepatic (HR) or systemic (SR). A comparison between different groups of recurrence was performed. A multivariable analysis for predictors of disease-free survival (DFS) was carried out.

Result: The recurrence was LR in 111 patients (38.2%), HR in 139 (48%) and SR in 40 patients (13.2%). The type of recurrence significantly influence overall (OS) and disease-free (DFS); the median (95% CI) OS and DFS survival was 33 (28.9–37.0) and 14 (9.5–18) months. By multivariate analysis Nodal status (N1) is significantly associated with HR (p = 0.001). Nodal Status influences time but not type of recurrence (p = 0.212). Microscopical margin residual (R1) is significantly more related with HR (p = 0.031). Nodal Status influences time but not type of recurrence (p = 0.212). Multivariate analysis nodal status (N1), Microscopical margin residual (R1) and microvascular invasion were independent predictors of DFS.
Abstracts

**Conclusion:** The majority of patients experience a liver recurrence within 1 year after resection and quickly die of metastatic disease. After curative resection nodal involvement, positive margin status and microvascular infiltration could suggest whose part of patients are at high risk of early failure.

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**P88**

The Safety of Extensive Resections in Patients with Locally Advanced Pancreatic Cancer


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**Introduction:** The safety of extensive pancreatic resection in patients with locally advanced ductal adenocarcinoma is still being studied.

**Objectives:** To estimate the safety of total duodenopancreatectomy (TDP) and corporocaudal resection with celiac axis and its branches excision (modified Appleby operation) in patients with locally advanced pancreatic cancer.

**Patients & Methods:** Analysis of complications and mortality rates after 12 TDPs and 5 modified Appleby operations in patients (mean age 54 ± 4.4 vs 52 ± 3.2 years) with locally advanced pancreatic ductal adenocarcinoma (2009–2010).

**Results:** According to CT and endoUS data before the operation tumors were considered borderline-resectable in 14 cases (70.6%). The resections of portal and/or superior mesenteric vein with direct veno-venous anastomosis or autovenous prosthesis were performed in 50% of TDPs and 40% of Appleby procedures, marginal vein excision in 17% and 60% respectively. Average operating time was 544 ± 152 vs 530 ± 120 min, average blood loss-1150 ± 152 ml vs 880 ± 560 ml, complication rate – 50% and 40% respectively. Relaparotomy was performed in 3 patients (25%) for evertation (2) and autovenous prosthesis thrombosis after TDP and in 1 patient (20%) with arterial hemorrhage after Appleby operation. Average hospital stay was 30.7 ± 12.6 and 32 ± 10 days. One patient died of sepsis on the 65th day after Appleby operation.

**Conclusion:** TDP and modified Appleby operation showed acceptable complication and mortality rates in patients with locally advanced pancreatic cancer, which allows using these modalities as a radical and palliative treatment.

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**P89**

Short-Term Results of Total Duodenopancreatectomies, Standard and Extensive Pancreatoduodenectomies in Patients with Malignant Pancreatic Tumors


The Vishnevsky Institute of Surgery, Hepatopancreatobiliary Surgery, Moscow, Russian Federation

**Introduction:** The safety of extensive pancreatic resection in patients with locally advanced ductal adenocarcinoma is still being studied.

**Objective:** To estimate short-term results of total duodenopancreatectomies (TDP), standard (SPD) and extended pancreatoduodenectomies (EPD) for malignant pancreatic tumors.

**Patients & Methods:** Prospective analysis of the short-term results of 110 pancreatectomies for malignant pancreatic tumors (2005–2010).

**Results:** 12 TDP, 50 SPD and 48 EPD were performed for ductal adenocarcinoma (94), neuroendocrine cancer (7), intraductal papillary mucinous carcinoma (8) and renal cancer metastases (1). All the TDPs were undertaken for tumor involvement of more than one anatomical part of the pancreas. Portal and/or superior mesenteric vein resection were performed during 4 SPDs (8%), 15 EPDs (31.2%), and 6 TDPs (50%), average amount of removed lymph nodes was 16, 28 and 34, R0-resection was done in 30(60%), 39(81%) and 9(75%) cases. The average blood loss was 1225 ± 818 ml, 1445 ± 1043 m and 1150 ± 952 ml, mean operating time was 405 ± 115 min, 511 ± 73 min and 544 ± 152 min respectively, hospital stay was 21.8 ± 10.9, 21.9 ± 6.9 and 30.7 ± 12.6 days. Overall complication and mortality rates were 60% and 6%, 54% and 6%, 50% and 0% correspondingly.

**Conclusion:** TDPs and EPDs performed in specialized department are as safe as SPD and can be standard modalities for malignant pancreatic tumors treatment to achieve the level of R0-R1 resection.

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**P90**

The Results of Duodenum-Preserving Pancreatic Head Resections for Chronic Pancreatitis


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**Background:** There are several resection modalities for treatment of invertebrate pain in chronic pancreatitis (CP) but the choice of the procedure remains a topic of discussion.

**Objective:** To evaluate long-term results of surgical treatment and quality of life in patients undergoing various options of pancreatic head resection for CP.

**Methods:** Prospective analysis of 239 patients surgical treatment, on whom Beger (108), Frey (64) and Bern (67) procedures had
been performed (2002–2009). Long-term results and quality of life (QoL) were assessed for 188 (78%) patients in 1-7 years with the help of the SF-36 questionnaire.

**Results:** Demographic and clinical parameters were comparable. The mean operating time for Beger, Frey and Bern procedures was 361 ± 59 min, 201 ± 32 min and 269 ± 37 min (p < 0.05), general morbidity – 26%, 14% and 13% (p < 0.05), blood loss – 840 ± 110 ml, 450 ± 140 ml and 630 ± 150 ml (p < 0.05), and the postoperative hospital stay – 17, 12 and 12 days (p < 0.05). A significant difference was found on these subjects between the Beger procedure and other DPPHR variants. Lethality was 0.4%. The QoL differs insignificantly, however full pain control, social and labor rehabilitation were achieved after the Beger procedure in 94% and 93%, after Bern in 93% and 93% and after Frey in 80% and 77%. There were 3 new cases of diabetes mellitus after two years follow-up.

**Conclusion:** The Beger and Bern procedures more frequently provide full and long-lasting pain control as compared to the Frey procedure. The Bern operation is as effective as a classical Beger for pain management, giving lesser morbidity.

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**P91**

**Spleen-Preserving Distal Pancreatectomy with Splenic Vessels Resection. Short Gastric: Supplying or Stealing?**

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**Background:** The knowledge of collaterals is important for distal spleen-preserving pancreatectomy with splenic vessels resection (SPDP SVR).

**Objective:** To clarify the sources of spleen blood supply after SPDP SVR.

**Methods:** Perfusion of the cadaveric left gastric and right gastro-epiploic arteries with a methylene blue solution after the occlusion of all arteries except for the short gastrics (SGA) (n = 20); Intraoperative color Doppler ultrasound (ICDU) for the evaluation of the arterial blood flow in the splenic hilum during distal pancreatectomy (n = 23) after the splenic artery clamping, following the clamping of the splenic and the left gastro-epiploic arteries and after the clamping of the splenic and the short gastric arteries; CT-angiography (CTA) of gastric and splenic vessels before and after SPDP DPSVS (n = 10).

**Results:** Effective direct or indirect (through the submucosal gastric arterial network) communication between the branches of the left gastric and the SGA was not revealed during the perfusion of cadaveric arteries; IDU never detected arterial blood flow in the splenic hilus after the clamping of the splenic and the left gastro-epiploic arteries, clamping of the SGA did not change the flow parameters; CTA after DPSVS never delineated short gastric vessels supplying the spleen. In all the cases the gastro-epiploic arcade was the main arterial pathway feeding the spleen.

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**P92**

**Incidence and Influence of R1-Status on Long-Term Outcome after Oncologic Pancreatic Resections**

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Objective: To clarify the sources of spleen blood supply after SPDP SVR.

**Background:** The introduction of standardized protocols for pathological work-up substantially changed the rate of R1 resections from about 20% up to 80% in pancreateobiliary malignancies over the past years. However, long-term follow-up data are still scarce. In the present study we aimed to investigate the incidence of R1 resections with a special focus on survival and tumor recurrence pattern after oncologic pancreatic resections.

Out of 265 pancreatic resections performed from 09/2003 to 09/2010 we included 97 patients with ductal pancreatic adenocarcinoma, 10 with ampullary cancer, and 21 with distal bile duct carcinoma. Various intra- and postoperative variables including our routine pathology report were assessed. Follow-up data were obtained by a telephone inquiry.

R1-resections were found in 57 (45%), R0-resections in 66 (52%), and R2-resections in 4 patients (3%), in one patient the R-status could not be assessed. The percentage of R1 resections remained largely unchanged over the study period and was highest (51%) in ductal pancreatic cancer. The R1 situation was located at the retroperitoneal resection margin in 79% (n = 45), at the transectional margin in 12% (n = 7), and elsewhere in 26% (n = 15) of the patients. Follow-up was available in 73 patients after 17 (median, range 1–75) months postoperatively. Survival was 56% in the R0-resected and 22% in the R1-resected group (p < 0.005) with a median survival of 21 months (range 1–75) and 13 months (range 2–42), respectively (p < 0.005). The percentage of patients undergoing adjuvant chemotherapy did not differ in the two groups. Tumor recurrence was diagnosed in 34% of R0-resected and in 66% of R1-resected patients (p < 0.01), local recurrences were more frequent in the R1- (44%) than in R0-group (17%) (p < 0.02).

Our 51% R1-resection rate in ductal pancreatic cancer indicates a high quality routine pathological work-up. R1 resections are predominantly located at the retroperitoneal resection margin and are associated with a significantly higher local recurrence rate. We confirm the importance of a detailed histopathological analysis on long-term outcome in oncologic pancreatic surgery.
**Abstracts**

**P93**

**The Influence of Pancreaticojejunostomy vs Pancreatogastrostomy on Postoperative Rate of Complications**

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**Introduction:** A Meta-Analysis of three RCTs could not detect any difference in the postoperative complication rate between Pancreaticojejunostomy (PJ) and Pancreatogastrostomie (PG) after resection of the pancreatic head.

We analysed the outcome after changing of the anastomosis technique from PJ to PG in a teaching hospital.

**Materials & Methods:** We evaluated 100 consecutive patients out of a prospective data base with partial duodenopancreatectomy because of pancreatic cancer, 69 of them with PJ between 5/2002–5/2008 (group A) and 31 with PG between 6/2008–6/2010 (group B). The postoperative pancreatic fistulas were graded according to Bassi et al. 2007.

**Results:** 58% (40/69) of patients in group A and 29% (9/31) of patients in group B suffered from postoperative complications. 24.6% (17/69) of patients in group A and 6.5% (2/31) in group B developed a pancreatic fistula (p = 0.05). No significance could be shown for fistula grading (p = 0.27).

There was no statistical significance between these groups regarding need of reoperation (p = .54), insufficient biliodigestive anastomosis (p = 0.585), wound infection (p = 0.431)and delayed gastric emptying (p = 0.197). Postoperative mortality was 5.8% (4/69) in group A and 3.2% (1/31) in group B (p = 0.585).

**Conclusions:** Conversion of anastomosis technique reduced the rate of pancreatic fistula in our hospital. A prospective multi-centre trial should be initiated to compare both techniques.

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**P94**

**Over-Expression of HDAC7 in the Cytosol and at the Plasma Membrane of Tumoral Cells in Pancreatic Adenocarcinoma Tissues**

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**Background:** Ductal adenocarcinoma of the pancreas (PDAC) is ranking 4 for patient death from malignant disease in Western countries. Growing knowledge about HDACs shows that they are regulators of growth, differentiation and cell death (apoptosis).

Despite relatively small number of specimens examined, we found in a previous paper that increased expression of HDAC7, a class IIa deacetylase, is significantly associated with adenocarcinomas of the pancreas.

**Findings:** In this study, we have extended our approach by analyzing more samples with pancreatic adenocarcinoma as well as normal pancreas specimens. A quantitative method of the staining intensity allowed to correlate the overexpression of HDAC7 with adenocarcinomas of the pancreas. In addition, the staining patterns clearly demonstrate the localization of HDAC7 in the cytosol and at the plasma membrane of tumoral cells in these malignant tissues.

**Conclusion:** Cytoplasmic localization of HDAC7 in pancreatic cancer could use the VEGF-PKD-HDAC7 axis in the settings of vascular disorders and could explain the potential metastatic of pancreatic cancer.

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**P95**

**Semaphorin 4D/CD72 Exerts Autocrine Promalignant Effects in Pancreatic Cancer**

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**Introduction:** Semaphorins are constituents of a large family of secreted and transmembrane molecules, which provide axonal guid-
Results: We investigated, whether Sema4D exerts autocrine pro-malignant effects in pancreatic ductal adenocarcinoma (PDAC).

Material & Methods: Pancreatic tissues of normal donors (n = 34) and of patients with pancreatic cancer (n = 69), as well as pancreatic cancer cell lines were processed under identical conditions by quantitative real time PCR analysis. The probability of autocrine effects was assessed by analysing growth and motility of pancreatic tumor cells upon siRNA-based modification of sema4D expression. Furthermore we performed immunohistochemical analysis to reveal concentration in tumor cells.

Results: QRT-PCR revealed triple overexpression of Sema4D in pancreatic cancer tissues compared to donor tissues (43±3 vs. 13±2; p<0.01). It originated from up-regulation of synthesis in nerves (Schwann cells) and immune cells (T- and B-lymphocytes, monocytes/macrophages) but not in tumor cells, which however showed high level receptor expression. Higher levels of Sema4D were associated with reduced survival. 6 out of 7 pancreatic cancer cell lines co-expressed Sema4D (low) and its receptors (high).

Conclusion: Inflammatory reactive changes in pancreatic parenchyma raise local level of Sema4D, potentially able to impact several direct (tumor cells) and indirect (angiogenesis, immune response) mechanisms influencing tumor progression. Although a paracrine effect on tumor cells may prevail, an autocrine regulation in a small population remains a possibility.

P97
Intrapancreatic Activated Glia Is a Hallmark of Pancreatic Neuropathy in Pancreatic Cancer

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Introduction: Nerves in pancreatic tissue undergo prominent alterations in pancreatic adenocarcinoma (PCa), including intrapancreatic neural hypertrophy and dense neural network formation, pancreatic neuritis and neural invasion. These neuropathic alterations lead to the abdominal neuropathic pain syndrome of patients with PCa. However, the role of glia cells as the key actor in peripheral neuropathies and pain has not yet been investigated in pancreatic neuropathy in PCa.

Objectives: To elucidate the activation state of peripheral glia, i.e. Schwann cells, in pancreatic neuropathy in PCa.

Material & Methods: To imitate the conditions in PCa microenvironment, human Schwann cells (hSc) were cultivated under hypoxia and within PCa cell supernatants for varying time periods. To assess the activation state of hSc, the three cardinal features of reactive glia, i.e. enhanced proliferation, cellular hypertrophy and upregulation of the intermediate filaments GFAP, nestin and vimentin under hypoxia. When exposed to components of PCa microenvironment, hSc showed increased proliferation, enhanced GFAP expression and a star-like cellular conformation (“stellation”).

Results: hSc demonstrate a prominent upregulation of GFAP, nestin and vimentin under hypoxia. When exposed to components of PCa microenvironment, hSc showed increased proliferation, enhanced GFAP expression and a star-like cellular conformation (“stellation”). In contrast, these parameters of glial activation were completely absent when hSc were exposed to colon cancer cell supernatants.

Conclusion: Intrapancreatic glia is specifically activated during PCa and bears all known major characteristics of reactive glia, as known from astrocytes of the central nervous system. This seminal demonstration of activated glia in a visceral neuropathy has profound implications for proper understanding of the neuropathic pain syndrome in PCa.
**Prognostic Molecular Imaging in Pancreatic Cancer Through Analysis of the Stromal Activity**


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**Introduction:** The tumor stroma forms more than 80% of the pancreatic tumor mass and therefore, it is of utmost importance to assess changes regarding stromal activity.

**Objectives:** To identify tumor specific stromal changes in pancreatic cancer MRI-imaging coupled with quantitative image analysis and immunohistochemistry was used.

**Methods:** Postoperative high resolution MRI imaging of resected specimens was carried out in 6 patients with chronic pancreatitis and 12 patients with pancreatic ductal adenocarcinoma. Stromal activity was assessed by IHC and quantitative image analysis (α-SMA, CD31, collagen and periostin expression). Prognostic value was tested separately on a cohort of 113 pancreatic cancer patients. Survival analysis was performed using Kaplan-Meier and Log-Rank analyses. Prognostic factors were determined using a Cox proportional hazards model.

**Results:** Postoperative high resolution T2-scanning correlated with histomorphological data. Among analyzed factors only periostin expression significantly differed in pancreatic cancer tissues compared to chronic pancreatitis tissues (lower in cancer, p = 0.01). Collagen expression correlated negatively (p = 0.03) whereas periostin expression correlated positively (p = 0.002) with microvessel density of the tumors. Pancreatic cancer patients with higher periostin expression survived significantly longer than the ones with low expression (29.7 months vs. 15.8 months, p = 0.01). High periostin expression was an independent prognostic marker among pancreatic cancer patients (p = 0.017, 95% CI: 1.1159 – 4.563).

**Conclusions:** MRI imaging is a promising method to assess stromal activity in pancreatic cancer, thereby providing an important tool in the differential diagnosis and estimation of the prognosis of pancreatic cancer patients.

**Development of Multiple Reaction Monitoring Techniques for the Quantification of Biomarkers of Pancreatic Cancer**


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**Introduction:** We are using proteomic techniques to identify potential blood-borne biomarkers for pancreatic cancer to aid earlier detection of the disease and improve prognosis. Samples collected, as part of a UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) from women who developed pancreatic cancer during the course of the trial, along with late stage cancer samples and disease controls collected at the University of Liverpool, have been subjected to biomarker analysis using iTRAQ technologies. Validation of some promising candidates using immune-based assays has proved impossible due to the lack of suitable antibodies. Multiple Reaction Monitoring (MRM) uses mass spectrometry to quantify proteins, overcoming the need for antibody-based assays.

**Objectives:** To established MRM for the detection and quantification of candidate serum biomarkers of pancreatic cancer.

**Methods:** Discovery data for candidate biomarkers are used to generate unique peptide MRM transitions (parent to product ion), which are evaluated using a trypsin-digested recombinant version of the protein of interest. Stable isotope labelled peptides are then developed for more accurate quantitation of potential biomarkers.

**Results:** For one of our proteins of interest, several peptides have been identified and a set of transitions selected for each. Preliminary data from non-fractionated serum samples have shown that these transitions can identify the peptides in a complex protein mixture.

**Conclusions:** MRM method development is proving to be a useful alternative validation technology when a suitable antibody is not available.
P100

Risk of Exocrine Pancreatic Cancer and Common Variation in Genes Involved in Inflammation and Tumour Progression: A Two-Stage Case-Control Study

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Introduction: While both genetic and environmental factors contribute to the etiology of exocrine pancreatic cancer (EPC), few genetic susceptibility factors have been clearly established.

Objective: To identify low-penetrance genetic variants for EPC in preselected genetic pathways related to inflammation and tumour progression.

Methods: A two-stage case-control study was carried out, studying 1,536 SNPs tagging the common variation in 110 preselected genes in 150 incident EPC patients and 439 controls recruited in hospitals from three regions in Spain (Stage 1). The 96 SNPs with strongest evidence of association were then studied in 763 EPC cases and 1,059 controls recruited as part of a population-based study in Ontario, Canada (Stage 2). Odds ratios (OR) and their 95% confidence intervals (CI) were estimated by logistic regression, adjusting for age, sex and region. Adjustment for smoking made no substantial difference to the results obtained.

Results: Five associations observed in Stage 1 were also observed in the larger sample in Stage 2. Combining data from both stages, the strongest evidence was for a common intronic SNP (minor allele frequency, MAF = 0.17) tagging variation in CD80 (per allele OR = 0.80, 95%CI = 0.68–0.93, p = 0.004). All five SNPs are currently being studied in a large collaborative case-control series of chronic pancreatitis, which can be considered an intermediate phenotype in pancreas cancer susceptibility.

Conclusion: Several common genetic variants potentially implicated in EPC susceptibility were identified. These findings, if replicated in larger independent studies, may point to as yet unexplored genetic pathways involved in EPC development.

P101

Analysis of DNA in Pancreatic Juice, Serum and Plasma from Patients with Pancreatic Ductal Adenocarcinoma, Chronic Pancreatitis and Other Benign Disease Controls


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Introduction: We have previously carried out K-ras mutation analysis on DNA extracted from pancreatic juice. However, pancreatic juice is difficult to obtain, therefore it would be advantageous to analyse DNA from blood instead.

Objectives: The aim of this study is to determine which clinical material (juice, serum or plasma) would be optimal for mutational analysis to distinguish pancreatic ductal adenocarcinoma (PDAC) from chronic pancreatitis (CP) and other benign disease controls.

Patients & Methods: DNA was extracted from matched pancreatic juice, serum and plasma samples from 187 patients with PDAC (n = 119), CP (n = 37) and other disease controls (n = 31). For DNA concentration analysis Real Time PCR (RT-PCR) was performed on the DNA with a control primer set to amplify both K-ras mutant and wild-type DNA. For K-ras mutation analysis, RT-PCR was performed on the DNA with 6 primer sets, one for each of the common K-ras mutations in PDAC (G12D, G12R, G12V, G12A, G12S, G12C).

Results: DNA concentrations were highest in pancreatic juice samples from patients with PDAC (mean = 2361ng/ml) and CP (mean = 2157ng/ml). Serum and plasma DNA concentrations were similar in samples from patients with PDAC (serum mean = 354ng/ml, plasma mean = 327ng/ml) and CP (serum mean = 438ng/ml, plasma mean = 226ng/ml). K-ras mutation analysis is in progress.

Conclusion: Despite the harsh conditions prevalent in pancreatic juice, free DNA is more abundant in this medium than in blood. This is contrary to previous expectations.

Although serum and plasma contain less DNA than juice there is sufficient DNA for K-ras mutation analysis to be performed and this is ongoing.
P102

Downregulation of Krüppel-Like Factor 4 Expression and TP53 Mutations Are Associated with High Frequency of Pancreatic Intraepithelial Lesions in Pancreatic Ductal Adenocarcinoma

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Introduction: The transcription factor Krüppel-like factor 4 (KLF4) may act both as an oncogene and a tumor suppressor in a tissue dependent manner.

Objectives: Studies on its role in pancreatic ductal adenocarcinoma (PDAC) progression and clinical outcome are warranted.

Materials & Methods: Loss of heterozygosity (LOH) in the 9q22.3–32 region and KLF4 gene expression were investigated in 35 PDAC, 6 pancreatic intraductal neoplasias (PanINs) and 6 normal ducts, isolated by laser microdissection, as well as their correlation with overall survival (OS) in patients treated with gemcitabine in the adjuvant setting. LOH was evaluated with 4 microsatellite markers and in situ hybridization, while KLF4 expression was studied by RT-PCR and immunohistochemistry. K-Ras and TP53 mutations were studied by sequence analysis.

Results: LOH in at least 1 locus was observed in 25 of 35 PDAC cases and in 5 of 6 PanINs, respectively. In particular, the loss of the D9S105 marker was present in 46.9% of PDAC and 83.3% of PanINs, becoming the most deleted marker, while no LOH in D9S105 was observed in normal Wirsung pancreatic duct. Lack of KLF4 mRNA expression was significantly associated with: (1) genomic deletion flanking KLF4 in PDAC and in PanINs, (2) lack of KLF4 protein expression, and (3) shorter OS. KLF4 and TP53 alterations were associated with high frequency of low-grade PanINs PDAC-associated.

Conclusion: These results suggest a relationship between D9S105 deletion and downregulation of KLF4 expression as an early event in PDAC progression, as well as a possible role of KLF4 as a prognostic biomarker in gemcitabine-treated patients.

P103

Synergistic Interaction of Novel Lactate Dehydrogenase Inhibitors with Gemcitabine in Hypoxic Models of Pancreatic Cancer

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Introduction: Hypoxia is a driving force in pancreatic cancer growth and metastasis. Since the muscle isoform of lactate dehydrogenase (LDH-A) constitutes a major checkpoint for the switch from aerobic to anaerobic glycolysis, we tested a series of novel N-hydroxy-2-carboxy-substituted indoles with Ki values for LDH-A reaching the low micromolar range (Granchi et al., J Med Chem 2011).

Materials & Methods: In vitro studies were performed in 14 pancreatic cancer cell lines, characterized by differential HIF-1alpha and LDH-A mRNA expression. The cytotoxic activity of the three most promising inhibitors (PI-FLY#21, 31 and 124) was evaluated with the combination index (CI) method. All these experiments were performed in both normoxic and hypoxic conditions (1% O2).

Results: LDH-A expression was detected in all the pancreatic cancer cells, and significantly increased under hypoxic conditions. The novel LDH-A inhibitors demonstrated a good antiproliferative activity, with IC50 values ranging between 9.9 and 20.3 uM in normoxic conditions, and they proved to be particularly effective under hypoxic conditions, with 100- and 2-fold reduction of IC50s in PP78 and PANC-1 cells, respectively. Furthermore, these compounds induced apoptosis, and synergistically enhanced the cytotoxic activity of gemcitabine (CI values < 0.5).

Conclusion: These data provide evidence that LDH-A is a viable target in pancreatic cancer cells, and novel LDH-A inhibitors display synergistic cytotoxic activity with gemcitabine, offering an innovative tool for optimizing chemotherapy in hypoxic pancreatic tumors.
**PMP22 Genetic Alteration and Modulation of PMP22 Expression by NSC-631570 in Pancreatic Ductal Adenocarcinoma (PDAC)**

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**Introduction:** Peripheral myelin protein 22 gene (PMP22) encodes a membrane protein of myelin in the peripheral nervous system, and PMP22 duplication causes the Charcot-Marie-Tooth 1A (CMT1A) phenotype. PMP22 is also capable of delaying the transition from G0/G1 to S phase. However, growth factors involved in PMP22 regulation, such as Insulin-like growth factor-II (IGF-II), are up-regulated after radiation in fibroblast cells, and might influence chemo-radiosensitivity. Since the compound NSC-631570 had a protective effect on human fibroblasts but not human tumour cells against ionizing radiation, and showed beneficial effects in phase II studies in metastatic and locally advanced PDAC patients, the aim of this study was to evaluate the interaction between PMP22, IGF-II and NSC-631570 in PDAC Primary Cell Cultures (PCCs).

**Materials & Methods:** DNA duplication of PMP22 gene was evaluated by PCR and specific digestion by the endonucleases EcoRI and NsiI in 13 PDAC tissues, 2 PCCs and PBMCs from 3 healthy subjects. PMP22 protein was evaluated in tissues and cells by ImmunoHistoChemistry (IHC). The PCCs were also exposed to IGF-II, NSC-631570, and their combination. Finally, expression of PMP22 was correlated with cell proliferation index.

**Results:** The PMP22 duplication was observed in 44% (7/13) of PDAC patients and in both PCCs. PDAC duplicated samples showed significantly higher score of PMP22 protein expression (p = 0.0262). PMP22 protein was correlated with decreased cell growth, whereas 400 nM IGF-II reduced PMP22 expression and increased cell proliferation. Conversely, the addition of 1μM NSC-631570 increased PMP22 expression, and overcame IGF-II induced proliferation.

**Conclusion:** This is the first study reporting PMP22 duplication in PDAC specimens and cells. This duplication was correlated with PMP22 expression. PMP22 protein was inversely related to cell proliferation and its inhibition by IGF-II might explain chemo-radiosistance caused by PDAC associated fibroblasts. However, NSC-631570 increased PMP22 expression and might synergize with anticancer treatments against PDAC.

**P105**

**Syndecan-3 Induces Neuropathic and Neuroplastic Alterations in Chronic Pancreatitis and Pancreatic Cancer**

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**Introduction:** Pancreatic cancer (PCa) and chronic pancreatitis (CP) are characterized by numerous neuroplastic alterations and a prominent upregulation of neurotrophic factors in the pancreas. Syndecan-3 (SDC-3), the neural representative of a family of cell-surface heparan proteoglycans, has very recently been identified to be a key receptor for numerous neurotrophic factors.

**Objectives:** Due to this overt link to neurotrophic signaling, the role of SDC-3 in pancreatic neuropathy in CP, in PCa and in cancer cell biology remains to be identified.

**Methods:** Expression of SDC-3 and its ligand pleiotrophin (PTN) was investigated in human normal pancreas (NP), CP, PCa tissues, human Schwann cells, perineural cells, ten different PCa cell lines (PCC) and newborn rat dorsal root ganglia (DRG) via QRT-PCR, immunoblotting, flow cytometry, immunocytochemistry and immunohistochemistry. MTT-proliferation- and neural-migration-assays were applied to analyze effects of siRNA-knockdown on PCC biology.

**Results:** SDC-3 and PTN are both upregulated in CP and PCa, mainly localized in the peri- and endoneurium of intrapancreatic nerves, in PCCs and fibrotic areas. Particularly high amounts of SDC-3 were found in the extracellular matrix consistent with a high number of sheared extracellular domains that serve as anchors for growth factors. SDC-3 expression in intrapancreatic nerves originates from undifferentiated endoneurial fibroblasts. Knockdown of SDC-3 prominently decreases the nerve-targeted migration of PCCs, but does not influence their proliferation.

**Conclusion:** SDC-3 is a decisive mediator of neural invasion (NI) in PCa. The generation of SDC-3 in endoneurial fibroblasts represents a novel mechanism for the generation of pancreatic neuroplasticity in CP and PCa.
**P106**

**Exocrine Pancreatic Tumors in Childhood: Data from the German Paediatric Tumor Registry**

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**Introduction:** Pancreatic tumors (PT) in childhood are rare. Standard therapeutic approaches are lacking. Our aim was to analyze treatment modalities and outcome in children with PT.

**Patients/Material & Methods:** Data of patients with exocrine PT below 16 years diagnosed between 1980 and 2007 were analyzed retrospectively. Data were obtained from the German Pediatric Tumour Registry. Medical records were evaluated and patients' data were pseudonymized.

**Results:** Patient records of 30 children were available, (10 male, 20 female, median age 11.2 years, range 3.1–16). In 19 patients a solid-pseudopapillary tumor (SPT) was diagnosed, in 7 patients a pancreatic carcinoma (P-CA) (5 acinar cell carcinoma (ACC), 2 ductal adenocarcinoma (DCA)), and in 4 patients a pancreatoblastoma (PBL). In 69% of the patients the initial radiological findings led to an incorrect tentative diagnosis. Initial histopathological diagnoses were differing from the reference pathology in 50% of the SPT and 45% of the P-CA. In the group of SPT survival rate was 100%, all patients underwent surgical resection. There were two cases of tumor relapse and one late secondary malignancy of the pancreas (DCA). In P-CA patients, survival rate (14%) was comparable to adult populations. In the PBL group the survival rate was 25%, worse than described in literature. Concepts of chemotherapy, radiotherapy, and time point of surgical intervention in P-CA and PBL were varying widely.

**Conclusions:** The establishment of a standardized treatment concept should be realised. Therefore a prospective data registration needs to be entrenched. Reference pathology and reference radiology should be involved in all cases of PT.

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**P107**

**Pancreatic Tumors in Children: The University of Verona Experience and Review of Literature**

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**Introduction:** Pancreatic tumors in children are extremely rare and may show different histologic patterns. The aim of the current study was either to analyze the experience of the University of Verona and to review the widest reports published in literature, in order to evaluate pathology, management and prognosis of such uncommon diseases.

**Patients/Materials & Methods:** A retrospective review of all patients aged between 0 and 18 years who were observed for pancreatic tumors at the Verona University Hospital from January 1990 to December 2010 was carried out. A literature review via Pubmed.org of the widest published experience in the field of pediatric pancreatic tumors was undertaken.

**Results:** In the study period 2746 histologically-confirmed pancreatic neoplasms were surgically treated at our institution; of these 20 (0.72%) were found in pediatric age and therefore eligible for the analysis. There were 15 females and 5 males, with a median age of 16 years (range 7–18 years). Two patients had MEN 1 syndrome. Surgical procedures included pancreaticoduodenectomy (DP) in 7 cases (35%), spleen-preserving left pancreatectomy (SP-LP) in 3 (15%), left pancreatectomy (LP) and splenectomy (SP) in 4 (20%), 2 middle pancreatectomy (MP) (10%), 3 enucleations (15%) and one cyst surgical aspiration (5%). There was no postoperative mortality. Postoperative complications occurred in 6 cases (30%) requiring one reoperation. The most frequent histotype was solid-pseudopapillary tumor (n=12, 60%) followed by 5 neuroendocrine tumors (25%), 1 serous cystadenoma (5%), 1 mucinous cystadenoma (5%) and 1 epithelial malignant tumor (5%). After a median follow-up of 49.6 months (range 6–234.2), there was no tumor recurrence in any case.

**Conclusions:** Compared to literature, our series of 20 surgically treated pediatric patients is one of the widest ever published. Unlike in adult patients, pancreatic tumors in children are usually represented by papillary cystic and neuroendocrine tumors. Once radical surgical resection is performed, a long term disease free survival can be achieved.

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**P108**

**Short-Term Changes in the Quality of Life of Patients who Undergo Surgery for Pancreatic Cancer**

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**Introduction:** Both pancreatic cancer and pancreatic surgery may profoundly affect quality of life (QoL).
Objective: To study the short term changes in QoL of patients who undergo surgery for pancreatic cancer.

Methods: SF-36 survey was completed before and 3 months after surgery by 76 (39 male) patients with pancreatic cancer.

Results: Mean age was 64.1 (24–83) yrs, postoperative stay 16.7 (7–41) days. Mortality was 0%, morbidity 48.7%, pancreatic leak rate 6.6%. There were 29 duodenopancreatectomies, 6 distal pancreatectomies, 11 total pancreatectomies and 30 palliative procedures. Preoperative QoL of cancer patients was lower than that of healthy German population: physical score (PS) 42.8 vs. 50.2, mental score (MS) 42.5 vs. 51.5, p < 0.001. Surgery reduced significantly PS to 37.6, p < 0.001; MS slightly improved, 44.0. Preoperative PS was lower in palliative vs. resected cases, 37.8 vs 46.0. Resective surgery reduced PS significantly 46.0 to 38.9 but slightly improved MS, whereas palliative surgery reduced both PS and MS. Best tolerated procedure was distal pancreatectomy, where (pre-to-postop difference) ΔPS was -5.8 and ΔMS +5.9. Worst tolerated was total pancreatoduodenectomy with ΔPS -8.1 and ΔMS -1.9.

Conclusion: Resectional surgery decreased physical health, though it still remained better than in palliative patients, and improved mental health, opposite to palliative procedures. Partial resections of the pancreas should be preferred to total pancreatectomy whenever possible.

P109
Results of the Duodenal Stromal Tumors Treatment
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Introduction: Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the digestive tract. Duodenal GISTs are relatively rare tumors and comprise 7–8% of all GISTS.

Objective: Analysis of the duodenal GIST treatment.

Method: Three men and four women (age 42–68 years) were primarily and repeatedly operated on for duodenal GISTs (2006-2009). Prospective analysis of treatment was performed.

Results: The sizes of a tumor varied from 2 to 15 cm. Pancreatoduodenectomies (PD) had been performed in three and pancreas-sparing infrapapillary duodenectomies (PSD) – in four cases. There was no mortality and postoperative course was uneventful in all the patients. The definitive diagnosis in all cases had been established after surgery by immunohistochemistry. A median-grade malignancy potential was estimated in three and high-grade – in two cases in tumor more than 5 cm in diameter. Tumor progression were revealed in two cases in 4 and 30 months after surgery followed by an adjuvant imatinibe mesylate therapy. Right hemihepatectomy in the other were performed due to incomplete answer to chemotherapy. At the moment all patients are alive and without signs of progression. There were no relapses in patients with median-grade malignant potential of the tumor.

Conclusion: Surgery is the main therapeutic approach in treatment of primary duodenal GIST. Considerable increase in survival can be achieved by timely and adequate surgery of primary and secondary tumors combined with adjuvant treatment and thorough follow-up.

P110
Surgical Aspects of the Celiacos-Mesenterial Arterial Aberrations
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Background: It is important to recognize celiac - mesenterial arterial variants (CMAV) in the preoperative planning of the abdominal procedures.

Objective: To define the potential danger of CMAV for different types of surgical procedures.

Method: Abdominal CT angiographies (CTA) of 250 consecutive patients (November, 2010 - February, 2011) were analysed prior to major pancreatic or hepatobiliary surgery. Variants of CM arterial anatomy were virtually anatomically confronted with the structures involved in different types of abdominal operations. The variant considered favorable in case of accessorial vessels and unfavorable in the presence of arterial replacement or transposition.

Results: The classic arterial anatomy was identified in 64.4% of cases. Accessorial hepatic arteries of Michels’ type 5 and 6 revealed in 4.4% and 1.2% of cases. Replacement aberrations were: Michels’ type 2 – 3.6%, type 4 – 1.2%, type 3 – 6.8%, type 8- 0.8%, type 9 – 2%, Hiatt’s type 6 – 0.8%, unclassified by Michels and Hiatt – 14.8% of cases. In total favorable variants were registered in 5.6%, and unfavorable in 30.0% of observations. Cases of the chronic abdominal ischemia and different types of organ-preserving procedures are forming the group of special interest. The abdominal collateral blood flow has to be investigated in all these patients before abdominal surgery to avoid the possible ischemia of the neighboring and remote organs.

Conclusion: The CM arterial variants are common and may be dangerous during abdominal operations. CTA is a reliable tool for identifying arterial aberrations and lesions preoperatively, making surgery more personalized and safe.

P111
Pancreatocduodenectomy with Portal Vein Reconstruction: Single Centre Results

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Introduction: Combined vascular and pancreatic resection improves long-term survival of patients suffering from ductal adenocarcinoma of the pancreatic head.
Objective: Evaluate the safety and outcomes of extended pancreateoduodenectomy with portal vein resection for pancreatic cancer.

Methods: From September 2006 to January 2011, there were 39 portal vein resections carried out during extended pancreatectoduodenectomy for malignancy. A prospectively collected database was analysed to look at morbidity, mortality and overall outcome.

Results: There were 20 female and 19 male patients with a mean age of 60.4 years (median 63). 20 (51.3%) patients had pre-operative biliary drainage (ERCP 19 and PTC 1). Nine patients with operative complications occurred in 5 (12.8%) patients with a 30-day mortality of 1 (2.6%). The type of portal vein resection was a wedge resection, with or without a patch, in 27 (69.2%) and complete resection with end to end anastomosis in 11 (28.2%) patients respectively. An interposition vein graft was used in 1 (2.6%) patient. There was no evidence of portal vein thrombosis in any patients during follow up. The median follow up in this study was 13 months (range 0 – 39). The actuarial 1 and 3 year survival was 35.5% and 4.8% respectively, with median disease free survival of 10 months (range 0 – 38).

Conclusion: Vascular resection combined with pancreatectoduodenectomy for pancreatic cancer increases local resectability without increasing mortality and morbidity rates in the setting of an expert referral centre and should not be a contraindication to a curative surgery.

P112 Late Postpancreatectomy Hemorrhage After Pancreatectoduodenectomy: Is It Possible to Recognize Risk Factors?

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Introduction: Postpancreatectomy hemorrhage (PPH) is a life threatening complication and remains one of the causes of morbidity following pancreatectoduodenectomy (PD). The causes of early bleeding are well recognized and usually are the result of intraoperative technical failure while the mechanism of late hemorrhage after pancreatic surgery is still unclear.

Objectives: To evaluate the incidence of PPH in patients undergoing PD and to explore the presence of factors related to its time of onset.

Patients & Methods: A prospective study including 96 patients who underwent PDs was carried-out. PPH was defined using the criteria of the International Study Group of Pancreatic Surgery.

Results: Twenty-eight out of 96 (29.2%) patients had a PPH; of these 96 patients, 22 (22.9%) developed late PPH. Surgical reoperation was performed in 2 of the 22 patients (9.1%). The association between late PPH and POPF was frequent (15 cases; 68.2%). At univariate analysis, the only factor significantly related to the presence of late PPH was a POPF (P<0.001). Multivariate analysis confirmed that the presence of a grade B POPF increased the risk of late PPH (P<0.001). The association of a POPF and late PPH is significantly related to the need for reoperation (P<0.006).

Conclusion: Late PPH in patients undergoing PD seems to be related to a POPF grade B. All patients with a pancreatic fistula grade B should be carefully followed in order to early detect those patients at high risk of late PPH.
P114
Intratumoral Vascular Growth Substantially Reduces Median Survival in Patients Undergoing Pancreaticoduodenectomy for Pancreatic Cancer
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Introduction: The impact on survival of histological features of pancreatic cancer (PC), such as tumor cells in intratumoral vasculature (V1), lymph vessels (L1) or perineural (PN1) spaces, are less studied than other common prognostic factors e.g., tumor size (Ts), differentiation (diff), R-status and lymph node (LN) metastases. Previously reported preliminary data showed that vascular tumor cell growth (V1) was an independent factor for R1-resection and LN-metastases.

Objectives: To evaluate the impact of V1 on survival in PC.

Patients & Methods: One hundred consecutive PD for PC were included and V, Ts, diff, number of LN-met and R1 status were determined. Chi-square test was used to identify confounders (p-value < 0.1) for the association between V1 and survival after PD. In a multivariable model, the effect of V1 on median survival was calculated using Laplace regression analysis.

Results: The median age was 68 (range 42–83) and the majority of patients were men (56%). V1 was associated with tumor size >30 mm (p = 0.08), low diff (p = 0.06) and >1 LN-met (<0.01). The distribution of other factors was not statistically different with respect to V1. The median survival was shortened by 11.1 months (95% CI: -17.5 – -4.7; p < 0.01) in patients with V1 compared to V0 when adjusted for Ts, diff and LN-met.

Conclusion: This study shows that tumor cells in intratumoral vasculature is an independent and negative factor for survival, emphasizing tumor cell biology as the main determinant, and the need to stratify tumors accordingly in future trails evaluating new treatment modalities.

Poster Session II
Clinical Science – Acute Pancreatitis II

P115
Ascorbic Acid Depletion and High Doses Vitamin C Treatment in Severe Acute Pancreatitis
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Introduction: The management of acute pancreatitis is very difficult. Recent studies support concept about key role of oxidative stress in pathogenesis of acute pancreatitis. Reactive oxygen species and related oxidative damage have been implicated in the initiation of acute pancreatitis.

Objectives: The aim of the study is role of ascorbic acid in pathogenesis and treatment of acute pancreatitis.

Materials and Methods: We studied 79 patients with acute pancreatitis. 34 patients with severe acute pancreatitis received vitamin C 4000 mg i.v. and 1200 mg N-acetylcysteine i.v. 35 patients were the control group. Ascorbic acid was measured by high-pressure liquid chromatography, cytokines – by ELISA.

Results: There was a significant decrease in plasma ascorbic acid concentration in patients with severe acute pancreatitis. High doses of ascorbic acid treatment decreased the frequency of progression, the development of infected necrosis and mortality. This significantly decreased blood levels of inflammatory cytokines, including TNF-alpha.

Conclusion: The use of high doses of vitamin C can reduce manifestations of ascorbic acid deficiency, ischemic processes, and the severity of oxidative stress in acute pancreatitis. Ascorbic acid has an immunomodulatory effect and improves outcomes of treatment.

P116
Treatment of Hypertriglyceridemia-Induced Acute Pancreatitis in Pregnancy by Therapeutic Plasma Exchange
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Introduction: Acute pancreatitis in pregnancy is often associated with severe morbidity. It is usually an antepartum problem occur-
ring in late pregnancy. AP in pregnancy is most often associated with gallstone disease or hypertriglyceridemia. Hypertriglyceridemia is the second most common cause of AP, when the serum triglyceride is >1000 mg/dL. In the third trimester of pregnancy, there is a threefold rise in serum triglyceride levels. Hypertriglyceridemia may be more severe in persons with familial hyperlipidemia, predisposing them to develop pancreatitis.

Objectives: Role of plasma exchange in treatment of hypertriglyceridemia-induced acute pancreatitis in pregnancy.

Materials & Methods: We studied 5 cases of gestational severe acute pancreatitis caused by hypertriglyceridemia. All patients had intensive supportive care with therapeutic plasma exchange (TPE). Fetal monitoring was performed before and after volume exchange with albumin replacement, preceded by 0.9% normal saline bolus. In one patient delivery of healthy infant at 36 weeks. In four patients emergency cesarean-section due to fetal distress with delivery of healthy infant at 29 and 33 weeks.

Conclusion: Fasting lipid profile should be regularly monitored during pregnancy due to the association of hypertriglyceridemia with development of acute pancreatitis in the mother. Therapeutic plasma exchange is effective method of treatment hypertriglyceridemia-induced severe acute pancreatitis in pregnancy.

P117

Endovascular Intervention in Severe Acute Pancreatitis Patients

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Introduction: The mortality among the patients with severe acute pancreatitis (SAP) remains the relatively high. Even 15–30% of the patients with SAP were died in the specialized centers. One of principal causes of lethality of patients with severe acute pancreatitis is multiorgan dysfunction. The improvement of the conventional therapy may decrease the morbidity and mortality rates in patients with SAP. Continuous regional arterial infusion (CRAI) of antioxidants, protease inhibitor and antibiotics were proposed as special therapy for SAP.

Objectives: Role of continuous regional arterial infusion in treatment of severe acute pancreatitis.

Materials & Methods: We studied 97 patients with severe acute pancreatitis. The first group (49 patients) received the protease inhibitor (aprotinin), antioxidant (querce tin) and the antibiotic (ertapenem, gatifloxacin) by continuous regional arterial infusion during 12–14 days and the second group (48 patients) received protease inhibitors, antioxidant, and antibiotics by intravenous infusion.

Results: Continuous regional arterial infusion in acute pancreatitis inhibits the proinflammatory response and stimulates compensatory anti-inflammatory response. The IL-10/IL-6 ratio of the patients with SAP was significantly increased after continuous regional arterial infusion. The combination of quercetin, a protease inhibitor and antibiotics in intraarterially, decreases the frequency of infection, limit the destructive process, reduced the number of surgical interventions and mortality. Continuous arterial infusion is effective in preventing bacterial translocation in acute pancreatitis, improves capillary circulation. After CRAI function of kidneys and liver much more quickly improved, the pulmonary complications decreased.

Conclusion: Combined inraarterial therapy of acute necrotizing pancreatitis reduces the need for surgical treatment and reduces mortality.

P118

Management of Pancreaticopleural Fistulae in a Specialist Pancreatic Unit

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Introduction: Internal pancreatic fistulae are uncommon sequela of severe acute pancreatitis. Due to their low prevalence, experience in the management of this condition remains sparse outside specialist centers and management remains controversial.

Objectives: We report our experience with pleuropancreatic fistulae (PPF).

Patients: Nine patients (3 males, median age 34 years [range: 32–74 years]) with PPF were managed in our unit between April 2006 to December 2010. The etiology of pancreatitis was alcohol (6), gallstones (2) and trauma (1). Seven patients had left pleural effusions, one bilateral and one a mediastinal collection (all with amylase content >1000 iu/dl).

Results: The median duration of inpatient stay during the acute episode was 38 days. CT alone was able to identify the disruption in 4 cases and a combination of CT and MRI localized the ductal disruption in all patients. Percutaneous drainage of thoracic and abdominal collections was performed in all patients. Two patients required surgery (thoracotomy with rib resection; pancreatic necrosectomy, colec tomy and ileostomy). Pancreatic duct stenting was achieved in four patients; sphincterotomy and stone extraction in one. All cases resolved following this management. The patient with mediastinal collection continues to suffer dysphagia. All patients remain well at a median follow up of 28 months.

Conclusion: Pleuropancreatic fistulae can present a challenging diagnostic dilemma. A multi-disciplinary approach addressing nutritional support and endoscopic therapy allows successful non-operative resolution in the majority of patients within specialist units.
**P119**

**Serum Elastase on the Third Day is a Valuable Predictor of Systemic Complications in Patients with Acute Pancreatitis**

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**Introduction:** Serum pancreatic elastase (E1) concentration rises significantly in acute pancreatitis (AP). Many studies confirmed that E1 has no value in prediction of complications on the first day. However, only few studies have shown its significance in prediction of severe disease cases on the third day.

**Objectives:** To evaluate the use and accuracy of E1 in the prediction of severity of AP.

**Patients and Methods:** In 156 admitted to our hospital with a confirmed diagnosis of AP, we measured E1 on the first and third day upon admission. Measurements were performed by immunoenzymometric principles, and referent values were as determined by the manufacturer (<3.5 ng/ml). Statistical analysis was performed using Mann-Whitney test and ROC analysis.

**Results:** We confirmed a statistically significant decrease of E1 between the first (median = 5.9, 95% CI 4.3–7.5) and third (median = 1.8, 95% CI 1.6–2.2) day (p < 0.001). We did not find a significant difference in E1 values on the first day between patients with and without complications (p = 0.249). However, a significant difference occurred on the third day (1.7, 95% CI 1.4–1.9 vs. 2.5, 95% CI 2.1–3.1; p < 0.001). ROC analysis was performed for the latter and confirmed a significant decrease of E1 in patients with complications on the third day (AUC 0.70; 95% CI 0.62–0.77; cut-off = 1.5; sensitivity 93%; specificity 43%; PPV 27%; NPV 96%; p < 0.001).

**Conclusions:** Our results showed that the decrease of E1 concentrations on the third day are significantly correlated with severe cases of AP and a higher rate of systemic complications.

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**P120**

**Epidemiology of Acute Pancreatitis in Northern Adriatic Region of Croatia During Last Ten Years**

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**Introduction:** Incidence rate and the etiology of acute pancreatitis (AP) varies in different parts of Europe. A small number of published studies show discrepant results in incidence rate of AP, ranging from 20 to 30 new cases per 100 000 inhabitants annually.

**Objectives:** The aim of this study was to present incidence rate of AP for North Adriatic Region in Croatia as well as to make epidemiological analysis concerning etiology, mean age, gender and severity of disease.

**Methods:** During a ten years period (2000–2009) we analyzed 922 patients admitted in our hospital with confirmed diagnosis of AP by history, clinical and laboratory findings and imaging methods. An epidemiological analysis is carried out on incidence, demographic data and etiology as well as severity of a disease based on a Ranson score.

**Results:** Incidence rate varied from 24 to 35/100 000 annually. Mean age was 60 ± 15.77 years. There were 53.2% of men and 46.8% of women. Most frequent etiology of AP was biliary in 60.5% and alcohol abuse in 19.3% of patients. According to the Ranson score, pancreatitis was considered to be severe in 43% of the cases.

**Conclusion:** In our region incidence rate of AP was around 30 per 100,000 habitants annually during last ten year period. The mean age at admission was 60 years and etiology was dominantly biliary. In our region, we have shown epidemiological characteristics of AP typical for Mediterranean countries.

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**P121**

**Accuracy of Scoring Systems in Prediction of Severe Acute Pancreatitis**

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**Introduction:** Different scoring systems have been widely used for early recognition of severe acute pancreatitis. Predicting development of systemic complications is very important to timely initiate adequate treatment and increase the rate of survival.

**Objectives:** To evaluate accuracy of various scoring systems as predictors for development of systemic complications in acute pancreatitis (AP).

**Patients & Methods:** A 150 patients with diagnosis of AP (71 male, median age 63 years, range 20–91 years) were admitted to our hospital in a 2-year period. We calculated APACHE II, APACHE III, and SAPS II scores for all patients on the first and third day of admission, Ranson and Balthasar scores according to references. ROC analysis was performed to assess accuracy of scoring systems in differentiation of patients with systemic complications and those without.

**Results:** ROC analysis confirmed that APACHE II on admission and on the third day (P = 0.039, and P = 0.028, respectively), Ranson (P < 0.001), and Balthasar (P < 0.001) scoring systems can significantly predict patients who will develop systemic complications. The largest AUC were measured for Ranson and Balthasar (0.75, and 0.79, respectively). Cut-off values to differentiate severe from mild cases of disease were APACHE II 9, Ranson 4, and Balthasar C. Analysis of APACHE III and SAPS II did not show statistical significance in prediction of the course of disease. Values of APACHE III and SAPS II on admission differed significantly from values on the third day, but without any diagnostic or prognostic significance.
Conclusion: APACHE II, Ranson and Balthasar scoring systems are still valuable predictors of development of systemic complications in AP.

P122
Waist Circumference Correlates with Disease Severity in Acute Pancreatitis
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Introduction: obesity is a well-known factor contributing to the etiology of acute pancreatitis (AP). 

Objectives: the aim of our study was to determine which obesity parameter correlates best with disease severity.

Patients & Methods: in this retrospective study, medical histories of 156 patients with AP (81 men and 75 women, mean age 64.2 ± 14.5 years, average APACHE II score 8.58 ± 4.07) were analyzed. Body-mass index (BMI), waist circumference, hip circumference and waist-hip ratio were retrieved and their correlation with local, systemic complications and death outcomes were compared using receiver operating characteristic (ROC) curves.

Results: among the researched parameters only waist circumference correlated with local, systemic complications and death outcomes. According to ROC curves, the cut-off value of 96 cm had 94.6% sensitivity and 40.3% specificity value in predicting systemic complications (p = 0.0018). The cut-off value of 103 cm had 68% sensitivity and 59.4% specificity value in predicting local complications (p = 0.0048). While the cut-off value of 100 cm predicted mortality with 80% sensitivity and 42.5% specificity value (p = 0.0031). Among other parameters, only waist-hip ratio – local complications ROC curve reached statistical significance; for cut-off value of 0.96, sensitivity was 80% and specificity 42.5% (p = 0.0101).

Conclusion: statistical analysis has shown that in our case BMI was a poor parameter and waist circumference had a better correlation in predicting complications, including death, in patients with AP. However, low specificity is the problem which will impede waist circumference from gaining a more pronounced role in everyday practice.

P123
Evaluation of Glasgow and APACHE II Scores and CRP Level in Serum in Prediction of Severity of Acute Pancreatitis
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The early prediction of the severity of an acute attack of acute pancreatitis (AP) has important implications for management and timely intervention. The aim of this study was to compare the accuracy of Glasgow and APACHE II scores and C-reactive protein (CRP) level in prediction of severity of acute pancreatitis.

Methods: Ninety one consecutive patients with acute pancreatitis primarily admitted were retrospectively studied. APACHE II score was recorded on admission, while Glasgow score and CRP levels were determined 48 hours later. Severity of AP was defined according to Atlanta classification system. Two study groups comprising 33 patients with mild AP (MAP) and 58 patients with severe AP (SAP) were compared. The accuracy of Glasgow and APACHE II scores, and CRP level, in prediction of severity of AP, using cut-off values of 8 and 3 points 150 mg/l, respectively (derived from ROC curves), were calculated.

Results: Mean values of Glasgow and APACHE II scores and CRP were 4 and 10 points and 331 mg/L, respectively in SAP group, while in MAP group it were 1 and 4 points and 62 mg/L, respectively. The sensitivity and specificity of Glasgow and APACHE II scores and C-reactive protein were 79% and 81%, 72.7% and 100%, 90.9% and 85.7%, respectively.

Conclusion: The CRP offers little, if any, advantage over the Glasgow and APACHE II score. CRP level and Glasgow score proved to be powerful a prognostic model as the more complicated APACHE II scoring systems, but with the disadvantage of a 24-hour delay.

P124
Circulating Levels of Adiponectin, Resistin and Proinflammatory Cytokine IL-18 in Acute Pancreatitis
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Background: Recent studies underline the role of white adipose tissue (WAT) not only as an energy storage depot but also as an active endocrine organ. Resistin and adiponectin, hormones produced by adipose tissue present the proinflammatory potential, however their role in AP was investigated only rarely.

Methods: The study group comprised 32 patients with alcoholic AP (median age 47.6 ± 16.7 years; 17 men and 15 women) and 30 controls (median age 50.7 ± 12.4 years; 15 men and 15 women). In all cases AP was classified as B according to Balthazar’s CT score and as severe according to Ranson’s criteria. The serum level of adiponectin, resistin, and IL-8 immunoassays were measured on admission, on the third and fifth day of hospitalization with ELISA.

Results: On the admission day serum resistin concentration in AP patients was significantly higher than in controls (12.9 ± 6.38ng/ml vs 4.06 ± 2.63ng/ml) and further increased on the third and fifth day of hospitalization (17.4 ± 4.32 and 25.8 ± 8.14ng/ml, respectively). On the admission day serum adiponectin level in AP patients was significantly higher than in controls (15362 ng/ml ± 1922 ng/ml vs 1350,3ng/ml ± 148,1 ng/ml) and further increased on the third (12945 ng/ml ± 1512 ng/ml) and the fifth day of hospitalization (14984 ng/ml ± 1776 ng/ml). The correlation between adiponectin and resistin as...
Conclusion: In the course of AP adiponectin and resistin level increase parallely with CRP. We speculate that those parameters may provide an additional tool for the prognosis and monitoring of AP.

P125
Antimediator Therapy as a Part of the Complex Treatment of Acute Destructive Pancreatitis
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Introduction: Acute destructive pancreatitis (ADP) remains a pressing problem of urgent surgery due to high morbidity and mortality rate. Inflammatory mediators (cytokines) are known to play one of leading roles in the development of ADP. But until now there were no effective cytokine kinesis activity inhibition agents available in everyday practice.

The purpose of this study: was evaluation of the effect of a NSAID lornoxicam on production of pro-inflammatory and anti-inflammatory cytokines by mononuclear cells (MNC) in peripheral blood of healthy donors (in vitro) and of ADP patients.

Materials & Methods: The group of healthy donors of peripheral blood consisted of 20 subjects. The group of ADP patients consisted of 110 subjects which was divided into 2 groups: 45 patients were treated with lornoxicam (introduced during the first 3 days at a dose 32, 24 and 16 mg, respectively) in addition to routine conservative therapy (main group) and 65 subjects underwent standard therapy only (reference group).

Results: The performed study demonstrated that lornoxicam inhibits production of both pro-inflammatory cytokines and anti-inflammatory cytokine by MNC in peripheral blood of healthy donors (in vitro) and of ADP patients.

Conclusion: Basing on the performed study, we can suppose that introduction of a NSAID into the complex therapy of ADP is pathogenetically substantiated.

P126
Pain-Related Gene Expression Profile During Caerulein-Induced Acute Pancreatitis in Mice
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Introduction: The nociceptive pathways involved in acute pancreatitis (AP)-associated pain are poorly characterised.

Objective: To determine the profile of gene expression (at the mRNA level) associated with pain signalling during caerulein-induced AP in mice.

Materials & Methods: AP was induced by 12 hourly i.p. injections of caerulein. Time-matched control groups received saline. At 0–48h, mice were euthanized and the dorsal root ganglia (T5–12) were harvested for RNA extraction. Plasma amylase activity was determined. Custom-made TaqMan® array fast plates (48 genes) were used and run on a StepOnePlus real time PCR system. Fold changes above 1.5 fold were subjected to statistical analysis (Mann-Whitney U test). Expression changes in AP groups were compared with the corresponding time-matched control groups and time-matched controls compared with control 0h.

Results: AP was confirmed by elevated plasma amylase (6–24h, peak at 24h). At 6h, the AP group showed trends for down-regulation of cholecystokinin receptor (CCKR)-B, 5-hydroxytryptamine receptor-1, tachykinin receptor-1 and galanin receptor-3 expression (P = 0.06). At 12h, CCKR-B showed a trend for up-regulation while at 24h, HTR-1d was up-regulated in the AP group (P < 0.03). At 48h, AP and control groups were comparable. Compared with the 0h group, the controls showed upregulation of histamine receptor-3 and voltage-gated potassium channel subtype 4.2 at 6h, metabotropic glutamate receptor-5 at 24h and voltage-gated sodium channel 1.9 at 48h.

Conclusion: The data suggest that in this model of AP relatively few genes display altered mRNA expression and 5HTRs may be involved in pain signalling.
The Role of Fingolimod and Sirolimus in the Therapy of Experimental Severe Acute Pancreatitis in the Rat
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Introduction: Severe acute pancreatitis (SAP) is associated with activation of the immune system, which leads to development of local and systemic organ failure, septic complications and high mortality. Cytokines derived from T-helpers may damage the acinus cells and thus determine the severity of disease.

Objectives: This study aimed at specific T-cell inhibition by a new class immunosuppressors (Sirolimus, Fingolimod and their combination) in order to reduce cell damage and improve the course of SAP.

Materials & Methods: A taurocholate model of SAP was used and 5 groups were compared: 1. Fingolimod; 2. Sirolimus; 3. Fingolimod+Sirolimus; 4. Cortisol 10 mg/kg; 5. Control NaCl. Drugs were applied i.v. at SAP induction, 6 hours later rats were sacrificed. IL-1, IL-6, IL-10, TNF-alpha, amylase, lipase were measured in serum and MPO tissue activity in pancreas, kidney, lung, liver and spleen. Edema, inflammation and necrosis were histologically determined in pancreas.

Results: Inflammatory reaction was significantly reduced in all 4 treated groups. Necrosis development was suppressed only by Fingolimod, Fingolimod+Sirolimus and Cortisol. IL-6 and IL-10 were significantly lower in these groups. Amylase was higher in all treated groups compared to the controls except for the Cortisol group. TNF-alpha, lipase and MPO activity were not affected by therapy.

Conclusion: Early specific suppression of T-helpers by Sirolimus and Fingolimod ameliorates the severity of SAP. Fingolimod reduces he development of pancreatic necrosis. Combination of both immunosuppressors did not show advantage to monotherapy with Fingolimod.

Small Intestinal Bacterial Overgrowth During Acute Destructive Pancreatitis in Rats
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Objective: Gut is recognized as main source of bacterial infection during acute destructive pancreatitis (ADP). Changes of amount of intestinal microorganisms may directly influence on rate of bacterial translocation to pancreatic tissue.

Aim: To investigate the changes of luminal and mucosal microbiota of small intestine during ADP.

Methods: In 70 Wistar rats ADP was induced by intraperitoneal injection of 250 mg/100 g of 20% L-arginine solution twice during 1 hour. Concentration of microorganisms in different parts of small intestine were investigated during 24–120 hours by bacteriological methods.

Results: In all parts of small intestine quantity of microorganisms has been increased throughout experiment. Main changes were found in distal ileum: level of Peptococcus spp., Staphylococcus spp., Clostridia spp. and especially Enterobacteria spp. reached 4,36–6,34 log CFU/g, whereas amount of physiologically useful autchthonous Lactobacteria spp., Bifidobacteria spp., E. feacalis felt twicely after 24 hours and they absolutely disappeared after 48 hours.在 jejunum and duodenum colonization by pathogenic strains of Clostridia spp. and Enterobacteria spp. were estimated in concentration 2,23–4,74 log CFU/g since 24 hours. Bacterial overgrowth in all parts of small intestine significantly correlated (p<0,05) with enhancing of bacterial translocation to pancreatic necrotic tissue.

Conclusion: During ADP increasing of amount of microorganisms appears in all parts of small intestine especially in distal ileum. Determination of small intestine bacterial overgrowth may be useful for prediction of infection complications of ADP.

Late But Not Early Activation of Trypsinogen is Dependent on Neutrophils in Acute Pancreatitis
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Introduction: Understanding the interrelationship between trypsinogen activation and inflammation in acute pancreatitis (AP) is of major importance for development of specific treatments for the disease.

Objectives: clarify the role of neutrophils in the pathophysiology of the experimental severe acute pancreatitis.

Methods: C57Bl/6 mice were pre-treated with anti Gr-1 antibody or control antibody before pancreatitis, which was induced by retrograde infusion of taurocholate into the pancreatic duct.

Results: Pre-treatment with anti-Gr-1 antibody caused reduction of neutrophils with 97%. Pancreatic trypsinogen activating peptide (TAP) and s-amylase levels were significantly increased 2 and 24 hours after induction of pancreatitis. Neutrophil depletion did not affect these parameters at 2 hours, but reduced values to normal after 24 hours. Pancreatic MPO and MIP-2 levels were significantly increased in the model after 24 hours. Anti-Gr-1 treatment caused a significant reduction of MPO, MIP-2, acinar cell necrosis, hemorrhage and oedema in pancreatic tissue after 24 hours. Similarly histology and MPO in the lung was normalized by neutrophil depletion. Intravital microscopy revealed a reduction of leucocytes with 97% also after anti-Gr-1 treatment.

Conclusion: Initial trypsinogen activation is indifferent of neutrophils, but a later activation is controlled by activated neutrophils and could be diminished by neutrophil depletion. Neutrophils contribute to pancreatic and lung tissue damage as well as MIP-2 formation in acute pancreatitis.
P130
Up-Regulation of CD45 in Acinar Cells of Rats with Acute Pancreatitis After Dexamethasone Treatment
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Introduction: CD45 is a transmembrane protein tyrosine phosphatase commonly expressed in haemopoietic cells, which play an important role in regulating immune responses.

Objectives: To study whether dexamethasone (Dx) is capable of modulating in rats with acute pancreatitis (AP) the expression of CD45 in pancreatic acinar cells, as they are the initial source of inflammatory signals during the disease.

Materials & Methods: AP was induced in male Wistar rats by retrograde infusion of 3.5% sodium taurocholate (NaTc) into pancreatic duct. Dx (1 mg/kg) was intraperitoneally administered 1 hour after inducing AP. In acinar cells the following was analyzed: phosphorylation of extracellular signal-regulated kinase (ERK) and c-Jun after inducing AP. In acinar cells the following was analyzed: phosphorylation of ERK and c-Jun after inducing AP. The role of AQP in the pathogenesis of acute pancreatitis needs further investigation.

Results: Dexamethasone (Dx) might exert its anti-inflammatory effect during NaTc-induced AP by up-regulating the phosphatase activity mediated by CD45.

Conclusions: Dexamethasone (Dx) might exert its anti-inflammatory effect during NaTc-induced AP by up-regulating the phosphatase activity mediated by CD45.

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P131
Effects of Toxic Factors on the Expression of Aquaporins in Human Pancreatic Ductal Cell Line
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Background: Aquaporins (AQPs) are water channels located in the plasma membrane that play critical roles in controlling the water transport of cells. Until now 12 AQPs have been identified. It is accepted that acute pancreatitis is a multicellular disease in which pancreatic ductal cells play an important role. Toxic agents inducing acute pancreatitis (such as bile acids and ethanol in high concentration) inhibit pancreatic ductal bicarbonate secretion, however, no information is available concerning the effects of the above mentioned agents on the regulation of AQP expression.

Aim: of this study was to investigate the effects of ethanol, bile acids and the inflammatory mediator TNF-α on the expression of AQPs.

Methods: Human pancreatic cell line of ductal origin (CAPAN-1) was treated with ethanol (EtOH; 1, 10, 100 mM), chenodeoxycholate (CDC; 0.1, 0.3, 0.5 mM), glycochenodeoxycholate (GCDC; 0.1, 0.3, 0.5 mM) or TNF-α (0.2, 20 ng/ml) for 6, 12, 24 and 48 hours and the mRNA expression of AQP isoforms (AQP1-12) was analyzed by real-time RT-PCR.

Results: All 12 AQPs were expressed in the CAPAN-1 cell line to a certain degree. AQP1, 3, 5, 6 and 11 were expressed at the highest levels while AQP2 and 4 were hardly detectable. In the CDC-treated group, the expression of AQP1, 3, 5, 6 and 11 decreased dose- and time-dependently. 24h treatment with 0.3 or 0.5 mM CDC highly downregulated the expression of AQP5 (the expression rate was less than 10% vs. the controls). Administration of 0.5 mM GCDC or high concentration of EtOH (100 mM) for 24h reduced the expression of AQP6 (20–30 and 30–40 % vs. the controls, respectively). Notably, there was a substantial recovery of the expression of AQPs at 48h in the GCDC and EtOH treated groups but not in the CDC treated group. 24h treatment with 20 ng/ml TNF-α downregulated the expression of AQP1, 5 and 6 (20–40% vs. the controls).

Conclusion: AQP1, 3, 5, 6 and 11 are strongly expressed in CAPAN-1 cells. Toxic agents downregulate the expression of AQPs. The role of AQP in the pathogenesis of acute pancreatitis needs further investigation.

Supported by OTKA, NKTH-TAMOP and MTA

P132
Intracellular ATP Depletion Induced by Non-Oxidative Ethanol Metabolites in Human Pancreatic Ductal Epithelial Cell Line
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Background: Excessive ethanol consumption is one of the most common causes of acute pancreatitis. Several studies suggest that the toxic effects of alcohol are mediated by its non-oxidative metabolites. Criddle et al. found that fatty acid ethyl esters (FAEE) induce reversible, dose-dependent calcium signalling and inhibit ATP production in isolated pancreatic acinar cells. However, no information is available concerning the effects of ethanol metabolites on pancreatic ductal epithelial cells (PDEC). The aim of this study was to characterize the effects of palmitoleic acid ethyl ester (POAEE) and palmitoleic acid (POA) on intracellular ATP level (ATP), in PDEC.

Methods: In our experiments human pancreatic adenocarcinoma cell line was used (CAPAN1). Different concentrations of ethanol, POAEE and POA were dissolved in standard HEPES solution. Changes in (ATP)i of CAPAN-1 cells were measured using microfluorometry.

Conclusion: PoaEE and PoA inhibit ATP production in pancreatic ductal epithelial cells.

Supported by OTKA, NKTH-TAMOP and MTA
**Results:** Administration of low concentration (10–50 mM) of ethanol did not induce (ATP) depletion; however, 100mM ethanol induced significant, but reversible (ATP), decrease. The non-oxidative ethanol metabolite POAEE had no significant effect on (ATP) level in neither of the tested concentrations (50–200μM). The free fatty acid POA, which is supposed to be the most toxic end product of non-oxidative ethanol metabolism, induced dose-dependent, significant and irreversible (ATP), depletion.

**Conclusions:** These results suggest that non-oxidative ethanol metabolites induce (ATP), depletion in pancreatic ductal epithelial cells, which can contribute to the development of acute pancreatitis. The effect of ethanol metabolites on ductal bicarbonate secretion needs further investigation.

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**P133**

**The Role of Neurokinin Receptors in the Inhibitory Effect of SP in the Pancreas**

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**Introduction:** Substance P (SP) is a well-known neuropeptide, which exerts its effect via neurokinin (NK) receptors. Recently, we have shown that SP inhibits secretin-stimulated fluid secretion in intact guinea pig pancreatic ducts and that this inhibitory effect of SP can be relieved by spantide, an NK receptor antagonist. In this study our aim was to investigate which NK receptor(s) mediate(s) the inhibitory effect of SP.

**Methods:** We isolated intra/interlobular ducts from guinea pig pancreas after an enzymatic treatment. The rate of HCO₃⁻ secretion was estimated by the alkali load technique using microfluorometry. Expression and localization of NK receptors were examined by immunocytochemistry.

**Results:** Basolateral administration of 10nM secretin significantly increased HCO₃⁻ secretion, which was completely blocked by application of 20nM SP. The NK1 antagonist RP67580 (10 μM) did not influence the inhibitory effect of SP. However, the NK2 antagonist, MEN10376 (10 μM) and the NK3 antagonist, SB218795 (10 μM) significantly reversed the inhibitory effect of SP by 42.5 ± 2.1 % and 68.1 ± 3.5 %, respectively. The NK1 receptors were localized to the luminal membrane, while the NK2 and NK3 receptors were identified both on the lateral and luminal membranes of the intra/interlobular ducts.

**Discussion:** In this study we characterized the localization of NK receptor subtypes in the guinea pig pancreas and showed evidence that SP inhibits HCO₃⁻ secretion via the laterally expressed NK receptors, namely the NK2 and 3.

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Abstracts

This work was supported by OTKA, Hungarian Academy of Sciences and National Development Agency.

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**P134**

**Assessment of Exocrine Pancreatic Function in the Conditions of Inhibition of NO-Synthases**

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**Introduction:** In our study it was showed that the inhibition of NO-synthases led to deficiency NO in pancreas, that conducted to infringement of mechanisms of regulation, it was accompanied by microcirculation changes, development of inflammation, dystrophy, apoptosis in pancreas. Our aim was to evaluate exocrine pancreatic function in the conditions of inhibition of NO-synthases.

**Methods:** Male 20 rats (Wistar), 20–22 week old, middle-weight (20.1 ± 3.5) g were used. NO-synthases were inhibited by Ng-nitro-L-arginin (Fluka) – 40 mg/kg, once a day, during 12 days. Assessment of exocrine pancreatic function estimated by definition of serum enzymes (amylase, lipase and trypsin). All rats were sacrificed, and pancreas was histologically examined.

**Results:** Histological examination of pancreas showed that as a result of blockade of NO-synthase in pancreatic tissue were formed morphological changes as inflammation with chronicity of the pathological process. Morphological changes were accompanied by changes function of external secretion of a pancreas. In six days the level of enzymes increased: significantly increased level of lipase and amylase in 1.7 times, the activity of trypsin – in 9 times. Further (on the twelfth day of pancreatitis of modelling) levels of amylase and lipase in the blood have considerably increased whereas trypsin activities, on the contrary, has considerably decreased.

**Conclusion:** The inhibition of NO-synthases leads to deficiency NO in pancreas, developed acute and then chronic pancreatitis and to changes of exocrine pancreatic function.
**P135**

**Mitochondrial Damage is Involved in the Pathogenesis of L-Lysine-Induced Acute Pancreatitis**

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**Introduction:** Large intraperitoneal doses of basic amino acids, such as L-arginine, L-ornithine or L-lysine, have been shown to cause pancreatic acinar cell injury.

**Objectives:** Our aim was to get insight into the mechanisms through which L-lysine damages the exocrine pancreas.

**Materials & Methods:** Male Wistar rats were injected intraperitoneally with 2 g/kg L-lysine and sacrificed 0-168 h afterwards. Biochemical and histological parameters of pancreatitis were determined. In particular we characterized the kinetics of L-lysine-induced mitochondrial damage, trypsinogen and nuclear factor-κB (NF-κB) activation which are commonly thought to play an important role in the development of acute pancreatitis. Isolated acinar cells were used to investigate the effect of 20 mM L-lysine (equimolar to a 2 g/kg dose) on Ca²⁺ signaling.

**Results:** Histology revealed interstitial edema, acinar vacuolisation, apoptosis and necrosis, and inflammatory infiltration in the pancreas. Serum amylase and lipase activities were significantly increased, whereas pancreatic amylase activity was decreased. L-lysine administration caused early pancreatic mitochondrial damage (from 1 h) that preceded the activation of trypsinogen (12-48 h) and NF-κB (24-168 h). Large concentrations of L-lysine inhibited the activation which are commonly thought to play an important role in the development of acute pancreatitis. Isolated acinar cells were used to investigate the effect of 20 mM L-lysine (equimolar to a 2 g/kg dose) on Ca²⁺ signaling.

**Conclusion:** The intraperitoneal administration of L-lysine induces severe acute necrotizing pancreatitis. Early pancreatic mitochondrial injury may lead to the development of acute pancreatitis.

**P136**

**Attenuation of Experimental Severe Pancreatitis by Inhibition of Glutaminyl Cyclase (QC)**

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Severe acute pancreatitis (AP) is characterized by pancreatic injury and systemic inflammation. MCP-1 plays an important role as proinflammatory chemokine in the pathogenesis of AP. MCP-1 is posttranslationally modified by N-terminal pyroglutamate formation by QC- and iso-QC.

We tested whether inhibition of QC could diminish pancreatic injury or cytokine and chemokine levels in mice with experimental severe AP.

**Methods:** AP was induced by retrograde injection of 2% taurocholate into the pancreatic duct. Controls received saline. The QC-inhibitor PQ529 (100mg/kg) was orally applied 1 hour before and 5 hours after induction of pancreatitis. Animals were sacrificed 24 hours after induction of pancreatitis. Amylase and lipase in serum were enzymatically measured.

**Results:** QC activity is present in exocrine pancreas cells and is mainly represented by iso-QC. Western blotting indicates that iso-QC is present in vesicular fractions of acinar cells. Application of QC-inhibitor strongly reduced amylase, lipase, MCP-1 and IL-6 in serum, and MCP-1 and IL-6 levels and trypsin activity in the pancreas.

**Conclusion:** Treatment of mice suffering from severe AP by a QC-inhibitor attenuates pancreatic injury. Reduction of intrapancreatic zymogen activation indicates a close relation between inflammation and cell injury.

**P137**

**Pancreatic Remnant Changes After Surgery**

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**Introduction:** Pancreatoduodenectomy is the procedure with 100 years history and is accepted as treatment of choice in pancreatic-biliary area malignancies. The late outcome of PD is monitored by

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immune-modulatory effects of p8.

It plays a key role in cellular stress response and is involved in inflammation in pancreatic tissue during acute experimental pancreatitis (AP).

Aim: Immunophenotyping of p8+/- mice during the phase of AP.

Method: Histological (pancreas, spleen, liver, lung, thymus) and flow cytometric analysis of the lymphocyte subpopulations (CD3, CD4, CD8, B220), macrophages (CD11b) and granulocytes (Gr-1) in whole blood and spleen comparing p8+/+ with p8+-/- mice before and after caerulein-induced AP. Significance level p<0.05.

Results: Untreated p8+/- mice showed a significant splenomegaly without differences in body weight in comparison to p8+/+ mice. H.E.-staining revealed architectural changes with partial reduction of lymph follicles/white pulp and internal structure. In addition these spleens had an increased iron deposition. Pancreas, lymph nodes, thymus, lung and liver did not differ evidently in histological sections.

During AP no differences in the number of B- and different T-lymphocytes subgroups were detectable between and p8+/+ and p8-/- mice. However p8-/- mice had untreated as well as during the AP a significantly increased number of granulocytes and myeloid-derived suppressor cells in peripheral blood.

Discussion: p8-/- mice reveal no obvious phenotype in development and behaviour but they have variations in composition of immune system and splenic constitution.

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P139
The Dynamics of Sonographic Indices of Pancreatic Fatty Dystrophy in Patients with Chronic Pancreatitis (CP) and Obesity During Treatment by “Grinization” Multinutrient Complexes

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The diagnosis of fatty dystrophy of the pancreas is very complicated. A CT scan is usually used.

Objective: to examine the dynamics of the sonographic signs of fatty dystrophy of the pancreas under the influence of treatment by “Grinization” multinutrient complex.

Materials & Methods: The study includes 64 patients with CP and obesity. The control group includes 30 healthy. Patients and healthy underwent a CT scan taking into account density of pancreatic tissue according to the Hounsfield scale. Moreover, an ultrasound histography of the pancreas that takes into account indicators of L, N, Kgst was performed. Besides, we calculated the F index (the formula includes the body mass index, atherogenetic index, as well as N and P indicators of ultrasonic histography). 32 patients received “Grinization” in a complex with the traditional treatment of CP (main group). 32 patients who were included into the comparison group, they received only traditional treatment of CP.

Results: There was a significant improvement in L (reduction), N and Kgst (increase) under influence of treatment in the main group. In the main group the F index significantly increased. A positive correlation between the F index and the density of pancreatic tissue according to the Hounsfield scale was revealed.

Conclusions: The ultrasound histography can be used to perform the diagnostics of pancreas fatty dystrophy in patients with CP and obesity. “Grinization” complexes must be included into the complex therapy contributed to the reduction of intensity in pancreas fatty dystrophy.
P140

The Clinical Picture of Chronic Pancreatitis on a Background of Obesity

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Peculiarities of clinics of chronic pancreatitis in patients with obesity are not studied.

Objective: to study peculiarities of clinical manifestations of chronic pancreatitis on a background of obesity.

Materials and Methods: The study included 64 patients with chronic pancreatitis on the background of obesity with various degrees. We analyzed complaints and data of palpation.

Results: Chronic pancreatitis, occurring on the background of obesity, in 53.1% of cases is characterized by intense abdominal pain which is localized mainly either in the epigastrium and both hypochondria, or in the epigastrium and right hypochondrium. 45.3% of patients with combined pathology are worried by expressed dyspepsia, mainly nausea and bitter taste in the mouth. Clinical manifestations of exocrine pancreatic insufficiency develop in only 6.2% of cases, and symptoms of diabetes — in 14.1% of cases. One-third of patients complain of aesthetic problems associated with obesity, about a quarter of patients has a low exercise tolerance. In more than a half of the patients painfulness in the Shoffar zone is present. In all patients a moderate increase of liver due to nonalcoholic steatohepatitis or non-specific reactive hepatitis was determined during palpation.

Conclusion: In patients with chronic pancreatitis on a background of obesity in a half of the cases there is an intense abdominal pain, dyspepsia; but the clinical symptoms of exocrine and endocrine pancreatic insufficiency occur rarely. Hepatic pathology is diagnosed in all cases.

P141

Pre-Malignant Pancreatic Alterations at Chronic Pancreatitis

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The aim of research: to study the inter-relations of inflamed and neoplastic pancreatic alterations at the different clinic-morphologic variants of complicated chronic pancreatitis (CP).

Methods & Materials: 802 patients with complicated CP were examined. They underwent 724 operations, among them – 574 low-invasive ones, 148 direct pancreatic surgeries, including 35 pyloro-preserving pancreatico-duodenal resections, 17 duodenal-preserving resections of pancreatic head, 74 medial resections of the pancreas. There was no lethality among all patients operated. The pancreatic fragments resected were investigated histologically. Pre-malignant alterations of ductal epithelium were assessed according to classification of pancreatic intra-epithelial neoplasm (Pan-IN, 1996); semi-quantitative pancreatic fibrosis estimation was performed (index G.Kloppel, 1996), the inflamed activity of pancreatic parenchyma was determined by lympho Leukocyte infiltration extent.

Results of investigation: Dysplastic alterations of pancreatic ductal epithelium had mosaic character without dependence on pancreatic organ inflammation, fibrosis extent and disease duration. Complex morphologic assessment of the whole sample has allowed to reveal the individual risk of pancreatic cancer to collect groups for post-operated treatment.

Conclusion: Patients with verified pre-malignant pancreatic alterations were dynamically examined during 8 or more years. There were no cases of pancreatic cancer development. The observation presented has shown the efficacy of complex treatment and secondary prophylaxis of pancreatic cancer.
The Preliminary Study of Relationship Between Occult Pancreaticobiliary and Biliary Stone

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Introduction: Pancreaticobiliary reflux is usually known as an important risk factor for biliary malignant, and usually occurs in patients with pancreaticobiliary maljunction(PBM). Recently, several reports have been published on the reflux of pancreatic juice to bile duct without PBM, this has been termed as occult pancreaticobiliary reflux(OPR). Recent years, several reports have found OPR is associated with biliary malignant closely, especially gallbladder cancer and maybe it have correlation with some biliary benign diseases.

Objectives: Try to reveal the relationship between occult pancreaticobiliary reflux and biliary stone.

Patients and Methods: We sampled bile from the bile duct in thirty-one patients without PBM who had undergone endoscopic retrograde cholangiopancreatography (ERCP) or surgery because of biliary stone. Measure the level of active amylase enzymes in the serum within 48 hours before ERCP or surgery and active amylase enzymes in the bile sampled from the bile duct immediately. We defined the level of active amylase enzymes in the bile no less than the level of active amylase enzymes in the serum as occult pancreaticobiliary reflux.

Results: The incidence of occult pancreaticobiliary reflux in patients with choledocholithiasis is 100%(8/8). The active amylase enzymes in the serum is 51.88 ± 19.79IU/L, the active amylase enzymes in the bile is 1047.75 ± 1317.26IU/L. The incidence of gallbladder stone is 80% (4/5). The active amylase enzymes in the serum is 37.25 ± 15.22IU/L, the active amylase enzymes in the bile is 94.5 ± 81.82IU/L. The incidence of occult pancreaticobiliary reflux in patients with choledocholithiasis and cholecystolithiasis at the same time is 75% (11/15). The active amylase enzymes in the serum is 45.22 ± 22.99IU/L, the active amylase enzymes in the bile is 2456.89 ± 3311.99IU/L. Additionally, we found occult pancreaticobiliary reflux didn’t happen in people with calculus of intrahepatic duct and choledocholithiasis at the same time (0/2) and calculus of intrahepatic duct(0/1).

Conclusions: Occult pancreaticobiliary reflux is associated with biliary stone closely.

Altered Brain Microstructure Assessed by Diffusion Tensor Imaging in Patients with Chronic Pancreatitis

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Introduction: In patients with painful chronic pancreatitis (CP) there is increasing evidence of abnormal pain processing in the central nervous system.

Objective: Using magnetic resonance diffusion tensor imaging, we characterized brain microstructure in areas involved in the processing of visceral pain and correlated these findings to clinical pain scores.

Methods: Twenty-three patients with CP pain and 14 controls were studied in a 3T MR scanner. Apparent diffusion coefficient (ADC) (i.e. diffusivity of water) and fractional anisotropy (FA) (i.e. organization of fibers) values were assessed in the amygdala, cingulate cortex, insula, prefrontal cortex and secondary sensory cortex. Daily pain scores and the brief pain inventory short form were collected one week before the investigation.

Results: In grey matter, the patients had increased ADC in amygdala, cingulate cortex, insula, and prefrontal cortex, as well as decreased FA values in cingulate cortex and secondary sensory cortex. In white matter, patients had increased ADC in insula and prefrontal cortex, and decreased FA values in insula and prefrontal cortex (all P-values <.05). No effect modifications from diabetes or alcoholic etiology of CP were seen, except from alcoholic etiology in anterior insula grey matter and prefrontal cortex white matter (both P = .03). Microstructural changes in cingulate and prefrontal cortices were correlated to the patients’ clinical pain scores (P < .05).

Conclusion: Our findings suggest that microstructural changes of the brain accompany pain in CP. The changes are likely a consequence of ongoing pain and structural reorganization of the neumatrix as also seen in other diseases characterized by chronic pain.
Clinical Significance of Transforming Growth Factor Beta-1, Monocyte Chemoattractant Protein-1, Soluble Type Fractalkine and Hyaluronic Acid in Patients with Chronic Pancreatitis and Pancreatic Adenocarcinoma

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1. Determination of circulating levels of chemokines, extracellular matrix components has been proposed as a reliable method to assess the activity of fibrogenetic processes in patients with pancreatic diseases.

2. The study aim was to examine serum levels chemokines (soluble fractalkine and MCP-1), cytokine (TGF-beta1) and marker of extracellular matrix i.e., hyaluronic acid (HA) in patients with chronic pancreatitis (CP) and pancreatic adenocarcinoma (PA) and to assess the correlation between them.

3. The study included 37 patients with CP, 30 with PA and 10 healthy controls. Serum TGF-beta1, MCP-1, soluble type fractalkine (s-Fr) and HA concentrations were determined by ELISA (Corgenix UK Ltd R&D Systems).

4. Patients with CP as compared with controls had significantly greater plasma HA (270,9 vs 44,9 ng/mL; p<0,03), TGF-beta1 (1359,9 vs 281,6 pg/mL; p<0,0001), s-Fr (2,054 vs 0,82 ng/mL; p<0,0005), but not MCP-1 (482 vs 320 pg/mL; p=NS) levels. Similarly, PA patients showed significant higher levels of HA, TGF-beta1, s-Fr but not MCP-1 than controls. In patients with CP duration more than 5 years serum level of s-Fr was significantly higher compared to CP patients with shorter disease clinical course. No significant differences between serum level of TGF-beta1, s-Fr, HA and MCP-1 depending on and smoking status, etiology, CP stage, endocrine insufficiency and other disease complications has been detected. In patients with PA no correlation has been found between tumor size, localization and endocrine dysfunction and serum MCP-1, TGF-beta1, s-Fr and HA levels.

5. Serum concentrations of TGF-beta1, s-Fr and HA concentration are elevated in patients with CP and PA, which confirm that pancreatic fibrosis plays a central role in both diseases. This study revealed a relation between the duration of CP and serum concentration of s-Fr. Moreover, the results suggest that the measurement of serum HA, TGF-beta1 and s-Fr could be a noninvasive approach for the detection of pancreatic fibrosis in the course of chronic pancreatitis.
**P147**

**Role of Nitric Oxide in Diagnostics of Exacerbation of Chronic Pancreatitis**

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**Objectives:** To evaluate clinical significance of nitric oxide level as criterion of exacerbation of chronic pancreatitis (CP).

**Patients & Methods:** Study involved 129 patients with CP (96 m & 33 f), mean age 46.9 ± 9.2 yrs. Intensity of pain was measured by 10-point rank scale. Nitric oxide (NO) level was counted in blood samples.

**Results:** As a diagnostic level of NO to identify exacerbation of CP was proposed concentration above 120 micromoles per liter. The direct correlation was found between the NO level and intensity of pain (r=0.69, p<0.01) and between the NO level and size of the head of pancreas associated with inflammation (r=0.59, p=0.04). In patients with intensity of pain more than 5 points the sensitivity of the NO level was 97%, specificity 57%. In patients with the size of pancreatic head more than 31 mm the sensitivity of the NO level was 42%, specificity 62%.

**Conclusion:** The evaluation of NO level may be used as an additional criterion of exacerbation of chronic pancreatitis.

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**P148**

**Assessment of Salivary Electrolytes in Chronic Pancreatitis**


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**Introduction:** CFTR partly governs fluid, chloride and bicarbonate pancreatic secretion. CFTR dysfunction, as in Cystic Fibrosis (CF), leads to pancreatic atrophy and fibrosis. Pancreatic bicarbonate decreases early in the course of chronic pancreatitis. Factors associated with chronic pancreatitis (smoking, alcohol and autoimmunity) may alter CFTR function, and some pancreatitis patients carry CFTR gene mutations. CFTR also controls salivary secretion. CFTR dysfunction affecting pancreatic secretion could be uncovered analyzing salivary secretion.

**Objective:** to assess salivary electrolytes in patients with proven chronic pancreatitis.

**Methods:** Basal and stimulated salivary secretion was collected protected from air-CO2 contamination from 34 non-smoking healthy subjects, 28 Cystic Fibrosis and 42 chronic pancreatitis patients of any etiology. Bicarbonate, pH, chloride, sodium and osmolarity were determined. A sweat tests was performed. Patients were studied for CFTR gene mutations (DGGE-direct sequencing).

**Results:** Chronic pancreatitis patients had higher chloride concentration in sweat than healthy controls (43.6±2.4 vs 30.2±2.2 mEq/L; p<0.0003), but less than CF patients (102.8±6.1). Chronic pancreatitis patients had lower salivary pH (6.74±0.05) and bicarbonate (6.6±0.9 mEq/L) than controls (7.05±0.04 and 8.6±0.6), but higher chlorate (46±3 vs 25±1 mEq/L) and osmolarity (115±8 vs 76±3 mOsm/L). Salivary pH, bicarbonate, chloride and osmolarity were similar in chronic pancreatitis and in CF patients. CFTR gene mutations were identified in 33% of chronic pancreatitis and in 100% of CF patients. In chronic pancreatitis sweat and salivary electrolytes were independent of the presence of CFTR mutations.

**Conclusion:** Sweat and salivary electrolyte abnormalities suggest global CFTR dysfunction in patients with chronic pancreatitis that may have pathophysiological implications.

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**P149**

**Pancreatic Exocrine Function and Cardiac Iron in Thalassemia Patients and Other Rare Anemias**

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**Introduction:** Patients with thalassemia major (TM) and other rare anemias need lifelong blood transfusions. Iron overload is a common cause in these chronically transfused patients. Cardiomyopathy due to cardiac siderosis and diabetes mellitus are well known complications in TM patients. The heart and the pancreas predominantly load non-transferrin-bound iron.

**Objectives:** A simply diagnostic method to identify patient at risk for this life-threatening complication is still missing. Liver iron concentration does not correlate with cardiac iron concentration. It has been shown that myocardial R2* measurement by MRI can recognize patients with cardiac siderosis, but this technique is not available so far in clinical routine in most thalassemia centers.

**Patients & Methods:** 27 transfusion dependent TM patients (age 11 – 47 years, 9 females), 12 other patients with iron overload due to blood transfusion (MDS, AML, sickle cell disease, diamond-blackfan anemia and congenital dyserythropoietic anemia) and 5 patients with resorptive iron loading (hereditary hemochromatosis and non-transfused thalassemia intermedia) had measurements of liver iron by ECG gated single breathhold multi-echo MRI-R2*, liver iron concentration by SQUID biosusceptometry, ferritin and pancreatic exocrine function by serum amylase and lipase, respectively.

**Results:** Lipase significantly correlated with cardiac R2* (R2 = -0.45, p=0.0023), while amylase only showed a negative trend (R2 = -0.29, p=0.057). No significant correlation (p > 0.2) was observed with any other parameter (age, liver iron concentration or ferritin). ROC analysis (area: 0.88) for detecting patients with cardiac siderosis by lipase revealed equal true positive and negative rates of 82 % at a lipase cut-off level of 19 U/L.

**Conclusion:** Patients at risk of elevated cardiac iron levels can be identified by the exocrine pancreatic function parameters serum lipase and amylase and should therefore in the case of subnormal pan-
creatic amylase or lipase levels urgently undergo cardiac iron assessment by MRI.

**Clinical Science – Chronic Pancreatitis III**

**P150**

Facilities of the Magnesium Preparation in the Treatment of Chronic Pancreatitis (CP)

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Data on magnesium deficiency in CP appeared in the literature in recent years. Nevertheless, preparations of magnesium in the treatment of CP were not used.

**Objective:** To evaluate the efficacy of Magne B6 preparation in the treatment of CP.

**Materials & Methods:** 48 patients with CP were examined. They were divided into 2 groups: 24 patients in each group. In addition to conventional therapy of CP in study group we administered Magne B6 (1 ampoule t.i.d.) for a month. Patients of a comparison group received only conventional treatment. The dynamics of clinical manifestations of CP were studied.

**Results:** Under the influence of treatment in the comparison group the pain disappeared in 5 (20.8%), decreased in 11 (45.8%), remained unchanged in 6 (25.0%), increased in 2 (8.4%) patients. In the main group dynamics of pain syndrome was more significant. The pain disappeared in 9, decreased in 13, remained unchanged in 1, increased in 1 patient, which is respectively 37.5%, 54.1%, 4.2% and 4.2% of cases. Inclusion of Magne B6 had a positive impact on dynamics of asthenic syndrome. In the main group, it disappeared or significantly decreased in 18 (75.0%) patients, in the comparison group — in 10 (41.7%) patients.

**Conclusion:** It is reasonable to include Magne B6 in treatment of CP. It contributes to more significant positive dynamics of pain and asthenic syndrome in comparison with conventional therapy.

**P151**

Saving Parenchyma Direction in Chronic Pancreatitis Surgery

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**Introduction:** uncorrected promptly pancreatic ductal hypertension in chronic pancreatitis (CP) has progressing flow with further development of severe complications, exo- and endocrine insufficiency.

**Objective:** To develop a new type of surgery in CP patients that eliminates pancreatic ductal hypertension and entirely maintains pancreatic parenchyma.

**Patients & Methods:** 65 patients were analysed: 57 (87.7%) men, 8 (12.3%) women, age 34–62. Mean age was 47. They all had severe forms of CP (calculose, pseudotumorose, fibrose-cystic). 34 patients had obstructive jaundice (bilirubin: 29.1–83.4 mmol/l). Wirsung’s duct diameter was 5–12 mm. Alcohol CP was in 59 (90.8%) patients, biliary – 2 (3.1%), idiopathic – 4 (6.1%). Patients were examined with CT, US, ERCP, intraoperative US, IgG, rheumatoid factor, endogen insulin, C-peptide, CA 19-9, parathyroid gland hormone, faecal elastase. Beger procedure was performed in 9 (31.1%), Frey – 13 (44.8%), Traverso-Longmire – 7 (24.1%) in control group (n = 29).

**Results:** One patient died in control group after Traverso-Longmire procedure. Bleeding from pancreaticojjunostomy was in 2 patients after Beger and Frey procedures. In up to 5 year term all patients had exo- and endocrine insufficiency; 2 patients still had pain in control group after Frey procedure. 2 patients had bleeding from pancreaticojjunostomy with no mortality in main group, 3 – remained diabetic and 6 – still had to have enzymes on every day base. No patient suffered of severe pain or dyspepsia in main group. Quality of life in both groups was examined by SF-36.

**Conclusion:** New parenchyma saving technique eliminates pancreatic ductal and biliary hypertension and has better results than resection type procedures in CP.

**P152**

Complications of the Proximal Pancreatic Resections for Chronic Pancreatitis

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**Objective:** An assessment of the complication rate after the proximal pancreatic resections for chronic pancreatitis (CP).

**Method:** A retrospective study of 223 cases of the proximal pancreatic resections for CP. The Beger procedure was performed in 102 (45.7%) cases, the Berne operation – in 46 (20.6%), the Frey procedure – in 13 (5.8%) and pancreaticoduodenectomy (PD) – in 62 (27.8%) cases. PD was pylorus-preserving (pPD) in 41 (66%) patients.

**Results:** Overall postoperative mortality was 3.1%. Complication rate for the procedure was the following: Berger – 22.5%, Frey – 7.7%, Berne – 14 30.4%, pPD – 63.4%, PD – 33.3%. After the Beger operation acute pancreatitis was observed in 10 (9.8%), pancreatic fistula in 9 (8.8%), liver abscess in 1 (0.98%), bile leaks in 5 (4.9%), duodenal wall necrosis in 1 (0.98%), bleeding in 10 (9.8%), liquid collections in 4 (3.9%) cases. After the Frey procedure acute cholecystitis was diagnosed in 1 (7.7%) patient. After the Berne modification acute pancreatitis in 6 (13%) cases, pancreatic fistula in 3 (6.6%), bile
leaks in 1(2.2%), bleeding in 2(4.4%) and peritonitis in 1(2.2%) cases were met. After PD bile leakage developed in 1(4.7%), bleeding – in 1(4.7%) and anastomotic leakage – in 5(23.5%) patients. pPD was accompanied with pancreatic fistula in 13(26.5%), liver abscess in 1(2.4%) and bleeding in 2 (4.8%) cases. General complication rate was significantly higher after pPDs comparing to duodenum-preserving procedures (p<0.05). Conservative tactics and mini-invasive measures were effective in 21.1% of patients with 12.5% reoperation rate.

**Conclusion:** Duodenum-preserving head resections are equally as effective as PD in CP and involve a lower mortality and complication rates.

**P153**

**Quality of Life in Chronic Pancreatitis Patients with Different Fibrotic Changes of the Pancreas**

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**Objective:** To study the influence the pancreatic fibrosis severity on the chronic pancreatitis (CP) patients quality of life (QoL) and pain intensity (PI).

**Methods:** Thirty six (82%) men and 8 (18%) women (mean age 42.9±10.3 years) with CP were prospectively assessed perioperatively. Berne modification – in 29, pancreaticoduodenectomy – in 1, Beger operation in 21 patients were performed. The QoL and PI were evaluated with the help of SF-36 questionnaire and visual analogue scale (VAS). The grade of the pancreatic fibrotic changes was determined morphometrically with the use of a standard LAS (Leica Application Suit) program (Leica Microsystems GmbH (Germany)) at magnification x 100. Connective tissue distribution area was measured by Values gauge, recalculated to the square of 1 mm² thereby allowing to get the mean values and fibrosis proportion. Spearman test was used as a correlation tool.

**Results:** The were no correlation between the grade of pancreatic fibrosis and any of eight SF-36 scales or PI score (PF-0.04, RP-0.09, BP –0.011, GH–0.268 VT–0.125, SF-0.086, RE–0.098, MH–0.15 VAS-0.227) (p>0.05).

**Conclusion:** In accordance with the data obtained the quality of life and intensity of pain doesn’t depend on the degree of pancreatic fibrotic changes in patients with CP.

**P154**

**Results of the Beger Procedure Without Proximal Pancreateoenterostomy and the Bern Operation for Chronic Pancreatitis**

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**Objective:** To compare the results of the Beger procedure without proximal pancreateoenterostomy (BwPPE) and the Berne modification (BM) for chronic pancreatitis (CP).

**Method:** Eighty two consecutive procedures for CP were prospectively analysed (2008–2011). The duration of surgery, postoperative complications and length of the hospital stay were assessed. The quality of life (QoL) and pain intensity (PI) were prospectively evaluated pre- and postoperatively (6–24 months) with the help of SF-36 questionnaire and visual analogue scale (VAS).

**Results:** The time of surgery for the BwPPE group was 292+/−51 vs 228+/−50 minutes for BM group (p < 0,05), the volume of the intraoperative blood transfusion was 672+/−525 ml vs 319+/−423 ml (p < 0,05), the duration of ICU stay – 3,3 vs 2.6 days (p<0,05), postoperative hospital stay – 26,3+/−12,9 vs 19,6+/−9,6 (p<0,05), complication rate – 28.2% vs 32.5% (14 cases), p>0,05. Patients QoL did not differ significantly: Physical Functioning index (PFI) after BwPPE was 53,6(50,4–56,7) vs 50,5 (45,7–53,0) after BM (p>0,05) and Social Functioning Index (SFI) was 47,2(35,5–50,7) vs 45,7(37–52,2), p>0,05. QoL in both subgroups was significantly after surgery. The pain intensity, evaluated by V AS was comparable: 2 (0–4) after BwPPE vs 3 (0–5) after BM (p>0,05). Exocrine and endocrine pancreatic function in both groups was comparable during follow-up. Diabetes mellitus was found 1,5 year after surgery in 1 case after BwPPE and once after BM.

**Conclusion:** Beger procedure without PPE is equally as effective as Bern modification in relieving pain and improving QoL in CP patients.

**P155**

**Long-Term Results of the Duodenal Dystrophy Treatment**

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**Background:** Duodenal dystrophy (DD) is the chronic inflammation of the aberrant pancreatic tissue in the duodenal wall and its management remains a topic of discussion fluctuating between pancreaticoduodenectomy (PD) and conservative treatment.

**Objective:** Assessment of long-term results of conservative and surgical treatment of the DD.

**Method:** Retrospective analysis of 38 case reports of the DD cystic forms treatment (2005–2010).
Results: Constant or relapsing abdominal pain was revealed in 100%, weight loss in 24(63%), vomiting in 11(29%) and jaundice in 8(21%) of cases. The most precise diagnostic methods were CT, MRI and endoUS. Twenty two patients were operated on by pancreatico – and cystoenterostomy (4), PD (13), total pancreatic head resection with the resection of the second part of the duodenum (2), duodenum-preserving pancreatic head resection (2) and partial gastrectomy (1). In five cases pancreas-preserving technique was used: resection of the second part of the duodenum (RSPD) with direct duodeno-duodenostomosis (2), RSPD with jejunal interposition (2) and subtotal dudeneectomy (1). Postoperative lethality was zero. Full pain control and all symptoms disappearance were achieved after pancreas-preserving procedures, in 11(85%) of cases after PD and in 16% of cases after the pancreatic head resections and draining procedures. In two cases the severe chronic “orthotopic” pancreatitis development of diabetes mellitus was observed after PD.

Conclusion: PD is the main surgical modality for DD treatment. Pancreas-preserving procedures can be the optimal methods for duodenal dystrophy surgery and real alternative to PD in cases of unaffected orthotopic gland.

Introduction: As the pancreas and the spleen lie in close proximity, splenic parenchymal complications (SC) may occur in the course of chronic pancreatitis (CP).

Purpose: to describe SC treatment and outcome, and find possible risk factors.

Material & Methods: We performed a retrospective record analysis and a subsequent prospective follow-up in a surgical series of 190 CP patients operated between 1996 and 2005. Average duration of CP was 16.81 years. Prevalence, treatment and outcome of SC patients were recorded. Statistical correlations of SC to 12 independent variables (possible risk factors) were calculated.

Results: SC prevalence was 4.73%. Nine male patients with alcoholic CP (mean age=43.3 years, mean CP duration =4.96 years) had: intrasplenic pseudocysts (n = 5), splenic infarction (n = 1), splenic rupture inside a huge pseudocyst enclosing the spleen (n = 1), subcapsular hematoma (n = 1) and spontaneous splenic rupture (n = 1 cirrhotic patient). Eight patients underwent splenectomy, and distal pancreatectomy was associated (excepting the splenic infarction). No postoperative deaths occurred. One intrasplenic pseudocyst was managed conservatively. We found that acute episodes, splenic vein thrombosis and distal pseudocysts are strong risk factors for SC (p<0.005). Amount of alcohol intake was not a risk factor, but it was correlated with acute episodes.

Conclusion: SC prevalence in our surgical CP series was higher than previously reported. SC occurs in young alcoholic males, early in the CP course. Presence of risk factors implies a closer monitoring, in order to prevent intra-peritoneal hemorrhage. Splenectomy (+ distal pancreatectomy) is usually required.

Heart Rate Variability in the Assessment of Vegetative Regulation in Patients with Chronic Pancreatitis (CP)

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Disorders of vegetative regulation in CP are not studied.

Objective: to study vegetative disorders in CP.

Materials and Methods: The study included 53 patients with CP and 35 healthy. Heart rate variability at rest and active orthostasis were examined. Parameters characterizing the activity of various parts of the vegetative nervous system were calculated: Mo — mode (humoral channel of cardiac rhythm central regulation); AMo — mode amplitude (central nervous unit of sympathetic regulation); VR — variational range (autonomic parasympathetic unit).

Results: Mo indices in patients with CP (0,92±0,05 lying and 0,73±0,02 standing) were not significantly different from control group (0,86±0,04 and 0,73±0,01, respectively), indicating the humoral regulation of the vegetative nervous system preserving in CP. Data of the AMo analysis were significantly higher (p <0,001) in CP patients lying 32,10±0,29 and standing 31,23±0,21; in the control group respectively 18,7±0,24 and 22,1±0,64. This indicates the strengthening of the sympathetic level of central regulation in patients with CP. VR indices in patients with CP were significantly higher than in healthy in the supine position (0,20±0,01 and 0,16±0,01, p<0,01), but decreased in CP patients in orthostasis (0,17±0,03 and 0,17±0,01); this reflects the violation of the parasympathetic autonomic regulation at rest and it's strengthening during exercise.

Conclusions: In CP there is a deviation by type of autonomous parasympathetic regulation reduction at rest, reduction of central vazoreflex and baroreflex mechanisms activity at rest and during exercise.

Endoscopic Stenting of the Pancreatic Duct in Patients with Chronic Pancreatitis – Long Term Results

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Objectives: Chronic pancreatitis with obstruction of the main duct often requires surgery. Some patients, however, refrain from surgery or can not be operated due to other problems, for example due to the thrombosis of the portal vein. The current prospective study investigated clinical success in 17 patients after initial endoscopic retrograde pancreatography and relapse rates during a 2-year follow-up period.

Methods: Seventeen patients with chronic pancreatitis (stage III according to the Cambridge classification) were treated by sphincterotomy and stenting. Main procedures were: endoscopic pancreaticography and relapse rates during a 2-year follow-up period.

Results: After initial endoscopic retrograde pancreatography and stenting. Main procedures were: endoscopic pancreaticography and relapse rates during a 2-year follow-up period.
terotomy and stent insertion. Endoscopic retrograde pancreaticography failed in 2 patients (total of 19 patients).

**Results:** Strictures were cannulated, dilated, and stones were removed with a Dormia basket in 13 of 17 patients. Extracorporeal shock wave lithotripsy was necessary in 5 patients. Polyethylene stents (7F-11.5F) were placed into the dilated pancreatic duct. Mean duration of internal pancreatic stenting was 5.6 months. Three of 17 patients had recurrence of pain during the first follow-up year after stent extraction; in the second follow-up year, another 2 patients had a relapse. Overall, patients’ assessment of the stent therapy revealed complete satisfaction in 17 of 19 patients.

**Conclusions:** Endoscopic stent therapy is a safe, minimally invasive, and effective procedure in patients experiencing pain attacks during chronic pancreatitis associated with dilated pancreatic duct. According to our results, a relapse rate of approximately 30% can be expected within 2 years after stent extraction. These patients may be treated by repeated stent therapy.

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**P159**

**Results of Pancreatic Head Resections for Chronic Pancreatitis with Small and Wide Duct**

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**Objectives:** To assess the results of the duodenum-preserving pancreatic head resection (DPPHR) for chronic pancreatitis (CP) with small and wide main pancreatic duct.

**Methods:** Prospective study of 85 consecutive patients underwent the Beger and Berne procedures. All the patients were divided into 2 groups depending on the width of the main pancreatic duct (MPD). Perioperative parameters, quality of life (QoL) and pain intensity (PI) were prospectively evaluated pre- and postoperatively with the help of SF-36 questionnaire and visual analogue scale (VAS) in 50(59%) patients with the duct < 6 mm (SD), and in 35 (41%) patients with the duct >6 mm in diameter (WD). Observation time: 6–24 months.

**Results:** Demographic and preoperative clinical parameters according to SF-36 and VAS data were comparable within groups (p > 0.05). Mean operating time in the SD group was 255 vs 272 minutes in WD group (p > 0.05), the blood transfusion volume was 410 ml vs 384 ml (p > 0.05), the mean hospital stay length was 19.5 vs 21 days (p > 0.05). ICU stay (2.6 days) and complication rates did not differ (p > 0.05) between the groups. Physical Functioning Index in SD group was 52.46-55 vs 52.3(50-55) in WD group (p > 0.05) and Social Functioning Index was 46.4(34-51) vs 46.2(41-50) (p > 0.05). The pain intensity decreased significantly and the difference was comparable: 3(1–5) for SD vs 2(0–4) for WD group (p = 0.05).

**Conclusion:** The Beger and Berne procedures are equally effective for the treatment of CP patients with small or dilated pancreatic duct.

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**P160**

**Results of Endoscopy and Surgery for Bile Duct Stricture Due to Chronic Pancreatitis**

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**Aim:** To compare the outcome of endoscopic (ET) and surgical therapy (ST) for benign bile duct stricture (BBS) due to chronic pancreatitis.

**Methods:** From 2003 to 2009, 39 patients were referred in our centre for BBS due to chronic pancreatitis. Sixteen (41%) patients underwent only transpapillary drainage (with tube exchange every 6 months or in case of obstruction) and 23 underwent surgical biliary drainage (after endoscopic procedures n = 17). Successful therapy was defined as a stent-free condition with no hepatic disorders (bilirubin, alkaline phosphatase). The follow-up was >6 months for all patients.

**Results:** Among patients treated by ET, mean number of biliary procedures was 3 (1–10) per patient (versus 1 for patients with ST) and the mean number of stent was 1.2 per procedure (metallic stents 35%, multiple plastic stents 60%). The mean length of stent intubation was 11 months. ET resolved jaundice in all jaundiced patients (10/10) and provided standardization of liver enzymes in 10/16 (63%). In ST group, the number of endoscopic procedures prior to surgery was 3 (1–10). The surgical procedure associated with biliary drainage (choledocho-duodenostomy n = 18, choledocho-jejunosotomy n = 3) was a Frey procedure in 12 patients, a pancreaticojejunostomy in 2 patients and left pancreatectomy in 2 patients. Success rate of ST was not significantly different from ET (87% vs. 63%, p = 0.08). The success was significantly longer (16.9 vs. 5.8 months, p = 0.01) in ST. The actuarial rate of success at 6-, 12- and 24-month was 73%, 73% and 67% respectively in the ST group and 75%, 67% and 0% respectively in the ET group (p = 0.04). Beyond 3 endoscopic procedures, the success rate at 6 and 18 months was 27% and 18% respectively.

**Conclusion:** Surgery increases long-term outcomes for bile duct stricture due to chronic pancreatitis. Beyond 3 endoscopic procedures, the success rate is low.

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**P161**

**Late Social Function and Symptoms Following Surgery for Chronic Pancreatitis**

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**Introduction:** Surgery for chronic pancreatitis improves short term pain control in 70–80%. The long term outcome is not well described.

**Objectives:** To report long term pain control and social function after surgical treatment tailored to the disease morphology.

**Methods:** We reviewed patients who had surgery for chronic pancreatitis between 1989 and 2010. We recorded indication for surgery, operation performed, postoperative complications, length of
stay, pain at final hospital follow-up. Telephone interviews determined current pain, employment and quality of life (QL).

Results: 34 men and 19 women had surgery at median age 46 years (range 18–72). The aetiology was alcohol in 23 patients, unknown in 22. There were 18 Beger procedures, 5 Frey procedures, 17 distal pancreatectomy, 9 pancreaticoduodenectomy and 4 other procedures including duct drainage. Median postoperative hospital stay was 10.5 days (range 4–77).

51 patients were followed for at least 6 months but only 13 for more than 2 years. Regular opiate use fell from 50% pre-operative (27 of 53) to 14 (26%) with 38 (72%) reporting absent or improved pain at final follow up. New onset diabetes developed in 10 (19%) patients. During follow-up 8 patients died.

27 of 45 (60%) surviving patients were interviewed median 2.5 years after operation. 16 patients were not using painkillers, 15 reported pain, but only 6 (22%) had pain the same as before operation. Of 24 patients of working age, 14 were able to work.

The mean overall QL score (QLQ C30) was 70.83 (range 16.67–100). Physical functioning (median = 83.33, range 13.33–100) and social functioning (median = 100, range 0–100) were similar to reference data.

Conclusions: The surgical management of chronic pancreatitis results in good long term pain relief in about 75% of cases. 60% of patients returned to employment, coinciding with high physical and social functioning scores. Long term QL was similar to reference data, suggesting that surgery can restore many patients to normal health status.

Other Topics

P162
Pancreatic Incidentalomas: How to Manage Them?
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Introduction: In the last years there has been an increase in the frequency of detecting pancreatic incidentalomas, defined as findings that are unrelated to the clinical indication for the imaging examination performed. The pathology and clinical outcome of patients with pancreatic incidentalomas have not been characterized. Although it is known that most incidental findings are likely benign and often have little or no clinical significance, incidental findings may be serious, and hence, when and how to evaluate them is unclear.

Objectives: to evaluate the incidental findings of the pancreas detected by US.

Patients and Methods: A database of 2408 consecutive abdominal ultrasound that were performed in 2009 was analyzed. Each patient having pancreatic incidentaloma by US was scheduled to undergo MRCP and CT scan for examining the lesion’s characteristics.

Results: 28 pancreatic incidentalomas (1,16%) were identified by US; 28,5% of multifocal versus 71,5% of unifocal lesions were incidentally diagnosed. One pancreatic incidentaloma (3,6%) was a solid lesion, 27 (96,4%) were cystic by US. IPMN was diagnosed in 15 patients (53,6%). Others findings included small cystic lesions (<1 cm) in 8 patients (28,6%) and a chronic pancreatitis, autoimmune pancreatitis and pancreatic cancer in one patient each (3,6%). Serous cystadenoma was seen in 2 patients (7,2%).

Conclusion: Most incidental findings can be detected by routine abdominal ultrasounds. However, the lesions needs to be characterized and so it’s recommended to examine closely them by MRCP and CT. Infact the exact diagnosis is fundamental for the correct management of the patient (follow-up? surgery?).
less than 25% as in major resective surgery for pancreatic cancer. With a complication rate of 25%, RFA has to be considered as a major surgery intervention and it has to be performed by a wide experienced in both general and pancreatic surgery team. In our experience, probe temperature is the best way to control both the efficacy and the adverse effects of pancreatic RFA.

Abstracts

P164

Pseudomyxoma Peritonei Caused by a Ruptured Intraductal Papillary Mucinous Carcinoma of the Pancreas: Report of a Case

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Introduction: Pseudomyxoma peritonei (PMP) is a clinical entity characterized by intraperitoneal deposits of mucin, and the vast majority of the cases are associated with a mucinous neoplasm of the appendix and ovary. Intraductal papillary mucinous neoplasm (IPMN) is a pancreatic tumor characterized by papillary growth within cystically dilated ducts filled with mucus. So far, only few cases of coexistence of PMP and IPMN have been reported in the literature.

Objectives: A case of pseudomyxoma peritonei resulting from rupture of invasive IPMN is presented.

Patients & Methods: A 74-year old man was admitted to our hospital for investigation of ascites. Computed tomography showed massive ascites throughout peritoneal space and a 3 cm-sized ruptured cystic tumor in the body of the pancreas. The ultrasonography-assisted aspirated fluid was gelatinous with a high concentration of CEA and CA19-9. Endoscopic retrograde pancreatography revealed a saclike outpouching suggestive of a rupture of the tumor. We diagnosed this case as PMP accompanied by ruptured IPMN, and distal pancreatectomy and debulking surgery of the mucinous material were performed. The histological features were consistent with invasive IPMC. The patient remains in good general condition with no signs of progression of PMP for 15 months.

Results: The tumor implants of PMP could possibly have been the result of mucous leakage by rupture of IPMN.

Conclusions: This case suggests the possibility that the spread of mucinous cells by rupture of IPMN might lead to the formation of PMP. The pancreatic resection for IPMC should be performed with a great attention regarding to the spread into the intrabdominal space of the malignant cells.

P165

Single-Institution Experience of Laparoscopic Pancreatic Surgery

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Introduction: Laparoscopic resection is regarded as safe and feasible in selected patients with benign pancreatic tumors. With increasing surgeon experience and growing data, laparoscopic resection is generating considerable attention and enthusiasm. We performed distal pancreatectomies attempted laparoscopically, while selected patients underwent laparoscopic pancreaticoduodenectomy and tumor enucleation.

Objectives: Current applications of laparoscopic approaches to left pancreatectomy, tumor enucleation, and pancreaticoduodenectomy for treatment of pancreatic tumors are considered in the available evidence demonstrating feasible and safety.

Patients: Laparoscopic distal pancreatectomy (LDP) 5cases (MCN3, IPMN1, Insulinoma1), pancreaticoduodenectomy (LPD) 1case (Cancer of the Papilla), and tumor enucleation 1case (Insulinoma) are performed.

Result: (1) MCN: The mean age of the 3 patients was 34.3 years, and were all women. The mean operative time, blood loss and hospital stay were 330min, 122ml, 8.6days. (2) IPMN: A 76-years-old women had the Φ40mm tumor of the tail of the pancreas. The operative time, blood loss and hospital stay were 295min, 100ml, 8days. (3) Insulinoma: LPD; A 63-years-old man had the Φ15mm tumor of the body of the pancreas. The operative time, blood loss and hospital stay were 440min, 200ml, 6days. Tumor enucleation; A 27-years-old man had the Φ17mm tumor of the body of the pancreas. The operative time, blood loss and hospital stay were 202min, 100ml, 8days. (4) Cancer of the Papilla: A 72-years-old woman had the T2 tumor with no involvement of lymph nodes. The operating time, blood loss and hospital stay were 558min, 70ml, 20 days. There were not the conversion, pancreatic fistula, readmission, reoperation, and mortality.

Conclusion: Laparoscopic pancreatic surgery can be performed safely and effectively in patients with benign or low-grade malignant neoplasms of the pancreas.

P166

Pancreatic Surgery in the Elderly: Analysis of a Single Centre Experience

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Introduction: The demographics of the UK population are changing with the fastest in those aged 85 and over. By 2033 the number of people aged 85 and over is projected to be more than double,
accounting for 5% of the total population. Therefore, it is important to understand the surgical outcome with increasing age to assist surgical decision making.

**Objectives:** Study mortality, length of stay, complications and survival in the elderly group that underwent pancreatic resection in our tertiary referral centre and compare their outcome with the younger cohort.

**Methods:** We reviewed 428 consecutive pancreatic resections at our institution over a 9-year period. Patients were divided into two groups (younger than 70 and older than 70 years old) and outcomes were analysed.

**Results:** 119 patients were aged 70 years or older and 309 patients formed the younger cohort. In the older age group, 82 (68.9%) resections were for malignant disease compared to 155 (50.2%) in the younger group. The mean length of stay for patients of the older and younger group was 15 days (range 3 – 91) and 14 days (range 3 – 144) respectively (p = 0.47). The overall incidence of complications was significantly higher in the older group (p = 0.02). The overall mortality was 2.8%, 3.4% in the older group compared to 2.6% in the younger group (p = 0.75). The median survival for the younger group was 28.5 months compared to 23 months for the older group (p < 0.05).

**Conclusion:** Elderly patients can safely undergo pancreatic resection and age alone should not preclude pancreatic resection. As expected there were more resections carried out for malignancy in the elderly which led to higher post operative morbidity but overall mortality was not significantly higher.

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**P167**

*Pancreatic Surgery on the Edge*

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**Introduction:** Recent studies showed that fusion plane of two pancreas primordia separates adult pancreas into two segments. That embryological characteristic allows to perform less extensive surgery in case of benign diseases or even low-grade malignancies. The advantages of segmental resections as a duodenum-preserving resection of the head of the pancreas, ventral pancreatectomy, uncinate process resection, and enucleation are significant.

**Case report:** We present a case 64-year old women who presented pathological mass in the epigastric region. CT scan revealed cystic tumor in pancreas head 10 cm in diameter. During exploration polycystic non-infiltrating mass was found in the head of the pancreas CBD was about 3cm in diameter, gallbladder was about 20cm long. The embryo fusion plane was identified and separated resulting in dorsal part pancreatic head resection. Any leakage was revealed on intraoperative pancreatography – ventral pancreatic duct was ligated on the top of uncinate process. Standard cholecystectomy was performed. T-drain was left in CBD. Roux-en-Y loop was created, pancreatic tail was anastomosed with jejunum end-to-end.

Two weeks later T-drain cholangiography and CT scan was performed and T-drain was removed with no symptoms of bile detenion.

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**P168**

*Intraductal Papillary Mucinous Neoplasia: What is the Optimal Management? A Single Center Experience*

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**Introduction:** The management of IPMNs remains still uncertain.

**Objective:** To evaluate the impact of different strategies for the management of IPMNs.

**Material & Methods:** From 2003 to 2010, we prospectively recorded demographic, clinical, radiological, pathological data and type of management of 132 patients. Surgical criteria were established according to International guidelines. Patients were divided into three groups. Group A (G1): patients with criteria selected for surgical treatment; group B (G2): patients without criteria selected for follow-up; group C (G3): patients with criteria and high surgical risk selected for follow-up. Failures of our strategy were a pathological diagnosis of IPMN adenoma in G1 or deaths for malignant IPMN in G2 and in G3. The intention to treat analysis was carried out. We evaluated the quality of life (QoL) using EORTC questionnaire.

**Results:** Seven (5.3%) patients had an IPMN type I, 98 (74.2 %) type II and 27 (20.5 %) type III. Surgical treatment was offered to 31 (23.5 %) patients (G1). Follow-up was carried-out in 101 (76.5 %) patients: 78 (77.2 %) without criteria (G2) and 23 (22.8%) with criteria (G3). Mean follow-up, sex and presence of co-morbidities were similar among the three groups. Mean age in G3 was higher than in G1 and G2 (74.3, 67.4 and 69.4 years, respectively; P = 0.040). Rate of success was lower in G1 than in G2 and G3 (83.3%, 98.7% and 100 %, respectively; P = 0.009). Mean survival was lower in G3 than in G1 and G2 (50.3, 61.7 and 63.1 months, respectively; P = 0.035) but none died for malignant IPMN in G2 and G3. QoL was similar among the groups.

**Conclusion:** Radiological follow-up should be offered as an alternative strategy to surgery for IPMNs in old patients having high surgical risk.
P169
Analysis of Endoscopic Ultrasound Guided Fine Needle Aspiration Biopsy (EUS-FNAB) in Pancreaticobiliary Region: A Single Centre Retrospective Study
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Introduction: EUS-FNAB is a method used for the cytological diagnosis of lesions in the pancreaticobiliary region.

Objectives: To assess the accuracy, impact on clinical management, complications and limitations of EUS-FNAB.

Patients & Methods: A retrospective study, university hospital. A total of 257 FNABs were performed in 249 patients (123 men, 126 women) with pancreatic, liver hilum or intraabdominal tumours with a mean age 62.8 years (22–84 years) from 2008 to 2010. 219 patients were enrolled in the final analysis (207 patients had solid, 12 patients had cystic tumors). The FNABs were performed by 3 physicians. The final diagnosis was based on histological verification or on further clinical course.

Results: Overall, 234 (91%) specimens were diagnostic, 23 (9%) were not. 1. Solid tumors: The sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) for the diagnosis of any cancer were 90.4%, 90%, 75% and 96.6%. 2. Cystic tumors: The sensitivity, specificity, NPV and PPV for the diagnosis of any neoplasia were 33.3%, 100%, 81.8% and 100%.

From the whole cohort, EUS-FNAB had a direct impact on the subsequent clinical management in 154 (60%) patients, particularly in those with advanced cancer (100%).

There were no major complications and 5 (2%) minor complications.

Conclusion: The EUS FNAB is a safe and accurate diagnostic tool for solid pancreatic tumors. For cystic lesions the results are limited. However, the EUS-FNAB findings directly influence the subsequent clinical management particularly in patients with inoperable cancer. Its role in patients referred for surgery remains controversial.

P170
Impact of Hospital Volume on Type of Surgery and Morbidity/Mortality in Elective Pancreatic Surgery – Results of the Middle German Prospective Evaluation Study Elective Pancreatic Surgery (PEEP)
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Introduction: The implementation of minimum quantities in pancreatic surgery in Germany was mainly based on several international volume-outcome-studies. These minimum quantities have been discussed controversially.

Objectives: One of the aims of the Prospective Evaluation Study Elective Pancreatic Surgery (PEEP) was to analyze the volume-outcome-correlation in pancreatic surgery in the Middle German region.

Patients & Methods: Between 01.01.2006 and 31.12.2009, 2086 consecutive patients with pancreatic diseases who were operated on in 26 participating surgical departments (among others 3 university hospitals) were prospectively included in this study.

Results: In total were performed: 1070 partial duodenopancreatectomies (DP), 73 total pancreatectomies, 259 distal pancreatectomies, 286 bypass surgeries, 190 explorative laparotomies, and 209 other surgeries. The morbidity and mortality rates were 35.8% and 4.4%, respectively (in case of DPs 42.8% and 5.1%, respectively). When compared to high volume hospitals (> 40 surgeries/year), DP were less frequently performed in with less than 40 surgeries/year (48.4% vs. 58.9%, p = .05). Consequently, the rates of bypass surgery and explorative laparotomies were higher in low and medium volume hospitals (16% vs. 9.7%; p = .002 and 10.8% vs. 6.1%; p = .006, respectively). On the other hand, no significant differences in morbidity and mortality rates could be found comparing surgical units with different surgical volumes (cut off levels 2,5,10,20,40 surgeries/year), neither for the complete range of surgery nor for DPs.

Conclusion: In Middle Germany, the mortality rate in elective pancreatic surgery is, independent from the hospital volume, about 5%. High volume hospitals, however, were found to have a higher frequency of (advanced) resections and lower frequencies of bypass and explorative surgery when compared to hospitals with lower case load.
Surgery for Pancreatic Cancer in the Elderly – Is It Justified?

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Introduction: Although morbidity and mortality after major pancreatic surgery has significantly improved over the past 15 years, surgical outcome and long-term survival of elderly patients is not known.

Objectives: This study aimed to investigate the morbidity, mortality, and long-term survival of elderly patients (>75 years of age) undergoing partial duodenopancreatectomy (PD/PPPD) for adenocarcinoma of the pancreatic head (PC).

Patients & Methods: During 2002–2008, n=208 PD/PPPD procedures were performed in our institution for PC of the pancreatic head, including 25 patients <55 years (group A), 148 patients >55 and <75 (group B) and 35 patients >75 years of age (group C). Tumor- and patient-specific data were collected and risk factors for postoperative morbidity, mortality, and survival were analyzed for all groups.

Results: There were no significant differences between groups with respect to gender, type of procedure (PPPD or PD), operation time, blood loss, tumor stage (UICC), tumor grade, R-status, lymph node ratio, 30-day mortality (0.0%, 4.1%, 0.0%), ICU length of stay (0.4, 0.5, 0.7 days), hospital length of stay (16.2, 18.8, 17.0 days) and adjuvant chemotherapy (40.0%, 40.5%, 40.0%). Extended resections including total pancreatectomies were more frequently performed in younger patients (32.0%, 22.9%, 11.4%; p < 0.05) and were associated with a higher rate of anastomotic leakages (8.0%, 6.8%, 5.7%), pancreatic fistulas (12.0%, 8.8%, 5.7%), surgical complications (28.0%, 21.0%, 17.2%), postoperative interventional procedures (12.0%, 9.5%, 5.7%) and reoperations (20.0%, 14.9%, 8.6%). A higher rate of preoperative cardio-vascular, pulmonary and metabolic comorbidities in elderly patients (group C) was significantly associated with a higher rate of postoperative non-surgical complications (12.0%, 23.6%, 345.3%; p < 0.001). The tumor-specific median survival (21.4 month) did not differ significantly between groups (p=0.11).

Conclusions: PD can be performed safely in elderly patients since age is not directly associated with postoperative surgical complications, reoperations, mortality, and survival. However, a higher rate of postoperative non-surgical complications should be taken into account.
P173
Quantitative Endoscopic Ultrasound (EUS) Elastography: Hue-Histogram vs Strain Ratio for the Differential Diagnosis of Solid Pancreatic Masses
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Quantitative EUS-elastography allows analyzing tissue stiffness. Elastography may be analyzed either by strain ratio (SR) or hue histogram analysis (HHA).

Aim: of the study was to evaluate the accuracy of SR and HHA for the differential diagnosis of solid pancreatic masses.

Methods: 60 consecutive patients (mean age 61 years, range 17–86, 30 male), with a solid pancreatic mass at EUS were prospectively included. Elastography was performed with linear Pentax-EUS and Hitachi-Preirus. For HHA, the tumor area was selected and analyzed. The mass (area A) and a peripancreatic soft reference area (B) were selected for SR analysis (quotient B/A). Final diagnosis was based on surgery and/or EUS-biopsy. Data are shown as mean (95%CI) and analyzed by ANOVA. Diagnostic accuracy was calculated.

Results: Size of masses was 33.3±19.0mm. Tumors were located in the head (n=35), body (n=19) and tail (n=6) of the pancreas. Final diagnosis was pancreatic adenocarcinoma (n=32), neuroendocrine tumor (NET) (n=6), pancreatic metastasis (n=7), and inflammatory masses (n=15). Results of HHA were 92.3 (79.2–86.1) in benign masses, 24.7 (21.5–27.4) in malignant tumors, and 15.5 (10.7–20.2) in NET (p<0.001). SR was 8.4 (2.7–14.0) in benign masses, 45.8 (34.3–51.3) in malignant tumors and 119.6 (44.9–194.3) in NET (p<0.001). Sensitivity and specificity of SR for diagnosing malignancy were 97.8% and 93.3% (cut-off 11.74) (AUC = 0.959), while those of HHA were 97.0% and 93.3%, respectively (cut-off 55.4) (AUC = 0.995).

Conclusion: Elastography is a very useful tool for the differential diagnosis of solid pancreatic masses. SR and HHA are equivalent methods for stiffness quantification.

P174
Pancreatic Surgery for Secondary Tumors to the Pancreas: Is It Safe and Effective?
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Background: Isolated metastases to the pancreas are rare. Only sparse data exists on possible treatment options for these patients. After recent advances in safety and efficacy of modern pancreatic surgery, metastasectomy has become a considerable treatment alternative. Here we report on surgical resection of pancreatic metastases in 26 patients at our institution.

Methods: All patients included in this study received a pancreatic metastasectomy between 1991 and 2010 at the University of Munich, Germany. Data was evaluated retrospectively.

Results: Of the 26 patients included in this report 54% were female. The median age of patients was 65 years. Renal cell carcinoma (RCC) was the most common origin of pancreatic metastases (n = 16; 62%). Other primaries include gall bladder carcinoma, leiomyosarcoma, colon cancer (all n = 2), and others. The median time interval between primary tumor and pancreatic resection was 5.3 [0 – 24] years. Eleven pancreatic head resections (42%), fourteen distal pancreatectomies (54%), and one total pancreatectomy were performed (4%). The estimated 3- and 5-year survival rates in this study group were 73.2% and 52.3%, respectively. The estimated median overall survival was 63 months (CI: 37.8 – 88.1 months). Patients suffering from synchronous metastases at the time of pancreatic surgery had a statistically significant shorter median overall survival time (11 months vs. 64 months). All other evaluated factors had no influence on morbidity and postoperative survival.

Conclusions: Surgical resection of metastases to the pancreas is safe and results in long overall survival. It should be considered in patients with isolated pancreatic metastases.

P175
Sclenic Artery Invasion in Pancreatic Adenocarcinoma of the Body and Tail: A Novel Prognostic Parameter for Patients Selection
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Introduction & Objectives: The value of splenic vessels invasion (which identified T3 tumors) in prognosis after resection for pancreatic ductal adenocarcinoma (PDA) of the body and tail has been scarcely investigated. Aim of this study was to evaluate prognostic factors in PDA of the body/tail, emphasizing the role of splenic vessels infiltration.

Methods: Between 1990 and 2008, 87 patients who underwent distal pancreatectomy (DP) for histologically-proven PDA of the body and tail were analyzed. Clinico-pathological prognostic factors for survival were evaluated. Univariate and multivariable analyses were performed.

Results: Postoperative morbidity was 31% with no mortality. The 1-, 3- and 5-year overall survival rates were 77%, 48% and 24.5%, respectively. Invasion of the splenic artery (SA) was observed in 19 patients (22%). Patients with SA invasion had a significantly worse prognosis compared with those without SA invasion (median survival: 15 vs. 39 months, p = 0.014). On multivariable analysis, adjuvant therapy, poorly differentiation (G3/G4), R2 resection, the presence of lymph node metastases, and SA invasion were independent predictors of survival.
**Conclusions:** Along with other well-known prognostic factors, invasion of SA is an independent predictor of poor survival in PDA of the body/tail. In the presence of SA infiltration, neoadjuvant treatment should be considered. SA infiltration might be reclassified from T3 to T4 tumor.

**P176**  
**Clinical Outcome of Laparoscopic Pancreas Surgery – Early Experience**  
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**Introduction:** Laparoscopy gives a new opportunity for surgical approach in gastrointestinal surgery. Minimally invasive surgery has been proven to be a safe and effective method also in pancreatic surgery.

**Objectives:** The aim of the study was to analyze a group of patients with laparoscopic distal pancreatectomy (LDP) operated in our Department.

**Patients & Methods:** We conducted retrospective study to analyze a group of 10 patients on whom LDP was performed between 2009–01.2011 (2M/8F).

**Results:** 12 of patients underwent laparoscopic procedures of pancreas. 10 patients underwent LDP. Median age was: 53,8 years. Preoperative diagnosis consisted cystic lesions in 8 cases, and 2 solid tumors. The mean operating time and hospital stay after LDP were respectively: 1h40 min and 9 days. There were no significant intraoperative complications like hemorrhage, perforation, etc. Readmissions, reoperations, and mortality after LDP were respectively: 33, 0 and 0%.

**Conclusion:** Our first experience in laparoscopic pancreatic surgery shows that LDP is good alternative for patients with low-grade malignancy and small tumors of the body and tail of pancreas. Difficulty in wide prevalence is that it must be performed by surgeons advanced in laparoscopies. Satisfying results in the group give us the motivation for selection of more patients who could have benefits from that type of intervention.

**P177**  
**Can MDCT Reliably Predict the Resectability of Pancreatic Cancer? Correlation of CT Data with Surgical and Morphological Results**  
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**Introduction:** In the absence of metastatic disease, assessment of vascular invasion becomes essential for determining resectability of pancreatic cancer.

**Objectives:** To evaluate the ability of multi-detector computed tomography (MDCT) to predict resectability of pancreatic cancer.

**Patients:** 95 patients with histologically proven pancreatic ductal adenocarcinoma underwent a preoperative contrast enhanced triphasic 64- and 256-slice MDCT (2009–2010). All the radiological data were divided into three groups: resectable (40), borderline-resectable (20) and unresectable (35) tumors. All the cases of resectable and borderline-resectable tumors were compared with surgical and morphological examinations. In 35 cases the patients were considered unresectable by MDCT because of distant metastases (n = 15) and local spread (n = 20).

**Results:** Fifty-one patient underwent radical and nine – palliative surgery. Of 40 patients deemed resectable after MDCT, 36 were operated on radically, two had peritoneal dissemination being resectable, and two had the SMA invasion (PPV-95%). Of twenty patients considered borderline resectable (BR) after MDCT, six were proved to be unresectable (SMA involvement) and fourteen underwent radical surgery (PPV-70%). When compared to surgery and pathology, the overall PPV of MDCT for resectability was 87% and 80%, respectively (four patients deemed resectable following MDCT had R1-margins at pathology).

**Conclusion:** MDCT is a reliable tool for preoperative staging of pancreatic cancer. The borderline resectable group of patients is of special interest. The PPV in this group is largely dependent on the surgeon’s ideology, as well as on the criteria used for BR cancer.
**P178**

**Sarcopenia in Resectable Pancreatic Cancer and Chronic Pancreatitis: A CT-Based Study**

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**Introduction:** Studies in a variety of metastatic malignancies showed sarcopenia, or muscle wasting, to be highly predictive of functional impairment, chemotherapy toxicity and mortality. However, the prevalence of sarcopenia in resectable pancreatic cancer has not yet been focus of research. Advanced chronic pancreatitis is also commonly associated with malnutrition.

**Objectives:** To evaluate sarcopenia in patients with resectable pancreatic adenocarcinoma and chronic pancreatitis by means of lumbar skeletal muscle index, determined by computed tomography (CT).

**Material & Methods:** We evaluated pre-operative CT-images of 16 patients with stage II pancreatic adenocarcinoma (Group I) and 19 patients with chronic calcifying pancreatitis or inflammatory mass in the head of the pancreas (Group II). Mean Body Mass Index was similar: 23.3 ± 3.1 and 22.5 ± 3.2 kg/m², respectively. Single axial CT-image on the level of the third lumbar vertebrae was assessed to measure cross-sectional areas (cm²) of skeletal muscle. The values were normalized for height to get the lumbar skeletal muscle index in cm²/m². The sex-specific sarcopenia cut-offs were 52.4 cm²/m² for men and 39.0 ± 5.4 cm²/m² in women.

**Results:** Group I: mean L3 muscle index was 42.5 ± 6.7 in men and 36.3 ± 7.4 cm²/m² in women, respectively. Group II: mean L3 index constituted 47.8 ± 8.0 in men and 39.0 ± 5.4 cm²/m² in women, respectively. There were 11/16 sarcopenic patients in Group I and 11/19 in Group II. The differences between Groups were not significant.

**Conclusion:** Muscle wasting is highly prevalent in patients with resectable pancreatic cancer and chronic pancreatitis, although sarcopenia in cancer patients seems to be more pronounced.


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**P179**

**Despite of Dramatic Drop in Hospital Mortality After Pancreaticoduodenectomy, Hospital Volume Still Has an Impact – A 15 Year Study in Finland**

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**Background:** During 1990–1994, 350 pancreaticoduodenectomies (PD) were performed in 33 hospitals in Finland, with hospital mortality of 10% (1). Hospital mortality correlated with annual volume, being highest in low volume hospitals (<5/year; 13%) and lowest in higher volume hospitals (>10/year; 4%). During the past decade, some centralization has occurred.

**Objectives:** Our aim was to analyse whether the risk for hospital mortality has changed and whether the hospital volume still has an impact.

**Materials & Methods:** National database for hospital discharges including information of surgical procedures and succumbs during hospitalizations for 2005–2009 was analysed and compared with the previously published results (1).

**Results:** The total number of PDs during the five year period doubled to 735 cases (population 5.1 millions) and the number of hospitals performing PDs decreased by 43% from 33 to 20. Overall hospital mortality decreased from 10% to 2% (p<0.001). Mortality decreased mostly in low volume hospitals: <5/year (11 hospitals) 4.5% (15 years earlier 13%; p<0.01), 5–10/year 2.3% (earlier 7%; p<0.05), and >10/year 1.3% (earlier 4%; NS). In two hospitals over 20 PDs were performed annually, with hospital mortality of 0.9%, which is significantly less than in the lowest volume cohort (4.5%, p=0.027). Theoretically, 8 hospital deaths could have been avoided, if all the PDs were performed in the 2 high volume hospitals.

**Conclusions:** The number of PDs has increased in Finland during past 15 years. In general, hospital mortality has greatly improved and is surprisingly low, with high international standard. A clear survival benefit remains, favouring high volume hospitals, which should encourage health care authorities and clinicians to continue with centralization of PDs in Finland.

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**P180**

**Frequency and EUS Characteristics of Pancreatic Metastases: A Consecutive Study of a Large Series of Solid Pancreatic Masses**

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Pancreatic metastases represent 2–3% of solid pancreatic masses. Differential diagnosis between metastasis and other pancreatic malignancies, like pancreatic cancer, remains a challenge.

**Aim:** to determine the frequency and EUS characteristics of pancreatic metastases in a large consecutive series of solid pancreatic masses.

**Methods:** 449 patients with a solid pancreatic mass evaluated by EUS from January 2006 to December of 2010 were identified from a prospectively collected endoscopy database. Out of them, those with a final diagnosis of pancreatic metastasis were included in the study. EUS was performed by the linear Pentax and Hitachi ultra-
sound devices. Patient characteristics and endosonographic features of pancreatic metastases were evaluated.

**Results:** 13 patients (2.9% of solid pancreatic masses) were finally diagnosed with metastasis by EUS-guided FNA. Mean age of patients was 65 years, range 51–83 years, 9 were female. Primary tumours were lung cancer (n = 3), GIST (n = 2), breast cancer (n = 2), gastric cancer (n = 1), colon cancer (n = 1), renal cancer (n = 1), sarcoma (n = 1), myeloma (n = 1) and teratoma (n = 1). Ten tumours were located at the head of the pancreas and 3 at the body. Mean size (± SD) of the metastases was 33.2 ± 12.4mm. They had a solid appearance (n = 12), hypoechoic (n = 11), heterogeneous (n = 13) and with poorly defined borders (n = 12) at EUS. Ten metastases were hypovascular, and 3 hypervascular. EUS features did not allow differentiating pancreatic metastasis from other pancreatic malignant tumors.

**Conclusions:** Pancreatic metastases represent 2.9% of solid pancreatic masses. EUS findings are indistinguishable from other pancreatic malignancies, thus EUS-guided FNA is required for final diagnosis.

### P181

**Importance of Multidisciplinary Approach to the Treatment of Pancreatic Cystic Neoplasms – A Surgical View**

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**Introduction:** Cystic neoplasms are lesions which detection rate systematically increases. Cooperation of surgeons, radiologists, gastroscopists, pathomorphologists make surgical decisions faster and easier, follow-up more accurate.

**Objectives:** The aim of the study was an analysis of patients operated in our Department whose histopathological examination indicates cystic neoplasms of pancreas.

**Patients & Methods:** Retrospective analysis covered 25 cases of patients (7M/18F) operated in our Department between 2005–2010 with postoperative diagnosis of cystic neoplasms.

**Results:** Between 2005 and 2010 – 250 major surgical procedures of pancreas were conducted, 25 patients were diagnosed with cystic neoplasms of pancreas, including 9 serous (1 cystadenocarcinoma serosum), 9 mucinous (2 adenocarcinoma mucinosum) and 7 IPMN (4 intraductal papillary mucinous carcinoma). In each case radiographic imagings were carried out (USG, CT, MR). 9 patients basing on the results of EUS and ERCP were qualified to operation, in each case first diagnosis suggest the cystic lesion. 10 patients were diagnosed with solid tumor, 9 others with suspicion of cystic lesion, other 3 with mixed solid-cystic and 2 with IPMN. In this group: 10 Whipple procedures, 12 distal pancreatectomies (4 laparoscopic distal pancreatectomies) and 2 total pancreatectomies were carried out. One patient died in postoperative period.

**Conclusion:** Multidisciplinary cooperation allows faster diagnosis and more appropriate choice of surgical procedures including minimally invasive surgery.

### P182

**Prognostic Profiling of 1071 Patients with Resected Pancreatic Cancer: A New Risk Stratification Results in Better Prediction of Outcome**

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**Background:** Surgery is the only therapy with potentially curative intention in pancreatic cancer.

**Objectives:** The present analysis aimed to determine prognostic parameters in a patient cohort with resected pancreatic adenocarcinoma with a special focus on the revised R1-definition.

**Methods:** Between 10/01 and 08/09, data from 1071 consecutively resected patients with pancreatic adenocarcinoma were prospectively collected in an electronic database. Parameters tested for survival prediction in univariate analysis included patient, tumor, and resection characteristics as well as adjuvant therapy. The parameters with significant results were used for multivariate survival analysis. Identified parameters with positive or negative prognostic effect were used to define risk groups and to assess the effects on patient survival.

**Results:** Age, ASA-score, CEA and CA19-9 levels, preoperative insulin-dependent diabetes mellitus, G-, N-, M-, R-, G-tumor classification, advanced disease, and LNR were all significant in univariate analysis, whereas gender, NYHA score, BMI, insurance status, type of surgical procedure, and adjuvant therapy were not. In multivariate analysis, age ≥70 years, preoperative insulin-dependent diabetes, CA19-9 ≥400U/ml, T4-, M1- or G3-status, and LNR>0.2 were independent negative predictors, whereas Tis/T1/T2-status, G1-differentiation, and R0-status (revised definition) were independently associated with good prognosis. Using these risk factors, patients were stratified into four risk-groups with significantly different prognosis; 5-year survival varied between 0% and 54.5%. Risk stratification resulted in improved survival prognostication within the predominant AJCC IIA and AJCC IIB stages.

**Conclusions:** A newly-defined prognostic profiling including the revised R1-definition discriminates survival of patients with resectable pancreatic adenocarcinoma better than the AJCC staging system, and may be of particular relevance for patient-adjusted therapy in the heterogeneous group of AJCC stage II tumors.
**P183**

**Significant Association Between DNA Repair Polymorphisms and Survival in Pancreatic Cancer Patients Treated with Gemcitabine/Platinum Combination Chemotherapy**

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**Background:** This multicenter study aimed at evaluating the association of candidate polymorphisms with outcome of pancreatic cancer patients treated with the equivalent polychemotherapeutic regimens cisplatin-epirubicin-capecitabine-gemcitabine (PEXG), cisplatin-docetaxel-capecitabine-gemcitabine (PDXG) and gemcitabine-capecitabine plus epirubicin-cisplatin intra-arterial infusion (EC-GemCap).

**Patients & Methods:** We examined 11 polymorphisms in 8 genes (ERCCI, XPD, XRCCI, CYPIB1, ABCB1, TS, CDA, and RRMI) in 122 stage-III/IV pancreatic cancer patients treated upfront with PEXG, PDXG or EC-GemCap. Univariate/multivariate analyses compared clinical (age/sex/PS/stage/CA19.9) and genetic parameters with overall-survival (OS)/progression-free-survival (PFS) and toxicity using Fisher’s, log-rank test and Cox’s proportional hazards model.

**Results:** Patients harbouring XPD-Gln751Gln, XPD-Asp312Asn→Asn312Asn or XRCCI-Arg399Gln→Gln399Gln genotype had a worse prognosis. A strong combined genotype effect was observed: patients with 0-to-2 and 3-to-4 risk-genotypes had median OS of 13.5 and 10.3 months, respectively (HR = 1.9, P < 0.001). XPD-Gln751Gln (HR = 2.7, P < 0.001) or combination of >2 risk-genotypes (HR = 2.7, P < 0.001), emerged as independent predictors for death-risk at multivariate analysis. No correlations were observed with toxicity. Conversely, XPD-Gln751Gln was associated with shorter PFS, and comparison with gemcitabine-alone-treated patients suggested its predictive significance for platinum-based regimens.

**Conclusion:** Polymorphisms of DNA-repair genes appear to be candidate biomarkers of primary resistance to gemcitabine/cisplatin-based polychemotherapeutic regimens, and may offer an innovative tool for optimizing chemotherapy in advanced pancreatic cancers.

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**P184**

**Characterization of the Anti-Pancreatic Tumor Cell Effect Induced by LBH589 and TSA and its Relation to HDAC Encoding Genes Expression**

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The effect of LBH589 and trichostatin (TSA), a standard drug used as histone deacetylase inhibitor (HDACi) toward the growth of pancreatic cancer cell lines was studied. Here, we examined for the first time, the HDAC family gene expression levels before and after drug treatment.

**Materials & Methods:** Several pancreatic cancer cell lines (Panc-1, BxPC-3, SOJ-6) and a normal human pancreatic duct cell line (HPDE) were used as histone deacetylase inhibitor (HDACi) toward the growth of pancreatic cancer cell lines was studied. Here, we examined for the first time, the HDAC family gene expression levels before and after drug treatment.

**Results:** There were no major significant changes of HDACs genes transcription in cells upon drug treatment. However significant variation in HDACs and SIRTs protein expression levels could be seen among individual cell samples. Some of HDACs reactive bands were barely visible: HDAC4 (BxPC-3 and HPDE) and HDAC7 (BxPC-3 and Panc-1). Moreover, drug treatment with either LBH589 or TSA induced significant decrease of HDAC2 and (≥3 and 9 fold, respectively) as well as SIRT1 (15 and 30 fold respectively) in the case of SOJ-6 cells, compared to control cell line. The in vitro results showed that LBH589 formulation exhibited similar tumor reduction efficacy as the commercial drug gemcitabine.

**Conclusion:** The data demonstrate that LBH589 induced the death of pancreatic tumor cell by apoptosis. In line with its in vitro activity, LBH589 achieved a significant reduction in tumor growth in BxPC-3 pancreatic tumor cell line mouse xenograft model. Furthermore, exploring the impact of LBH589 on HDACs encoding genes expression revealed for the first time that some of them, depending on the cell line considered, seem to be regulated during translation.
Erythropoietin, Erythropoietin Receptor Expression and Signaling in Pancreatic Cancer

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Introduction: The effects of erythropoietin (Epo) in cancer patients have been controversially discussed. Data on Epo and Epo receptor (EpoR) expression and functionality are inconsistent.

Objectives: We investigated the expression of Epo/EpoR and Epo-mediated signaling in human pancreatic ductal adenocarcinoma (PDAC).

Patients & Methods: Blood (n=87) and tissue (n=104) was collected from PDAC patients. Hemoglobin, Epo/EpoR protein and mRNA expression levels were analyzed and compared with those of patients with chronic pancreatitis (CP) and healthy donors. Data obtained were analyzed by nonparametric statistics, uni- and multivariate Cox regression analysis. Epo/EpoR signaling was analyzed in PDAC cell lines.

Results: Anemia was present in 35% of patients. Serum Epo levels correlated inversely with hemoglobin, but the observed Epo concentrations in PDAC patients were lower than expected as suggested by observed/predicted ratio calculation based on healthy donors and CP patients. In patients with metastatic PDAC Epo protein in serum and Epo mRNA levels in tissue were significantly elevated. Moreover, high serum Epo (>16 mU/mL) was an independent prognostic factor for worse patient survival. In histologic PDAC samples, distinct tumor cells stained positive for EpoR. In accordance, PDAC cell lines expressed Epo/EpoR mRNA and EpoR protein. Stimulation of PANC-1 cells with Epo triggered downstream signaling via the PI3K/Akt pathway. However, Epo had no significant effect on growth and chemoresistance to gemcitabine and 5-fluorouracil in vitro.

Conclusion: Anemia has a high prevalence in patients with PDAC. Epo serum and mRNA transcript levels are significantly higher in advanced tumor stages, and tumors express functional EpoR in vitro. Further studies are required to determine the role of endogenous or exogenous Epo in PDAC patients.

EGFR-independent Mechanism of Erlotinib in Pancreatic Ductal Adenocarcinoma Cells

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Introduction: The EGF receptor (EGFR) plays a role in proliferation, migration and adhesion. A placebo-controlled phase 3 trial demonstrated that the EGFR inhibitor erlotinib in combination with gemcitabine was especially efficient in a subgroup of patients developing erlotinib-induced skin toxicity grade 2 or higher. However, EGFR expression was not predictive for response or disease stability and the erlotinib/gemcitabine combination was equally efficient in patients classified EGFR positive as well as negative.

Objectives: To find novel erlotinib targets in pancreatic cancer.

Material & Methods: Human and murine PDAC cell lines were used as a model. Inhibitor concentrations 50% (IC50) were determined in 20 cell lines using MTT assays. RNAi was used to deplete erlotinib targets. Linker-compounds of erlotinib and gefitinib were synthesized and coupled to epoxy-activated Sepharose 6B. Target profiles of erlotinib and gefitinib were determined in an erlotinib sensitive cell line using a chemical proteomics approach combining affinity enrichment of compound targets and quantitative mass spectrometry.

Results: IC50 values for erlotinib in pancreatic cancer cells range between 11.3 mM to no response. After depletion of the EGFR with RNAi, no significant change in the therapeutic response of pancreatic cancer cells towards erlotinib was observed. Mass spectrometric analysis of erlotinib binding proteins revealed six kinases binding to erlotinib with higher affinity (Kd 0.09 mM to 0.358 mM) than the EGFR (Kd 0.434 mM). In contrast, the EGFR inhibitor gefitinib binds only one kinase with higher affinity than the EGFR.

Conclusion: Erlotinib is a multiple kinase inhibitor in pancreatic cancer cells.

The Bile Acid Deoxycholic Acid Induces DNA Damage in Pancreatic Cell Lines

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Introduction: Pancreatic cancer represents a leading cause of cancer death throughout the World; the median survival time is around six months with a low five-year survival rate of around 3–5%. Many aetiological factors have been considered to play a role in pancreatic cancer; among these is bile reflux into the pancreas, thought also to contribute to the development of pancreatitis. Previous studies with oesophageal cell lines have shown bile acids, notably deoxycholic acid, to induce DNA damage.

Objectives: To investigate if bile acids induce DNA damage in pancreatic cell lines as found in oesophageal cells.
Cell Cycle Checkpoint Function and Status of p16, p21 and p53 in Pancreatic Cancer Cell Lines

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Introduction: Cell cycle arrest in response to DNA-damage is an important mechanism in normal human cells. It is disrupted in most human tumours. Among others, function of p53, p16 and p21 is essential for cell cycle checkpoint functions. Doxorubicin induced DNA intercalation leads to DNA-damage and allows evaluation of G1/S and G2/M checkpoint function.

Objectives: Objective of this study was to evaluate G1/s and G2/M checkpoint function in relation to p16, p21 and p53 status in pancreatic cancer cell lines.

Materials & Methods: Nine pancreatic cancer cell lines (Miapaca2, Capan2, Panc1 and 6 patient derived pancreatic cancer cell lines) as well as RKO cells (colon cancer / control) were treated with Doxorubicin for 24 and 48 hours. Protein- and RNA-Expression of p16, p21 and p53 was measured in untreated cells and after 24 and 48 hours. Cell cycle analysis including function of G1/S and G2/M checkpoint was evaluated by means of flow cytometry. Gene status of p53 was evaluated using exon sequencing.

Results: All but one cell line (PAXF 1657) showed a p53 mutation resulting in an nonfunctional protein. Expression of p16 was only detectable in Capan2 cells. Treatment with Doxorubicin could induce expression of p53 in 7 cell lines and expression of p21 in 4 cell lines. Expression of p16 was not inducible. G1/S checkpoint function was disrupted in all pancreatic cancers but intact in RKO cells (p53 wild type). In contrast, G2/M checkpoint was functional in all tested cell lines.

Conclusion: Nearly all of the evaluated commercially available and patient derived pancreatic cancer cell lines lack p53 function due to mutation and have no detectable or inducible expression of p16. Accordingly, G1/S checkpoint function is deficient. Since G2/M checkpoint function was intact, a p53 independent mechanism must be supposed.
**P190**

**AT13387, a Novel HSP90 Inhibitor Induces Cytostatic Effects in Pancreatic Cancer Cell Lines**

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**Introduction:** Gemcitabine the main standard of treatment for pancreatic cancer is still relatively ineffective. Heat shock protein 90 (HSP90) is a molecular chaperone affecting multiple key cellular signalling pathways including the PI3K/Akt and MAPK pathways of particular importance in pancreatic cancer.

**Objectives:** To undertake preclinical evaluation of AT13387 (Astex Therapeutics) a novel HSP90 inhibitor in pancreatic cancer cell lines.

**Materials & Methods:** Eight pancreas cancer cell lines were used. Cell proliferation was measured using EZ4U assay (Biomedica). Cell cycle and apoptosis (annexin-FITC vs propidium iodide) analysis were carried out by flow cytometry and apoptosis was also measured by PARP cleavage. Expression of client proteins and phosphorylation was assessed by western blotting.

**Results:** AT13387 inhibited proliferation of all cell-lines with IC50 values of 29nM-325nM, similar to other cancer types (10-400nM). AT13387 did not induce apoptosis, but treated cells accumulated in G0/G1 and G2/M phases of the cell cycle (p < 0.05). In Suit-2 and Miaepaca2 cell lines, growth inhibition was not maintained following drug removal, suggesting a cytostatic effect of AT13387 not previously reported in other cell types. AT13387 treatment resulted in down-regulation of HSP90 client proteins, including those in PI3K/Akt and MAPK signalling pathways, and up-regulation of the HSP70 co-chaperone (p = 0.001). The sensitivity to AT13387 was observed in a gemcitabine resistant cell-line SUIT-2GR (gemcitabine IC50 60-fold higher than parental cell-line) with a similar effect on cell cycle distribution.

**Conclusion:** AT13387 inhibited proliferation of multiple pancreatic cancer cell-lines including one resistant to gemcitabine suggesting potential as a novel treatment for pancreatic cancer.

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**P191**

**Disrupting a Nuclear NFATc2 Stabilization Loop Confers Cancer Growth Suppression by Zoledronic Acid**

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**Introduction:** The aminobisphosphonate zoledronic acid (ZOL) has elicited significant attention due to its remarkable anti-tumoral activity, though its detailed mechanism of action remains unclear.

**Aims:** To analyze whether and how ZOL suppresses tumor growth both in vitro and in vivo in pancreatic cancer.

**Methods:** Using a panel of pancreatic cancer cells, we examined the growth suppressor activity of ZOL by 3H-thymidine incorporation and flow cytometry. Immunoblotting, Site directed mutagenesis, RNAi, immunoprecipitation and immunofluorescence were conducted to characterize the GSK3β-NFAT stabilization/ubiquitination pathway. Xenograft mice models were employed to define the biological relevance of the GSK3β-NFATc2 pathway in pancreatic tumor growth.

**Results:** Our data show that GSK3β stabilizes nuclear NFATc2 through a phosphorylation dependent mechanism. GSK3β targets three serine residues located at the SP2 motif of NFATc2 to prevent the transcription factor from HDM2 mediated ubiquitin transfer (at K-684 and K-897) and subsequent proteasomal degradation. Treatment with ZOL inhibits GSK3β kinase activity, thus disrupting NFATc2 phosphorylation and stabilization. In addition, ZOL induces nuclear accumulation of HDM2, which then binds to NFATc2 and transfers ubiquitin to lysines K-684 and K-897, allowing the rapid proteasomal degradation of the oncogenic factor. Conversely, introduction of phosphor-mimicking mutation protects NFATc2 from ubiquitination and degradation and accelerates pancreatic cancer growth in vitro and in vivo in a xenograft tumor model.

**Conclusion:** This study identifies a novel GSK3β-NFATc2 stabilization pathway with important pro-proliferative functions in pancreatic cancer. In addition, we provide first mechanistic evidence that ZOL targets this key pathway to induce NFATc2 degradation and to suppress pancreatic cancer growth.

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**P192**

**Maspin Expression in Pancreatic Ductal Adenocarcinoma Cell Lines and in their Membrane Vesicles**

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**Introduction:** Maspin expression was originally found in breast cancer and it is associated with proapoptotic effects and the inhibition of angiogenesis and migration. Its role in pancreatic malignancies is
still controversial. Membrane vesicles were found recently as a novel type of cellular communication.

**Objectives:** It has been described that two pancreatic ductal adenocarcinoma (PDAC) cell lines (MiaPaCa, Panc1) grown in 10% FCS medium are lacking the expression of maspin. Our main goal was to investigate the role of maspin under special circumstances.

**Materials & Methods:** All experiments were completed after 48 hours of incubation in serum-free medium, cell viability and apoptosis/necrosis were checked by FACS. Maspin expression of MiaPaCa and Panc1 cells were analyzed by immunocytochemistry and FACS. The separation of membrane vesicles from cell supernatant was conducted using differential centrifugation and gravitational filtration.

**Results:** While Panc1 cells exhibited no maspin expression in all experiments, after serum-free incubation MiaPaCa cells showed a slight positivity in both immunocytochemistry and FACS. Furthermore, the presence of maspin was detectable in MiaPaCa membrane vesicles.

**Conclusion:** Maspin seems to be involved in cell-cell communication of PDAC cells under special circumstances (e.g. unfavourable microenvironment, hypoxia). These results are suggesting a role of the protein in cancer survival.

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**P193**

**Role of the MUC4 Mucin in the Resistance to Gemcitabine of Human Pancreatic Cancer Cells**

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**Introduction:** Gemcitabine (Gemzar®), a fluorinated analog of deoxycytidine, is the main chemotherapy in pancreatic cancer, but survival remains weak mainly because of a high resistance of tumours to the drug. Alteration in the expression of actors of nucleoside metabolism such as Equilibrative/Concentrative Nucleoside Transporter (hENT1, hCNT1/3), deoxycytidine kinase (dCK) and ribonucleotide reductase (RRM1/2) may lead to a decrease of gemcitabine efficiency as well as an increased expression of Multidrug-resistance Related Protein (MRP) family. Recent works have shown that mucins and especially the membrane-bound MUC4 mucin may confer an advantage to tumour cells and modify their susceptibility to drugs.

**Objective:** Study the cellular mechanisms responsible for gemcitabine resistance linked to MUC4 expression.

**Material & Methods:** Adenocarcinomatous pancreatic cell line CAPAN-2 was used to establish deficient clones in MUC4 (MUC4-KD) by RNA interference. The IC_{50} index was determined and viability measured by tetrazolium salt test. Expression of dCK, hENT1, hCNT1/3, RRM1/2 and MRP3/4/5 was evaluated by quantitative-PCR and activation of Akt, Erk1/2, PKA, Bax and Bcl-X_L was studied by western-blotting.

**Results:** Loss of MUC4 increased CAPAN-2 sensitivity to gemcitabine (IC_{50}=34.8±1.2 nM) compared to control cells (IC_{50}=52.9±2.2 nM). At 48 hours of treatment, decrease in MRP4 and increase in hCNT1 were observed. Sensitivity of MUC4-KD clones was correlated with increased Bax and decreased Bc1-X_L expression, and decreased Erk1/2 phosphorylation.

**Conclusion:** This work suggests that the mucin MUC4 and actors of gemcitabine metabolism represent potential genes to target to ameliorate gemcitabine response of pancreatic tumours.

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**P194**

**Parallelized Functional Characterization of Pancreatic Cancer Candidate Genes on Reverse Transfection Cell Microarrays**

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**Introduction:** In previous high-throughput analyses, we generated expression profiles of ~2000 candidate genes in primary tissues and model systems of pancreatic cancer. 88 high priority candidate genes were selected for experimental functional characterization.

**Objectives:** To analyze potential roles of the 88 genes in parallelized assays in transformed and non-transformed cell lines and to select highly relevant candidates for further in-depth characterization.

**Methods:** The parallelized analyses were performed in the “reverse transfection” format. In this approach, overexpression- and knockdown-constructs are spotted in regular arrays together with transfection reagents on glass slides. Cells are cultivated on the slides, incorporating and expressing the different constructs. The effects are analysed by fluorescence-based assays.

**Results:** Candidates and controls were downregulated and over-expressed as fusion constructs with fluorescence proteins in carcinoma cell lines (PANC-1, SUIT007) as well as non-transformed cells (HEK293) in the presence or absence of serum. Several candidates were identified as target genes for serum stimulation (alteration of subcellular localisation) and/or showed influence on proliferation (Ki67-staining), apoptosis resistance (cleaved caspase 3-assay), cell differentiation (staining for E-Cadherin and Vimentin). Several candidates were selected for individual in-depth characterization; these analyses are ongoing.

**Conclusion:** ‘Reverse transfection arrays’ are an efficient technology to identify tumor-relevant genes and characterize important functional roles with high throughput.
Knockdown of Kinesin Motor Protein Kif20a Leads to Growth Inhibition in Pancreatic Ductal- and Neuroendocrine-Cancer Cells

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Introduction: To characterize potential molecular drug targets in pancreatic cancer, Kif20a, a member of the kinesin superfamily involved in trafficking of molecules and organelles was investigated.

Methods: Detection of Kif20a as a druggable candidate was made by combined evaluation of various high-throughput gene analysis panels. In vitro analyses were made in pancreatic ductal adenocarcinoma (PDAC) and neuroendocrine cancer (NEC) cell lines using quantitative realtime-PCR, immunohistochemistry, immunofluorescence, immunoblot analyses and MTT assay. To assess the glycosylation status of Kif20a, Tunicamycin was used as an inhibitor.

Results: Immunohistochemical analysis of paraffin embedded pancreatic tumor samples showed a stronger staining in cancer than in healthy pancreatic tissues. Stronger immunostaining was also observed in several altered acinar cell clusters in chronic pancreatitis. Immunofluorescence analysis of pancreatic ductal- and neuroendocrine cancer cells lines showed nuclear and cytoplasmic localization of Kif20a. mRNA and protein expression of Kif20a was comparable in three PDAC and three NEC cell lines. Knockdown of Kif20a with small interfering RNA molecules has led to 35–40% and 15–30% reduction of proliferation in PDAC and NEC cell lines, respectively. Tunicamycin treatment of PDAC cells showed a decreased level of N-glycosylation of Kif20a.

Conclusion: With an upregulation of more than 10-fold in pancreatic cancer cells, Kif20a appears as a suitable candidate for inhibiting tumor growth in pancreatic cancer.
**P197**

**Adenosquamous Carcinoma of the Papilla of Vater Associated with a Small Bowel GIST: A Case Report**

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**Introduction:** Most tumors of the papilla of Vater are adenocarcinomas and other histological types are less frequent. Adenosquamous carcinoma of the papilla is a rare tumor and only three cases have been reported in the literature in the last ten years.

**Objectives:** We present a case of an adenosquamous carcinoma of the papilla of Vater associated with a small bowel gastrointestinal stromal tumor of the jejunum.

**Patients & Methods:** A 81-year-old woman presented at a local hospital because of obstructive jaundice. An abdominal CT scan showed a dilatation of the common bile duct and the Wirsung duct down to the papilla of Vater, where an area of thickening and contrast enhancement of about 2 cm was present. A solid lesion of about 5.3 cm adherent to a jejunal loop was also seen. The patient underwent to endoscopic biliary stenting and then she was referred to our Hospital. A FDG-Positron Emission Tomography showed an area of hypermetabolism and there are the signs of chronic pancreatitis.

**Results:** Histology revealed an adenosquamous carcinoma of the papilla of Vater (size 4 cm in diameter; T4, N1, M0, G2) and a gastrointestinal stromal tumor (size 4 x 4.5 cm, 1 mitosis/50Hpf, low grade risk according to 2002 Fletcher classification) of the small bowel. Postoperative course was uneventful. The patient is alive and well without evidence of relapse 8 months after surgery.

**Conclusion:** The association between adenosquamous carcinoma of the papilla of Vater and small bowel GIST has never been reported in the English literature.

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**P199**

**Ratio of Histology-Proven IPMN in Patients with Initial Suspicion of IPMN**

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Intraductal papillary-mucinous neoplasia (IPMN) represents a rare cystic intraductal tumor of the pancreas. Currently, 50% of these tumors are estimated to develop to invasive carcinomas following long term intraductal growth. However, up to date, it remains insecure how many patients with cystic changes of the pancreas suffer from IPMN and how the disease course develops under various therapeutic strategies.

The purpose of the present investigation was therefore to follow the disease course, subtype of disease and therapeutic consequences in patients with IPMN.

**Patients & Methods:** Between 2005 and 2010, 92 patients with cystic pancreatic changes of undefined underlying causes with the primary suspicion of IPMN were evaluated at our center. The assessment of the clinical data was performed on the basis of our general data registration, and, in addition, by means of special patients and general practition directed questionnaires. Results of diagnostics, disease subtypes and clinical course were analyzed.

**Results:** In addition to the imaging by CT and MRT, endosonography and ERCP were required for the diagnosis. 35 patients with a proof of intrapancreatic pathologic abnormalities were identified, 11 of these suspicious for IPMN, 12 carcinomas, whereas in 13 patients...
malignancies or IPMN could be definitively ruled out. In 14 patients a resection of the pancreatic head was performed, in addition 4 left-sided pancreatic resections and 4 other resections of the pancreas. Histologic assessment revealed the proof of intraductal neoplasias in 12 patients (13%, 5x PanIN 1A oder B), 5 patients had invasive carcinomas. 2 patients died during the observation period, however unrelated to intraductal neoplasias.

Conclusions: In the majority of patients with the primary suspicion of IPMN, the disease could be excluded by refined diagnostic strategies; this led to a pancreatic resection in 4 patients with benign disease. The results support the current recommendations to search for surgical resection in the case of IPMN suspicion on the basis of diagnostic imaging.

P200

Differentiated Surgical Therapy for Congenital Hyperinsulinism

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Introduction: Congenital hyperinsulinism is a rare, heterogeneous disease in neonatology. The focal and the diffuse forms are distinguished by genetical analysis and 18F-L Dopa-PET-CT. Whereas the focal form can be cured completely by enucleation or partial pancreatic resection, medical therapy of diffuse cases consists of diazoxide, octreotide and glucagon. When medical treatment fails surgical therapy is indicated to prevent brain damage. We have abandoned, however, near-total pancreatic resections because the rate of diabetes is very high – later in puberty.

Objectives: We adopted an innovative surgical approach: We try to identify the recently described atypical cases with segmental distribution by laparoscopic biopsies in order to find the small ridge between recurrence and diabetes by staged limited resections.

Methods: Clinical observation study

Results: 17 out of 20 focal cases have been cured completely by partial pancreatic resection. The remaining three are well controlled by medication and refused further surgery. In 4 cases a Roux-en-Y pancreaticojunostomy was necessary to drain the distal pancreas. 4 lesions in the pancreatic tail have been resected by a minimal invasive approach. There were no surgical complications besides one pseudocyst. Early results of surgery for diffuse cases are encouraging, but the follow-up time so far is too short to draw definitive conclusions.

Conclusion: Surgical therapy for congenital hyperinsulinism remains a demanding challenge. Long-term follow-up is necessary because many problems arise as late as in puberty.

P201

Complications After Resective Surgery for Pancreatic Cystic Neoplasms. Results from a Middle-High Volume Surgery Department for Pancreatic Surgery

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Introduction: Pancreatic cystic lesions have become a common finding in clinical practice. Five per cent of these lesions are premalignant or malignant neoplasms.

Objectives: To analyze the rate of complications after resective surgery for pancreatic cystic neoplasms (PCN) in comparison with surgery for pancreatic ductal adenocarcinoma (PDAC).

Materials & Methods: Between January 2000 and December 2009, all patients that underwent radical pancreatic resection for PCN and PDAC were identified from a prospective database and compared for complications’s rate and grading.

Results: A total of 88 patients (mean age 68.5 years; female 58%) underwent pancreatic resective surgery; 20.5% patients had PCN and 79.5% had PDAC. Overall complication and mortality rates were 53% and 4.5%, without significant differences between the two groups of patients and between medical and surgical complications. There was not a difference in complications grading among the two groups of patients. PDAC patients showed a trend for a higher rate of postoperative pneumonia than PCN patients (19% vs 6%, respectively), while PCN patients showed a higher rate of postoperative pancreatic fistula (POPF; 44% vs 17%, respectively).

Conclusions: The morbidity and mortality rates found in the two groups of patients were similar. Nevertheless a more careful POPF surveillance is required for PCN patients due to the higher rate of POPF than PDAC patients.

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Pancreatic Cystic Lesions – Insidious Surgical Issue

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Introduction: Pancreatic cystic tumors (PCT) represents several pathomorphological features with tricky symptoms and usually long course. Cystic tumors are of inflammatory, benign or malignant origin. The morphological term indicates presence of cystic spaces within the tumor mass. The symptomatology of cystic tumors is often scanty. Some patients presented exo- or endocrine insufficiency, full-
ness in epigastrium and pain. Jaundice, and weight lost are relatively rare features.

**Material & Methods:** Authors analyze the clinical course, tumor detection and surgical treatment of 19 patients with cystic lesions operated on between 2003 and 2011. Medical history, symptoms, primary diagnosis and final one and additional test confirming the lesion origin were analyzed.

**Results:** The period between first symptoms of PCT and definitive treatment vary from 2 to even 780 weeks. The most frequent symptom was pancreatic exocrine insufficiency required supplemental enzyme therapy. Patients usually were chronically medically treated by family doctors until clinical status change. This event was usually due to complications or malignancy development. Although lesions usually fit the criteria “worrisome features” the biopsy, neoplastic markers and cystic content was analyzed very seldom.

**Conclusions:** The awareness of General Practitioners, Radiologists and Gastroenterologists should be maintained by interdisciplinary meetings to pick up cystic pancreatic lesions and offer definitive diagnosis and adequate treatment on time.

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**P203**

**Pancreatic Endocrine Tumours: What is the Real Operative Risk and Survival?**

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**Introduction:** Well-differentiated pancreatic endocrine tumors (PET) are usually resected even if nonfunctioning or metastatic to the liver.

**Objectives:** The aim of this study was to assess factors influencing disease-free survival after PET resection according to presentation.

**Methods:** From 1995 to 2007, 118 patients (median age 51 years) underwent PET resection (37 pancreaticoduodenectomies [PD], 43 distal pancreatectomies [DP], 27 enucleations [EN], 10 medial pancreatectomies [MP] and 1 total pancreatectomy), associated with liver metastases (LM) in 21(18%), resected in 19(16%). Disease-free survival (DFS) was evaluated using Kaplan-Meier and compared with Log rank test.

**Results:** 83% and 75% of PET were sporadic and nonfunctioning, respectively. Postoperative mortality was 1.7% (1 EN, 1 MP). According to 2000 WHO classification, 24% were benign lesions (B), 25% of uncertain behavior (UB) and 51% carcinomas (N+=45, M+=21). After a median follow-up of 51.5 months, 5-year DFS was 72% (B=100%, UB=94% and carcinoma=57%). Recurrence in UB tumors occurred in 4 of 5 cases after 7 years of follow-up. Of the 32 (72%) nonfunctional, < or = to 2 cm, without radiologic metastases PET, 23 (72%) were B, 6 (19%) were UB and 3 (9%) were carcinoma (N+). For this group, the 5 and 10 years DFS was 100% and 80% respectively (2 recurrences at 85 and 130 months).

**Conclusions:** Nonfunctioning tumors < or = to 2 cm are malignant in only 9% of cases and their recurrences are rare and late. Since postoperative mortality is not nil even if after limited resections, the benefit/risk balance of surgery should be precisely discussed case by case. In other presentations, surgery is justified by a low mortality rate in a more aggressive disease.
**P205**

**Microvascular Density (MVD) in Pancreatic Neuroendocrine Tumors (PNET): Correlation with MDCT Post-Contrastographic Pattern and the Neoplasms Nature**

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**Introduction:** Couvelard et al demonstrated that benign tumor (ADN) showed higher MVD with respect to borderline tumor (BRD) and well differentiated carcinomas (WDC).

**Objective:** aim of our study was to correlate MDCT post-contrastographic patterns of PNET with their MVD and biological behaviour (ADN, BRD and WDC).

**Materials & Methods:** We compared 12 patients, who underwent quadriphasic MDCT study in early arterial (15”), pancreatic (30”), venous (70”), delayed (180”) phases. Three different post-contrastographic patterns were identified: pattern A (early arterial/ pancreatic enhancement and rapid wash-out, 4 cases); pattern B1 (early wash-in and no wash-out, 4 cases) and pattern B2 (enhancement only in venous or delayed phase, 4 cases). Greatest lesion dimension was measured. CT findings were compared with MVD in surgical pathological specimens (expressed by number of vessels/surface unit after CD34 staining; six fields for each patient) after pancreatic surgical resections.

**Results:** After surgical resection, pathological analysis demonstrated 2 ADN, 5 BRD and 5 WDC. We demonstrated that all ADN were associated with pattern A, showing high MVD (average level: 463 vessels/mm²); 3/4 lesions showing pattern B1 were BRD, with middle level of MVD (average level: 373 vessels/mm²) while 3/4 lesions with pattern B2 were WDC, demonstrating low level of MVD (average level: 237 vessels/mm²). We obtained statistically significant differences (p<0.0001) among the 3 different CT patterns and their MVD.

**Conclusions:** In our opinion the MDCT post-contrastographic pattern and the MVD of PNET can suggest their biological behavior.

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**P206**

**Autologous Pancreatic Islet Transplantation (IAT) as Endocrine Tissue Rescue in Patients Undergoing Completion Pancreatectomy Because of Pancreatico-Jejunostomy Failure**

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**Objective:** We tested the safety and feasibility of IAT in pts undergoing completion pancreatectomy because of anastomotic leak after pancreatoduodenectomy

**Methods:** Between November 2008 and September 2010, 7 pts were recruited (4M/3F, age 52±17 yrs). Six of 7 were cancer-bearing pts (two ampullary cancer; two bile duct cancer; one pancreatic cancer; one neuroendocrine carcinoma; one focal pancreatitis). Completion pancreatectomy was performed 18±9 days after PD because pancreatic fistula with delayed bleeding (4 pts), sepsis (2 pts) and acute pancreatitis (1 pt). Islets were obtained and purified by the pancreatic remnant (64±18g) as for allogenic transplantation.

**Results:** Isolation was possible in 6/7 pts (it failed in pt with acute pancreatitis for pancreas necrosis). Mean islet yield was 2,746±957 IEQ/g of tissue, resulting in transplantation of 1,966±1,090 IEQ/kg body weight. Islets were transplanted within 24h by percutaneous transhepatic intraportal infusion (3 pts) or by intraoperative portal vein infusion (1 pt). Due to the presence of pre-existing portal thrombosis, islets were infused into iliac crest in one pt. Three pts had IAT-related minor complications, including partial portal vein thrombosis (2 pts) and perihepatic hematoma (1 pt). Two pts died (acute pancreatitis, IAT unrelated bleeding relapse). The other pts are alive at a median follow-up of 299 days. Pts #2 (2,157 IEQ/kg) gained (at day +118) and maintained insulin free regimen until last observation (day +746). Pts #1, #4, #6, #7 showed transplant partial function. At six months follow-up, C-peptide, insulin requirement and HbA1c were 0.86±0.66ng/ml, 0.27±0.19UI/kg/day and 7.2±0.6%, respectively. No symptomatic hypoglycemia or hepatic metastases were recorded.

**Conclusion:** IAT is a safe and feasible procedure to improve glycemic control after completion pancreatectomy.
**Abstracts**

**P207**

*Cystic “Feminine” Pancreatic Neoplasms in Men. Do Any Hormonal and/or Phenotypic Alterations Correlate with these Uncommon Entities?*

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**Introduction:** Mucinous cystic neoplasm (MCN) and solid pseudopapillary neoplasm (SPN) of the pancreas are uncommon hormone related pancreatic tumours (HRPTs) with a clear predominance in young women.

**Objectives:** To investigate the possible association between HRPTs development in males and phenotypic and sex hormone alterations.

**Patients & Methods:** A retrospective analysis of our database was performed between the date February 1990 and December 2010 searching for male patients with HRPTs. Risk factors for sexual dysfunction (age > 65, severe diabetes, alcoholism, atherosclerosis) were considered exclusion criteria. We investigated secondary sexual characteristics development, sex hormones level and overall sexual dysfunction degree according with the International Index of Erectile Function (IIEF) Questionnaire.

**Results:** We initially identified 25 patients [(MCN: n = 16 (64%); SPN: n=9 (36%)]. At follow-up, five patients were lost, eight resulted dead and three were excluded according with exclusion criteria. We finally enrolled 9 patients (MCN: n = 5; SPN: n = 4). Puberty occurred within physiological age for 7 patients (Mean:13.3 years; SD: ± 1) while it was mildly delayed in 2 cases. Signs of gynecomastia were not showed from adolescence until surgery in whole series. Three patients revealed mild sexual dysfunction at IIEF score, along with low testosterone level in two cases. Another patient with low level of testosterone was affected by secondary azoospermia.

**Conclusion:** In this study, the first in literature with similar aim, hormonal and/or sexual dysfunction was present in 30% of HRPTs. Unfortunately, the small sample size along with the rarity of these lesions, make further trials to be needed for reliable conclusions.

**Basic Science – Pancreatic Cancer IV**

**P208**

*Hedgehog Inhibition with the Orally Bioavailable Smo Antagonist LDE225 Represses Tumor Growth and Prolongs Survival in a Transgenic Mouse Model of Islet Cell Tumors*

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**Background:** This study was designed to evaluate the role of the Hedgehog (Hh) pathway in tumor progression of murine islet cell tumors. Blockade of aberrant Hh activation has recently been proposed as a therapeutic target, but effects in models of islet cell tumors with a new orally bioavailable Smo antagonist LDE225 have not been examined.

**Material & Methods:** To asses in vivo effects transgenic Rip1Tag2 mice, which develop islet cell tumors, were treated with vehicle or LDE225 (80 mg/kg/d) from week 5 until death. Treatment started at 5 weeks of age and was continued until death. The resected pancreata were evaluated macroscopically and microscopically by immunochemistry and quantitative real-time PCR was performed for Hh target genes with RNA from islet cells, isolated from treated and untreated Rip1Tag2 mice.

**Results:** LDE225 significantly reduced tumor volume by 95% compared to untreated control mice. Hedgehog inhibition with LDE225 significantly prolonged median survival in the used transgenic mouse model (105 vs. 116 days; p = 0.02). Quantitative real-time PCR was performed for downstream Hh target genes with RNA from islet cells, isolated from treated and untreated Rip1Tag2 mice.

**Conclusion:** This is the first study to show that the orally bioavailable Smo antagonist LDE225 may provide a new option for therapy of islet cell tumors.
**Introduction:** Pancreatic serous cystadenomas (PSC) may present atypical clinical or radiological features, thus mimicking other cystic tumors, such as neuroendocrine tumors (NET).

**Objectives:** The aim of this study was to assess, in PSC, immunohistochemical expression of somatostatin receptor type 2 (SST2) and somatostatin receptors scintigraphy (SRS) positivity.

**Patients & Methods:** This retrospective study (1995–2010) included 27 patients with PSC proven by pancreatic biopsy (n = 1) or resection (n = 26). 8 patients with von Hippel Lindau (VHL) disease were operated on for an associated NET; 2 patients underwent surgery for a symptomatic PSC; 16 patients were operated on for an associated NET; 2 patients underwent surgery for a symptomatic PSC. A score (0–200) was calculated for each tumor by multiplying staining intensity (no staining = 0; weak 1; strong 2) by the percentage of stained cells.

**Results:** The mean SST2 score was 105. 24/26 (92%) of PSC were SST2 positive: 6 (23%) with a score of 200, 12 (46%) with a score between 100 and 200, and 6 (23%) with a score < 100. 2 (40%) of the 5 SRS performed in non VHL patients were positive, with a moderate fixation. Interpretation of the SRS performed in VHL patients was difficult because of PSC/NET association in this disease.

**Conclusion:** PSC must be added to the list of SST2 positive tumors, and SRS can be positive in PCS. When the imaging of PSC is atypical, SRS positivity can mislead to the diagnosis of NET.
Characterization of Membrane Vesicles in Pancreatic Ductal Adenocarcinoma Cell Lines

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Introduction: Membrane vesicles (MV) are cell fragments representing a recently identified form of intercellular communication. The MVs seem to be involved in numerous physiological and pathological processes and besides their effect on tumorigenesis, in some cases they might also act as diagnostic markers or prognostic factors.

Objectives: We wanted to establish a method which could be used in routine work and allows to isolate and detect MVs and to examine their intravesicular content.

Materials & Methods: All experiments were performed on routinely grown monolayer cell cultures of pancreatic ductal adenocarcinoma (PDAC) cell lines. The MVs were isolated from the supernatant of cell lines growing in serum-free medium using a special isolation procedure. Then MVs were subjected to further investigation by Fluorescence Activated Cell Sorting (FACS). To confirm our results alternative techniques such as electron microscopy (EM), atomic-force microscopy and light scattering were used.

Results: Viability and apoptosis/necrosis of our cells were analyzed by FACS. Through staining the MVs with a lipophilic membrane marker (PKH) it is demonstrated that the particles thought to be MVs based on forward and side scatter data are truly membrane-bounded particles. MV samples were also examined by EM and light scattering showing the same results seen on FACS.

Conclusion: We proved that our method is suitable for isolation of MVs produced by PDAC cells. Our hope is that MVs might be used as diagnostic markers or prognostic factors in pancreas adenocarcinoma patients.

Abstracts

P213

Human Pancreatic Fibroblasts Promote Epithelial to Mesenchymal Transition (EMT) in Pancreatic Cancer Cells by Enhancing EMT Transcription Factor Signalling

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Activation of EMT in cancer cells promotes neoplastic invasion and metastasis. EMT is caused by aberrant expression of transcription factors (ZEB1/ZEB2, Snail, Slug) involved in embryonic development. Fibroblasts from tumor microenvironment have been implicated in local and metastatic tumor expansion.

Aims: To investigate the role of pancreatic fibroblasts (PF) in EMT activation in pancreatic cancer cells and to identify the transcription factors involved.

Methods: Human PFs were isolated from pancreatic specimens obtained from unaffected margins of pancreatic adenocarcinoma and intraductal papillary mucinous tumors, and from chronic pancreatitis. PF were cultured until complete cellular activation, as assessed by expression of α-smooth muscle actin, vimentin and fibronectin. Human pancreatic cancer cells Panc-1 were exposed to PF conditioned medium (PF-CM) and EMT analyzed by cell morphology (phalloidin staining), migration, and E-cadherin expression (quantitative RT-PCR and immunoblot). Gene expression of Snail, Slug, ZEB1, and ZEB2 was analyzed by quantitative RT-PCR, and their activity modulated by RNAi.

Results: PF-CM from all types of activated PFs induced EMT changes in Panc-1 cells, as shown by morphological transition from cobblestone shaped to fibroblast-like cells, enhanced cell migration, and E-cadherin down-regulation. Panc-1 cells showed high basal nuclear expression of ZEB1 as detected by immunostaining. mRNA and protein levels of ZEB1 and ZEB2 did not further increase upon PF-CM exposure, but expression of Snail and Slug were greatly enhanced. RNAi downregulation of ZEB1 or/and ZEB2, but not Snail and/or Slug, reverted E-cadherin expression. Cell migration was not inhibited by any single RNAi transcription factor downregulation.

Conclusion: Activated pancreatic fibroblasts enhance tumor aggressive behavior by fueling the combined effects of ZEB1/ZEB2, Snail and Slug.
**P214**

*In Vivo Diagnosis of Murine Pancreatic Intraepithelial Neoplasia and Early-Stage Pancreatic Cancer by Molecular Imaging of Cathepsin Activity*

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**Introduction:** Pancreatic ductal adenocarcinoma (PDAC) is a fatal disease with poor patient outcome often resulting from late diagnosis. To date methods to diagnose early-stage PDAC are limited and the detection of preinvasive pancreatic intraepithelial neoplasia (PanIN) in vivo is impossible.

**Objectives:** To improve patient outcome it is essential to develop novel imaging strategies for the early detection of curable disease.

**Material & Methods:** Genome-wide gene expression profiling and immunohistochemistry were used to identify cathepsin proteases as targets for molecular imaging of mPanIN lesions and early-stage PDAC. In vivo confocal fluorescence laser microscopy (CFL) was performed in genetically engineered mice carrying mPanIN lesions or early-stage PDAC by using a cathepsin B, H, L and S activatable near-infrared fluorescent (NIRF) probe or the unspecific contrast agent fluorescein in a double-blind study.

**Results:** CFL imaging of cathepsin activity reliably detected low-grade mPanIN lesions on the cellular level and, importantly, allowed discrimination from high-grade mPanINs and early-stage PDAC. CFL imaging revealed high sensitivity and specificity for neoplastic disease, since only low probe signals were detected in normal pancreas and pancreatitis. In contrast, it was not possible to identify and distinguish low- and high-grade mPanINs and PDAC by fluorescein-imaging.

**Conclusion:** CFL imaging of cathepsin-activity allows the detection of mPanINs and early-stage PDAC in real-time in vivo. This method is highly sensitive and specific and proved superior to clinically established fluorescein-enhanced imaging. Translation of this endoscopic technique into the clinic should tremendously improve the management of patients at risk for PDAC.

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**P215**

*Interference with Estrogen Receptor Signaling Inhibits Human Pancreatic Adenocarcinoma Growth*

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**Introduction:** The role of estrogen receptor (ER) signaling in pancreatic cancer is unknown. Recently, we demonstrated that expression of the isoform ER beta correlates with an adverse prognosis in patients with pancreatic cancer.

**Objectives:** To show that raloxifene, a specific estrogen receptor modulator (SERM), suppresses in vitro and in vivo tumor growth by interfering with ER beta signaling in human pancreatic adenocarcinoma.

**Material & Methods:** The human pancreatic adenocarcinoma cell line L3.6pl was cultured and exposed to raloxifene in vitro, and cell proliferation was determined by the BrdU assay. To analyze the specificity of raloxifene induced effects, ER knockdown was performed using siRNA specific for ER alpha and ER beta. In an in vivo model of orthotopic tumor xenografts in nude mice, raloxifene was administered daily, and tumor growth was monitored. Expression of ER beta and the proliferation marker Ki-67 were determined by immunohistochemistry.

**Results:** Raloxifene treatment resulted in a potent, dose dependent reduction of proliferation in vitro over a nanomolar dose range. This effect was completely reversed by siRNA knockdown of ER beta but not ER alpha, indicating an ER isotype specific signaling. In vivo, orthotopic tumor growth, as well as lymph node and liver metastases, was significantly suppressed in raloxifene treated mice. Analogous to the in vitro data, Ki-67 expression in vivo was significantly reduced in raloxifene treated mice, while ER beta expression was not changed in vivo.

**Conclusion:** Inhibition of ER beta signaling by raloxifene results in a potent reduction of human pancreatic adenocarcinoma growth in vitro and in vivo. Treatment with SERMs may be an attractive therapeutic option in subjects expressing the ER beta isotype.
The Combined Analysis of miRNA and mRNA Expression Levels in Normal and Pancreatic Cancer Tissues Allows the Identification of Mirna Targets

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Introduction: MicroRNAs (miRNAs) are a recently recognised class of non-coding short RNAs that play a role in post-transcriptional gene regulation by reducing the stability of target mRNA molecules. Many miRNAs are implicated in pancreatic tumorigenesis.

Objectives: of this study was to profile the expression of miRNAs in pancreatic ductal adenocarcinoma (PDAC) and normal pancreas in order to predict their putative target transcripts by the combined analysis of mRNA expression levels in the same tissues.

Materials & Methods: We evaluated miRNAs and mRNAs expression levels in PDAC (n=9) and normal pancreas (n=9) by using Nanostring nCounter Human miRNA Expression Array (664 Human miRNAs) and Affymetrix Human Gene 1.0 ST Array (interrogates 28,869 well-annotated genes), respectively. Normalization of miRNA and mRNA array datasets was performed. Various techniques were used to predict miRNA-mRNA interactions.

Results: There were 22 miRNAs and 518 mRNAs whose expression was significantly altered in PDAC compared to normal tissue (adjusted P<0.05). Crossed analysis of miRNA and gene data was then performed with respect to the presence of a miRNA seed (6-mer, 7-mer or 8-mer) in the 3’UTR of a given gene. This was further limited to reveal 15 upregulated miRNAs and 148 downregulated genes in PDAC; with the genes having at least 1 seed for any up-regulated miRNA in its 3’UTR. Interestingly, several of the genes identified are known tumour suppressors in PDAC.

Conclusion: Combined analysis of miRNA and mRNA expression levels in PDAC has allowed us to identify target transcripts of specific miRNAs. Several are currently under investigation.

Pancreas Specific Expression of Oncogenic p110αH1047R Induces Pancreatic Intraepithelial Neoplasia and Pancreatic Cancer

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Introduction: Oncogenic Kras induces pancreatic ductal adenocarcinoma (PDAC). Yet it is still unclear which signaling pathways downstream of oncogenic Kras are essential for tumor induction. The phosphatidylinositol 3-kinase (PI3K) pathway is one of the main targets of oncogenic Kras and is found to be aberrantly activated in a variety of human cancers.

Objectives: Aim of this work was to study the role of the PI3K pathway in pancreatic carcinogenesis.

Material & Methods: To achieve pancreas specific activation of PI3K signaling, we generated a conditional constitutive active allele of the PI3K subunit p110α (p110αH1047R). The p110αH1047R expression cassette with a 5’ loxP flanked stop-cassette (LSL) was introduced into the murine Rosa26-Locus (R26) by homologous recombination. LSL-R26p110αH1047R/+ mice were crossed with the Ptf1aCre/+ line to express p110αH1047R specifically in the pancreas.

Results: Ptf1aCre/+; LSL-R26p110αH1047R/+ mice develop murine pancreatic intraepithelial neoplasia (mPanIN) and metastatic PDAC with a latency similar to the established KrasG12D model. Tumor cells from Ptf1aCre/+; LSL-R26p110αH1047R/+ mice show the same genetic alterations as tumor cells from the Kras model (e.g. loss of p16INK4a expression) and also respond similarly to pharmacologic inhibition in vitro. Finally, selective inhibition of the PI3K pathway induces a cytostatic response in KrasG12D driven tumor cells in vivo.

Conclusion: Activation of PI3K signaling in the pancreas is sufficient to induce mPanINs that progress to PDAC. Using this novel model of pancreatic carcinogenesis we identified PI3K as the main downstream effector of oncogenic Kras. This new model will provide new opportunities for the development of novel targeted therapeutic interventions.
FOLFIRI Regimen as Second/Third-Line Chemotherapy in Patients with Advanced Pancreatic Adenocarcinoma Refractory to Gemcitabine and Platinum-Salts: A Retrospective Series of 70 Patients

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Background: Gemcitabine-based chemotherapy (CT) is a standard of 1st-line CT in advanced pancreatic adenocarcinoma (PAC) and 5-FU/oxaliplatin combination is an option for 2nd-line (Oettle, J Clin Oncol 2005). Data suggested a potential efficacy of 5-FU/irinotecan CT (FOLFIRI) as 1st-line treatment (Taieb, Ann Oncol 2007) or in gemcitabine/platinum-refractory advanced PAC (Yoo, Br J Cancer 2009; Gebbia, Am J Clin Oncol 2010). We aimed to retrospectively evaluate the efficacy and safety of FOLFIRI regimen as 2nd/3rd line CT in advanced PAC.

Methods: All consecutive patients with advanced PAC (01-2005/05-2010) and OMS≤2, received FOLFIRI-1 (irinotecan 180 mg/m² D1, n = 60) or FOLFIRI-3 CT (irinotecan 100 mg/m² D1 D3, n = 10) after failure of gemcitabine and platinum-based CTs as a systematic policy in our institutions. Data analyzed: tumor response, time to progression (TTP), overall survival rate (OS) and grade 3–4 toxicities. Subgroup analyses were performed to identify prognostic factors.

Results: 70 patients were studied. Median age was 60 years (range: 24–81); 52.9% were male; 30 (42.9%) were PS 0, 26 were PS 1 and 14 were PS 2. Cancer was locally advanced in 15.7% and metastatic in 84.3% of patients. Before FOLFIRI regimen, patients received 1 line (n=24, 34.3%), 2 lines (n=40, 57.1%) or ≥ 3 lines (n=6, 8.8%) of CT. TTP with last previous line was 3.8 months. Using FOLFIRI, tumor control was achieved in 31 (44.3%) patients (PR: 5, SD: 26). Median TTP was 3.2 months (CI95%: 2.5–4.2), median OS was 6.7 months (CI95%: 5.4–8.9). Dose adaptation was required in 39 (55.7%) patients. Eighteen (25.7%) patients had grade 3–4 toxicities (haematologic n = 13, digestive n = 6). Febrile neutropenia occurred in 3 patients. There was no toxic death. PS 2 was significantly associated with poor TTP (0.9 months, HR = 6.66, p < 0.001) and OS (2.5 months, HR = 3.95, p = 0.001).

Conclusions: FOLFIRI regimen after failure of gemcitabine- and platinum-based CTs for advanced PAC has acceptable toxicity and interesting efficacy limited to patients in good condition (PS 0-1). FOLFIRI regimen should be tested as 1st line CT in patients with advanced PAC.

Avascular Pancreatic Minitumors: A Platform for Drug Screening – An In Vitro Model for Studying Pancreatic Cancer

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Pancreatic cancer is characterized by exceptionally strong fibrosis and pancreatic stellate cells (PSCs) are the major player in synthesizing extracellular matrix (ECM) upon their activation. The interaction/communication between PSCs and pancreatic ductal adenocarcinoma (PDAC) cells is essential for inducing stroma/ECM production, pancreatic cancer progression and general therapy resistance.

Compared to traditional 2D cell culture, cells in a three-dimensional context demonstrate different behavior and functions as reflected by building up a microenvironment that more closely mimics the one observed in native tissue. This feature is especially critical for testing drug efficiency, as cellular response to drugs is profoundly affected by environmental cues.

Our aims were to build up a more reliable drug screening system. To this end we set up and compared 2D and 3D cell cultures containing either human PDAC and PSC cells alone or in combination.

Among PDAC cells, panc-1 cells are the most commonly used which are also able to form spheres in vitro. We used panc-1 cells to build mono-spheres and compared them to their 2D counterpart. The ability of different drugs to reduce viability in panc-1 spheres was much lower than in 2D cultures. Cells in 3D compared to the 2D culture showed higher gene expression for ECM proteins as collagen and fibronectin, for growth factors as PDGF and VEGF, as well as for protein like Cox2.

In order to more closely resemble the in vivo PDAC situation, we co-cultured panc-1 and PSC cells, allowing them to interact in the formation of hetero-spheres in which PSCs localized in the cortical area and were identified e.g. by ASMA (a marker for activated PSCs). These avascular minitumors were further characterized with respect to cellular crosstalk and chemoresistance behavior.

We conclude that 3D cultures are much more resistant to chemotherapy compared to their 2D counterpart offering a more predictive platform for drug screening before proceeding to more expensive in vivo models and clinical trials. The avascular minitumors can be considered as an alternative in vitro cell model for studying pancreatic cancer development and fibrosis from a more complete perspective.
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P220
Intraoperative Prediction of Postoperative Pancreatic Fistula by a Histological Score Based on the Frozen Section
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Introduction: Postoperative pancreatic fistula (POPF) is a major complication after resective pancreatic surgery.

Objective: This study aimed to identify histomorphological features of the pancreatic remnant which may be useful for the early risk prediction of POPF development.

Methods: Twenty-five patients, 3.6% of 696 resections over a period of 5 years, who developed clinically significant POPF (grade B, n = 17 and grade C, n = 8) were matched for age, gender, diagnosis, comorbidities, surgeon and type of surgical procedure with 25 control patients who did not develop a POPF. Pancreatic duct size and index, fibrosis grade, fat content, edema, signs of chronic and acute inflammation were measured at the resection margin using slides of the frozen sections and then compared.

Results: POPF rate after left resection was 12.2%, significantly higher than after pancreaticoduodenectomy 2.6%. POPF group was characterized by a longer ICU and total postoperative stay, higher rate of reoperations and total postoperative complications. Their pancreata were softer at palpation, 88% vs 56%. Their pancreatic duct was smaller, 2.5 vs 3.2 mm, and pancreatic fat content higher, 16% vs 8%. Signs of chronic pancreatitis, interlobular fibrosis, inter- and intralobular fat content and duct size were predictors of POPF development. A score including these parameters identified high-risk patients with a sensitivity of 92% and specificity of 84%.

Conclusion: These data suggest that a simple histological score based on the findings of the frozen section may already intraoperatively predict the risk of POPF development.

P221
Efficacy of a Fluted Drain with Continuous Suction on Pancreatic Fistula After Pancreaticoduodenectomy
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Introduction: Pancreatic fistula (PF) is the most prevalent cause of morbidity after pancreaticoduodenectomy (PD). The most crucial management for PF is adequate drainage of the amylase-rich fluid by peripancreatic drains.

Objective: The aim of this study was to evaluate the efficacy of the fluted drain with continuous suction for the management of PF in comparison with the conventional drain.

Material & Methods: Our study consisted of two parts: a basic experiment to investigate the effects of the fluted drain on the management of PF in an animal model, and a retrospective review of 42 patients with PF after PD.

Results: In the basic experiment, Blake drains could accomplish complete drainage of fluids through channels along the sides while holes of Duple drains could not remove fluids collection completely. In an animal model, no collections of fluid were detected around the Blake drains. When leakage occurred, it did not lead to abdominal abscess, and a drain canal formation linking the anastomosis with the extracorporeal orifice was demonstrated all along the drainage route. In the clinical study, 28 patients received Blake drains (B-group) and 14 received Duple drains (D-group). Grade C fistulas with abdominal bleeding developed in only 2 patients in the B-group. All the patients in the B-group healed with conservative treatment (P < 0.01), and none of them required percutaneous drainage or reoperation (P < 0.05).

Conclusions: Blake drains may be efficient therapeutic tools in patients with grade B fistulas. The basic experiment affirms that Blake drains provide excellent drainage and contribute to the formation of drain canals effective in localizing and controlling PF.

P222
Continuous Suction Drainage to Avoid Severe Pancreatic Fistula After Pancreaticoduodenectomy
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Introduction: Pancreatic fistula is a possible cause of lethal complication. Adequate drainage after pancreaticoduodenectomy can prevent from increasing severity.

Objectives: We verified practical effectiveness of three continuous suction drainages after pancreaticoduodenectomy.

Patients & Methods: This is a retrospective review of the patients who underwent pancreaticoduodenectomy for a broad range of periampullary and pancreatic pathologies in our hospital. Eighteen patients who developed pancreatic fistula were examined. We have used Pancreatic fistula was diagnosed according to the International Study Group for Pancreatic Fistula (ISGPF). Pancreaticojunostomy was performed using duct-to-mucosa anastomosis or complete drainage. Reconstruction was undertaken with Child procedure. All patients were divided into 2 groups, those who had two drain (Winslow + back side of pancreaticojunostomy) and those who had three drain (lower group + undersideoef left hepatic lobe). We examined the severity in two groups based on the ISGPF.

Results: There were no differences in the background of the two groups. Pancreatic fistula of 2 groups occurred at the same frequency in two groups based on the ISGPF.

Abstracts

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quency (28%). But there was a 44% severity (ISGPF B,C) rate in lower group and no severity in later group. Four patients required AUS-guided percutaneous drainage. Notably, the all of abscess site spread underside of left hepatic lobe. All the severe patients developed an infection 7 days after surgery.

**Conclusions:** Introduce continuous suction drainage could prevent the abscess from early spreading into the abdominal cavity. Because abscess from pancreatic fistula invariably accumulated underside of left hepatic lobe, the drainage at this point decreased severity rate.

**P223**

**Does Postoperative Pancreatic Fistula Affect the Quality of Life in Patients Undergoing Pancreatic Surgery?**

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**Introduction:** Postoperative pancreatic fistula (POPF) is a major complication after resective pancreatic surgery.

**Objective:** To test the hypothesis that quality of life (QoL) at 3 months postoperatively is worse in patients with POPF compared to those without POPF.

**Methods:** The SF-36 survey was completed before and 3 months after surgery by 174/296 patients who underwent pancreatic surgery within a year at a high-volume pancreatic center. 12 cases of clinically significant POPF were compared to 12 control patients without POPF or any other major complication who were matched for age, sex, diagnosis and surgical procedure.

**Results:** There were 4 cases of chronic pancreatitis, 5 malignancies and 3 benign tumors of the pancreas who underwent 5 duodenopancreactectomies and 7 distal pancreactectomies. Mean age was 61.7 yrs vs. 61.8 yrs in the control group, p = 0.98. Postoperative stay of POPF patients was 23.3 d vs. 16.8 d, p = 0.09. Surgery caused a significant drop in physical health score, whereas mental health score increased postoperatively in all cases. In the POPF group physical score fell from 50.3 to 39.4, in the controls from 46.0 to 38.7. The preop-to-postop score difference was respectively -11.0 vs. -5.8, p = 0.37. Mental score increased in the POPF group from 47.8 to 51.1 and in the controls from 47.4 to 50.7. The score difference was 3.3 vs. 3.1, p = 0.98. No differences between the groups were observed in the individual 8 items of SF-36.

**Conclusion:** Development of postoperative pancreatic fistula did not contribute to the observed changes in physical and mental quality of life due to resective pancreatic surgery.

**P224**

**Perioperative Outcome After Laparoscopic and Conventional Major Pancreatic Resections**


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**Introduction:** Despite the expansion of laparoscopic surgery, laparoscopic resections of the pancreas are only performed in a small number of specialized centers. Prophylactic operations in case of cystic tumors and premalignant lesions offer a broad spectrum of indications for laparoscopic resections of the pancreas.

**Objectives:** The objective was to compare perioperative outcome after conventional and laparoscopic pancreatic resections in a single centre.

**Patients & Methods:** Between 1997 and 2010 we performed 145 open resections of the pancreatic tail (open-tail) and 605 open resections of the pancreatic head (open-head). Since 8/2009 we performed 17 lap. resections: 8 of the pancreatic tail (lap-tail) and 9 of the pancreatic head (lap-head). Reconstruction was performed over a 6 cm minilaparotomy.

**Results:** There was no conversion in the group lap-tail. Perioperative parameters were not different compared to the open-tail group concerning time of operation (174 vs 287 min) hospital stay (19.5 vs. 26.8 days) major complication, pancreatic fistula (37% vs 21%) or mortality (0% vs 2.1%). In the lap-head group there were 3 conversions for oncological reasons. Compared to the open-head group, results did not differ concerning operation time (436 vs 456 min) hospital stay (23.3 vs. 25.43 days) major complication, pancreatic fistula (22% vs 15%) or mortality (0% vs 3%).

**Conclusion:** Lap. pancreatic resections show a trend towards shorter operation time and hospital stay and did not differ in perioperative outcome compared to open operations. Laparoscopic pancreatic resections are a reasonable alternative and should be further established and evaluated in specialised centres.

**P225**

**Surgery After Neoadjuvant Therapy for Primarily Irresectable Pancreatic Cancer: Perioperative Outcome and Survival in 257 Patients**

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**Background:** In pancreatic cancer (PanCan) a complete macroscopic resection plus (radio)chemotherapy is the only potentially curative treatment. Many patients present with locally advanced tumors that are primarily irresectable.

**Aim:** To assess the results of surgery after neoadjuvant therapy for primarily irresectable PanCan.
**Methods:** From a prospective database all consecutive patients undergoing surgery from 09/03 to 09/10 after neoadjuvant therapy for primarily irresectable PanCan were identified. Main criteria for irresectability were involvement of the celiac axis and superior mesenteric artery. Resection rates, perioperative results and survival were analyzed.

**Results:** Of 257 pats. 199 (77.4%) had received chemoradiation, 58 (22.6%) chemotherapy only. 120 (46.7%) pats. underwent resection, 137 (53.3%) exploration only. 47 (39.2%) multivisceral and 45 (37.5%) vascular resections (11 arterial reconstructions) were performed. In the resection group, there were 6 (5%) ypT0 tumors, 29 (24.2%) R0-, 57 (47.5%) R1-, 14 (11.7%) R2-resections. Overall morbidity and mortality were 30.7% and 5.0% and associated with multivisceral/vascular resections. At the last follow-up 38 patients were still alive with a median follow-up of 11 months. Median survival was significantly longer after resection (12.7 months) than after explorations (8.7 months).

**Conclusions:** In primarily irresectable PanCan R0/R1-resections can be achieved in up to 40% of patients that undergo surgery after neoadjuvant therapy and result in survival rates similar to that observed for primarily resectable PanCan.

### Table

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<th>Distal Resection n=28</th>
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<td>n=31 (16%)</td>
<td>n=2 (6%)</td>
<td>n=0</td>
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<td>Pancreatic fistula (grade B/C)</td>
<td>n=30 (16%)</td>
<td>n=4 (11%)</td>
<td>n=3 (11%)</td>
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<td>n=83 (43%)</td>
<td>n=13 (37%)</td>
<td>n=9 (32%)</td>
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<tr>
<td>Hospitalization/days (median, range)</td>
<td>18 (11–92)</td>
<td>22 (11–47)</td>
<td>16 (11–52)</td>
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<tr>
<td>Mortality</td>
<td>n=6 (3,1%)</td>
<td>n=0</td>
<td>n=1 (3,6%)</td>
</tr>
</tbody>
</table>

**Conclusions:** Our results meet the „high volume quality standards of a center for pancreatic surgery with regard to the number of resections per year, morbidity, and mortality.

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**P226**

**Pancreatic Surgery at the University Hospital of Rostock: Results of 265 Consecutive Pancreatic Resections**

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**Background & Aim:** The benefit of surgical center formation has become a focus of interest in Germany during the past years. It is well documented that a high case load of complex gastrointestinal resections in so called „high volume centers significantly improves morbidity and mortality. We aimed to analyze this effect on pancreatic surgery performed at our institution.

**Patients & Methods:** A total of 265 consecutive patients underwent open pancreatic surgery between 09/03 and 09/10. There were 152 patients with pancreatic/ampullary/distal bile duct cancer, 90 with chronic pancreatitis, and 23 with benign/borderline tumors. Data were assessed by a standardized documentation sheet and entered in a computer database (ACCESS®).

**Results:** A pylorus-preserving or classical pancreaticoduodenectomy was performed in 153 (58%) and in 39 (15%) patients, respectively. A duodenum preserving pancreatic head resection (DPPHR) was performed in 35 (13%) patients. Twenty-eight (11%) patients underwent a distal resection, 7 patients a total pancreaticoduodenectomy, and 3 patients other resections. This corresponds to an average of 38 resections per year. Our results are shown in the table below.

**Conclusions:** In primarily resectable PanCan R0-, R1-, R2-resections can be achieved in up to 40% of patients that undergo surgery after neoadjuvant therapy and result in survival rates similar to that observed for primarily resectable PanCan.

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**P227**

**Preoperative Imaging Based Criteria Predict Pancreatic Fistula Rate After Pancreaticoduodenectomy**

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**Introduction:** Morbidity after pancreaticoduodenectomy (PD) is high. Pancreatic fistula (PF) due to insufficiency of the pancreaticojejunostomy is considered the main cause of morbidity after PD. Methods to predict PF would be helpful in the counseling with the patient. We previously demonstrated an increased risk for PF in large volume pancreatic remnants after distal pancreatectomy.

**Objectives:** To evaluate if imaging assessed pancreatic remnant volume (PRV) or duct area (PDA) affect the risk for PF after PD.

**Patients & Methods:** From our prospective registry at Karolinska all patients undergoing PD between September 2007 and November 2010 were included. Preoperative CT investigations were analyzed by a radiologist blinded to the postoperative outcome. The PRV and PDA were calculated based on the alleged transection line.

**Results:** A total of 182 patients (mean age 66) were investigated. The diagnosis was malignant in 144 (79%) and benign in 38 (20%). PF according to the ISGPF-classification occurred in 37 patients (20%). The mean PRV was 36.9 ± SD 15.5 cm³. Mean DA was 4.6 ± SD 3.0 mm². In univariate analysis, a large volume of the pancreatic remnant (OR: 1.052, CI: 1.026–1.078; P ≤ 0.001), and a small duct area (OR: 1.052, CI: 1.026–1.078; P ≤ 0.001) increased the risk of PF. In multivariate analysis both factors maintained their impact on PF risk.

**Conclusion:** A large PRV and small PDA increase the risk of PF. Preoperative CT-based assessment offers a way to predict this risk of morbidity and thus in counseling the patient before PD.
**P228**

**An Algorithm Based on Amylase Value in Drains and Ultrasound Abdominal Imaging for the Prediction of Postoperative Pancreatic Fistula**

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**Introduction:** Prediction of pancreatic fistula (PF) after standard pancreatic resections is essential for an appropriate postoperative management. In this respect, measurement of amylase value in drains (AVD) on postoperative day (POD) 1 has been shown to be a clinically relevant tool.

**Objectives:** To assess whether ultrasound imaging on POD 3 is a predictive factor of postoperative PF and whether it can be employed in combination with AVD.

**Patients & Methods:** Patients who underwent standard pancreatic resections between September 2009 and August 2010 were analysed with uni- and multivariate models. The interaction between potential risk factors was assessed using a decisional-tree algorithm.

**Results:** 173 patients were included in the study. The overall incidence of PF was 31.2%. Along with AVD on POD 1 (cut-off 5000 UI/L), the finding of a peripancreatic collection at ultrasound examination on POD 3 was a risk factor of PF (binary logistic regression, p < 0.0001). Both the variables were selected by the model for the construction of a decisional algorithm. Patients were first stratified by AVD on POD 1. For an AVD < 5000 UI/L (rate of PF = 11.3%), ultrasound had a PPV of 0.1% and a negative predictive value (NPV) of 90.8%. For an AVD ≥5000 UI/L (rate of PF = 70.7%), ultrasound had a PPV of 100% and a NPV of 43.6%.

**Conclusion:** The finding of a peripancreatic collection at ultrasound imaging on POD 3 is a risk factor of PF. The proposed algorithm based on AVD on POD 1 and ultrasound examination on POD 3 can be used for the prediction of postoperative PF.

**P229**

**Pancreatic Stent Insertion Does Not Reduce the Risk for Pancreatic Fistula After Distal Pancreatectomy. Results of a Randomized Controlled Clinical Trial**

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**Introduction:** Pancreatic fistula (PF) is the major cause for morbidity after distal pancreatic resection (DP). Transapillary pancreatic stenting (PS) has been claimed to offer downstream control and to be beneficial for the treatment of established PF.

**Objectives:** The current RCT was done to test if prophylactic transpapillary PS reduce the risk of PF after DP.

**Patients & Methods:** Patients planned for DP at Karolinska University Hospital during October 2006 to December 2010 were assessed and randomized to either standard DP (DP) or to intra-operative ERCP with insertion of a PS before transection of the gland (DP-PS). DP was done in a standardized manner transecting the gland by a stapler. The outcome was included in an intention to treat analysis. Follow up time was 30 postoperative days.

**Results:** Of 64 patients planned for DP, 49 patients were randomized. 25 DP and 24 DP-PS. In two of those a stent could not be accurately applied. The number of clinical significant PF (ISGPF Grade B or C) between DP (6/25, 24%) and DP-PS (11/24, 45.8%) were not significantly different (p = 0.113). Another ISGPF 4 grade A PFS were observed in DP vs. 2 in DP-PS (ns). Both operative time (DP-PT 305 ± 23 vs. DP 234 ± 16 min; p = 0.023) and mean hospital stay (DP-PT 20.8 ± 14.7 vs. DP 13.6 ± 6.6; p = 0.045) was prolonger by DP-PT.

**Conclusion:** This RCT shows that prophylactic pancreatic stenting, to offer downstream control, does not reduce the risk for PF after DP.

**P230**

**Duodenectomy is a Safe Alternative to High Risk Pancreaticoduodenectomy for Premalignant Duodenal Lesions**

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**Introduction:** Pancreaticoduodenectomy (PD) on an normal pancreas translates into a high-risk (HR) pancreatico-jejunal anastomosis, associated with increased morbidity and pancreatic fistula rate (PF), especially in overweight patients. Pancreas-preserving duodenectomy (PPD) for pre-malignant duodenal lesions with a normal pancreas could possibly be a safer alternative than a high risk PD.

**Objectives:** To compare the postoperative outcome after PPD and high risk PD (HR-PD).

**Patients & Methods:** All patients undergone PPD or HR-PD between 2006 and 2010 were retrieved from the Karolinska prospective registry. Demographics, length of stay (LOS) and post-operative morbidity and mortality were analyzed.

**Results:** Forty HR-PD and 15 PPDs were identified. PPD were younger (48 vs 64 yrs, p = 0.001) but more overweight (67% vs 30%, p = 0.01). Comparing PPD and HR-PD no differences were seen in total morbidity. However, fewer PPD patients exhibited PF (13% vs 38%), severe (Clavien score ≥ 3b) complications (13 vs 30%), ICU stay (6.8 vs 20%), reoperation (6.8 vs 25%), mortality (0 vs 2.5%), and shorter LOS (17 vs 26 days), but the numbers were too small to be reach statistical significance. Operative time were shorter and intraoperative blood-loss less with PPD than HR-PD (319 min and 616 ml vs 422 min and 1027 ml respectively, p < 0.001).

**Conclusion:** From this small series we can conclude that PPD is done within shorter time and less blood loss with comparable, if not a slightly better, postoperative outcome than HR-PD. Hence, PPD is preferable in resection of premalignant duodenal lesions.
Distal Pancreatectomy Using Blumgart’s Principal: Reduction of Pancreatic Fistulas Using U-Sutures and Patches

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Introduction: Pancreatic fistulae (PA) are among the most common complications contributing significantly to morbidity and mortality after distal pancreatectomy (DP). Tangential shear-forces to the pancreas capsule and parenchyma occur when using conventional suture techniques while stapler closure might bruise the parenchyma and leads to tissue disruption. Both are thought to be responsible for pancreatic leakage after DP.

Objectives: We recently reported a reduced PA-rate after partial duodeno-pancreatectomy when using transpancreatic U-sutures according to L.H. Blumgart. The underlying principle of a shear-force-free closure technique was adapted for pancreatic closure after DP.

Patients & Methods: 20-patients who underwent DP were enrolled prospectively. Demographics, co-morbidities, operative data and outcome parameters were analyzed. PF were rated in accordance to the ISGPF classification. The transection of the pancreas was performed by scalpel. U-sutures were used for pancreatic closure while Ethisorb-patches (0.5–0.7x5cm) served as an abutment following a selective pancreatic duct closure.

Results: The mean age of patients enrolled was 54.1-years, the BMI 26.9kg/m². Most patients enrolled (70%) were operated for malignant disease receiving multivisceral resection. The mean operation time was 182-min and the postoperative hospitalization 17-d. Uncomplicated grade-A and B fistulas occurred in only 2 patients (10%) while no patient showed a grade-C fistula.

Conclusion: The present pancreatic closure technique yield to a low PF rate when compared to the literature most likely related to a shear-force free suture technique with a balanced ventro-dorsal parenchyma compression.
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