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Abstracts

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**Oral Sessions**

**SIGNALING IN PANCREATIC CELLS**

**S2-1**

**CAN ENUCLEATION OF BD-IPMN BE CONSIDERED AS A DIAGNOSTIC/ THERAPEUTIC OPTION FOR TRANSPLANTED PATIENTS? A CASE REPORT**

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**Background:** The incidence of incidentally found cystic tumors of the pancreas has increased tremendously during the last years. The diagnosis and management of these lesions remain, in many cases controversial. No data are available regarding the clinical history of these lesions in patients undergoing immunosuppressive treatment.

**Case report:** A 65 years old woman previously liver transplanted due to familial amyloidosis. After transplantation she developed stricture of the bile duct anastomosis that was repeatedly and successful treated endoscopically. At the pre-transplant CT-scan a suspected multifocal branch duct (BD)-IPMN of the pancreas was observed. The biggest lesion at that time was 15 mm in diameter and located in the pancreatic tail. During follow-up after transplant, a progressive increase in size of this cystic lesion was observed until the last CT in autumn 2011 when the mean size was 35 mm. No sign of degeneration (symptoms, mural nodules) were observed. Following the IAP guidelines for treatment of BD-IPMN the patient was evaluated for surgery. Due to immunosuppressive regimen, and thus related increased risk for major surgery, a surgical enucleation of the lesion for diagnostic and therapeutic purpose was done. The post-operative course was uneventful. The pathological diagnosis was BD-IPMN with low grade dysplasia.

**Conclusion:** Transplanted patients are more prone to develop complications after major surgery and at higher risk to develop cancer. Enucleation of suspected pre-malignant lesions of the pancreas may therefore be a useful approach to confirm diagnosis but also to treat this kind of lesions.

**S2-2**

**SEROTONIN REGULATES PROLIFERATION OF PANCREATIC ACINAR CELLS.**

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**Background:** Pancreatic acinar cells are able to regenerate following tissue injury; however the extent of regeneration is limited. Serotonin (5-hydroxytryptamine, 5-HT) is critical to promote cellular regeneration in the liver, an organ which shares the developmental origin with the pancreas. This study aims to investigate whether 5-HT modulates regeneration in the pancreas following pancreatic tissue injury and loss.

**Methods:** Cirrhosis induced pancreatitis and 60% pancreactomy were performed in wild type and tryptophan hydroxylase 1 knocked-out (TPH1-/-) mice, which have markedly reduced peripheral levels of serotonin. Proliferative ability of pancreatic acinar cells was evaluated over a period of two weeks by biochemical and immunohistochemical methods.

**Results:** Reduced availability of 5-HT delayed acinar cell proliferation at the G1/S-G2/M transition following experimental pancreatitis. This delay was characterized by accumulation of the cell cycle arrest cyclins D and E and delayed expression of the growth factors VEGF and TGF. In addition, the pancreas of TPH1-/- mice showed blunted up-regulation of the progenitor cell markers Notch-1, Hes-1 and Sox9 and enhanced expression of the differentiation-specific transcription factors Ptf1 and Mist-1 compared to wild type mice. Interestingly, blunted up-regulation of progenitor cell markers was also observed in TPH1-/- mice following pancreactomy.

**Conclusion:** Our results indicate that 5-HT is necessary for cell cycle progression but not initiation in pancreatic acinar cells. We identified a 5-HT-mediated regulation of progenitor cell markers following pancreatic tissue injury and loss. These findings reveal that 5-HT regulates acinar cell proliferation and provide a strong foundation to clarify the mechanisms promoting pancreatic regeneration.

**S2-3**

**AMINO-ACID DEPLETION AND GROWTH FACTOR DEPLETION INDUCE AUTOPHAGY VIA DIFFERENT SIGNALING PATHWAYS**

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**Background & Aims:** Experimental evidence supports a role for autophagy in both, cancer development and suppression. The phosphatidylinositol-3-kinase complex, which consists of Beclin-1 and hVps34, Akt14 and Vps15 is involved in autophagy induction in non-transformed human cells. We characterized the induction of autophagy under different nutrient conditions in transformed pancreatic cancer cells.

**Methods:** PANC-1 and CAPAN-2 cells were treated with amino-acid (AA) and growth factor (GF) depletion. hVps34 and Beclin-1 were depleted by siRNA and the interaction of both was investigated by co-immunoprecipitation (co-IP). The effects of autophagy on apoptosis were measured by DNA fragmentation and necrosis via LDH-release and FACS-analysis.

**Results:** Autophagy can be induced by AA and GF depletion in cancer cells, but the induction is weaker compared to non-transformed cells. Silencing of hVps34 blocks induction of autophagy whereas silencing of Beclin-1 does not. To analyze whether reduced binding of Beclin-1 and hVps34 is responsible for the different response in vivo we performed co-IPs. Interestingly, AA depletion led to a different binding pattern of Beclin-1 to hVps34 when compared to FBS withdrawal. Furthermore, the cell death pathways were affected differently under AA and FBS depletion. Autophagy induced through AA depletion resulted in increased apoptosis. In contrast, autophagy induced by FBS withdrawal had an anti-apoptotic function. There was no effect on apoptosis in cells treated with Beclin-1 siRNA.

**Conclusions:** Autophagy induced through AA-depletion differs from that induced by FBS-withdrawal in respect to its role on cell death and the signaling mechanisms involved.

**S2-4**

**ETHANOL AND NON-OXIDATIVE ETHANOL METABOLITES INDUCE INTRACELLULAR ATP DEPLETION AND INHIBIT BICARBONATE SECRETION IN HUMAN PANCREATIC EPITHELIAL CELLS**

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**Introduction:** Pancreatic ductal epithelial cells (PDEC) have important roles in the maintenance of pancreatic integrity and bicarbonate secretion. Excessive ethanol consumption is one of the most common causes of acute pancreatitis, but the effects of ethanol metabolites on PDEC are unknown. The aim of this study was to characterize the effects of ethanol and ethanol-derived metabolites on PDEC.

**Materials and methods:** Changes of intracellular ATP level ([ATP]) pH (pH) and Ca2+ concentration ([Ca2+]i) of CAPAN-1
cells were measured using microfluorometry in human pancreatic adenocarcinoma cell line (CAPAN-1).

**Results:** The administration of high concentration (100mM) of ethanol and palmotiloic acid (POA) (100-200μM) induced (ATP) depletion. Ethanol in low concentration (10mM) induced Ca²⁺-spikes, however 100mM ethanol had only moderate effect on [Ca²⁺], 200μM POA induced sustained [Ca²⁺], elevation, which was significantly decreased by the administration of 20mM caffeine and 10μM rhenium red. The plateau phase of the Ca²⁺ signal was inhibited by 1μM gadolinium cotransporter (NBC), Cl⁻/HCO₃⁻ signal was inhibited by 1μM gadolinium cotransporter (NBC).

**Conclusion:** Ethanol and non-oxidative ethanol metabolites induce (ATP), depletion, [Ca²⁺], elevation and inhibit pancreatic ductal bicarbonate secretion. The impaired bicarbonate secretion can contribute to the development of acute pancreatitis.

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

**ACUTE PANCREATITIS - CLASSIFICATION AND ADVANCES IN THERAPY**

**S3-1**

**BRIDGING THE GAP BETWEEN BENCH AND BEDSIDE: SYSTEMATIC REVIEW OF TREATMENT IN EXPERIMENTAL ACUTE PANCREATITIS**

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**Introduction:** Experimental animal models of acute pancreatitis (AP) are well characterised, have been used to investigate disease mechanisms and test potential therapies before human trials.

**Objective:** To evaluate current evidence for the treatment of experimental AP and assess the translation of these preclinical studies into randomised clinical trials (RCTs) in patients with AP.

**Methods:** A comprehensive online search of Medline, Embase, Pubmed and the Cochrane Library was conducted by two independent reviewers of all published preclinical studies and corresponding RCTs of AP treatment undertaken from the first reported studies to January 2012.

**Results:** 142 compounds have been tested in 257 experimental studies. Of these, only 21 compounds have been tested in 116 RCTs. Modes of action included microcirculatory modification (Trials (T) 38, Compounds (C) 19; RCTs 4, Multiple compounds in individual RCTs (CRCT 4), anti-inflammatory agents (T 31, C 21, RCTs 0), eicosanoid modulators (T 32, C 16; RCTs 3, CRCT 1), immune-modulators (T 35, C 23; RCTs 13, CRCT 5), protease inhibitors (T 31, C 12; RCTs 34, CRCT 5), secretion inhibitors (T 28, C 13; RCTs 40, CRCT 2), antioxidants (T 18, C 8; RCTs 14, CRCT 4) and compounds with multiple actions (T 24, C 16; RCTs 6, CRCT 2).

**Conclusion:** While attrition is expected in drug development, our findings identify a significant translational gap between animal studies and RCTs in AP. We propose standardised reporting of preclinical studies to improve the quality, comparability and translation of experimental AP treatment.

**S3-2**

**INFECTION OF PANCREATIC NECROSIS IN EXPERIMENTAL NECROTIZING PANCREATITIS INDUCES SUSTAINED BACTEREMIA AND INCREASES PANCREATITIS SEVERITY WHICH IS ONLY PARTIALLY REVERSED BY ANTIBIOTIC THERAPY.**


**Introduction:** Infection of pancreatic necrosis in necrotizing pancreatitis increases the lethality.

**Aims/Objectives:** To examine the mechanisms underlying this clinical circumstance we used a model of primary infected pancreatic necrosis in taurocholate induced pancreatitis in mice.

**Materials and Methods:** Acute necrotizing pancreatitis with sterile necrosis (SN) was induced by retrograde injection of 4% taurocholate in the common bile duct of Balb/c mice, infected pancreatic necrosis (IN) was induced by co-injecting 108 CFU E. coli. For antibiotic therapy 10 mg/kg bodyweight moxifloxacin were administered intravenously (AIN). After 6, 12, 24, 48 and 120 hours animals were sacrificed and serum as well as SIRS related organs were examined.

**Results:** Prolonged bacteremia occurred when infected acinar cell necrosis was induced (24h CFU E. coli in blood; bacteria only not detected, IN 12±63). Infection of pancreatic necrosis with E. coli further increased the pancreatic damage (histology score 24h: SN 17.8±2.6 vs. IN 23.7±2.2; p<0.001) and the systemic complications such as the pulmonary vascular leak (albumin in bronchoalveolar lavage 6h: SN 151.0±57.7 μg/ml vs. IN 219.5±76.2 μg/ml; p<0.05). Additionally, infected necrosis induced impaired hepatic function with reduced serum glucose concentrations (24h: SN 167.0±35.6 mg/dl vs. IN 106.9±12.7 mg/dl; p<0.001). Moxifloxacin treatment reduced the systemic inflammatory response (serum IL-6: IN 330.5±336.6 vs. AIN 38.7±25.5 pg/ml; p<0.001) and restored liver function (serum glucose: IN 105.8±12.7 vs. AIN 155.7±39.5 mg/dl; p<0.001).

**Conclusion:** Infection of pancreatic necrosis induces sustained bacteremia and increases the systemic complications in acute necrotizing pancreatitis. Initial antibiotic therapy reduces the inflammatory response and restores liver function.

**S3-3**

**DIAGNOSING INFECTED NECROTIZING PANCREATITIS: CLINICAL SIGNS, GAS BUBBLES OR ROUTINE FINE-NEEDLE ASPIRATION?**

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S3-4

ENDOSCOPIC TRANSLUMINAL STEP-UP APPROACH VERSUS SURGICAL STEP-UP APPROACH IN PATIENTS WITH INFECTED NECROTIZING PANCREATITIS (TENSION): DESIGN AND RATIONALE OF A RANDOMIZED CONTROLLED MULTICENTER TRIAL


Methods and results:

Objective: To determine the additional value of gas bubbles seen on CECT and FNA cultures in patients who underwent intervention for suspected infected necrotizing pancreatitis.

Methods: Post-hoc analysis of 208 patients who underwent intervention for suspected infection in a prospective cohort of 639 patients with necrotizing pancreatitis. Final diagnosis was based on the culture taken during the first intervention (drainage or necrosectomy). FNA was not used routinely.

Results: Prior to intervention, 88/208 patients (42%) showed gas bubbles on CECT, 28/208 patients (13%) underwent FNA and in 92/208 patients (44%) there were no gas bubbles and no FNA was performed (clinical signs group). Baseline characteristics did not differ between the three groups. Median time between admission and the first CECT with gas bubbles was 22 days (IQR 13-37 days) and to the first FNA 17 days (IQR 13-37 days). Ultimately, infected necrotizing pancreatitis was documented in 74/92 patients (80%) in the ‘clinical signs’ group, 83/88 patients (94%) who had gas bubbles on CECT and in 24/28 patients (86%) who underwent FNA. Mortality (22%) did not differ between the three groups (P=0.391).

Conclusion: Gas bubbles are seen in 40% of patients with infected necrotizing pancreatitis. The diagnosis of infected necrotizing pancreatitis can generally be based on clinical signs or on gas bubbles on CECT, routine confirmation by FNA is not needed.

ORAL SESSIONS

EPIDEMIOLOGY IN PANCREATIC DISEASES

S4-1

SOLID AND PSEUDOPAPILLARY TUMOURS OF THE PANCREAS: ARE THE EPIDEMIOLOGY AND IMAGING FEATURES CHANGING?

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Solid and pseudopapillary tumours (SPT) are rare pancreatic tumours with dysregulation of the wnt signalling pathway, known to be large in size and affecting young women. Due to the trends in imaging methods, their presentation of may have changed over the past years.

Aim: to retrospectively revisit the epidemiologic and radiological features in a series of patients with resected SPT.

Methods and results: between 2002 and 2011, 36 patients (28 women, 8 men), median age 30 yrs (14-57) underwent surgery for a SPT. The diagnosis of pancreatic tumour was suspected following non specific abdominal pain (n=24) or fortuitously (n=12). It was located in the head (n=19), the neck (n=10) or the body/tail (n=7). All patients underwent CT scan, MRI and EUS. In doubtful cases, EUS-biopsy or somatostatin-receptors scintigraphy (SRS) were performed in 12 and 6 patients, respectively. In 9 cases, there was a differential diagnosis with a neuroendocrine tumour (NET) (n=6) or a mucinous cystadenoma (n=3). Histological examination of biopsies concluded to a SPT in 7/12 cases; there was hesitation between a NET and a SPT in 2 cases; the material was not contributive in the 3 remaining patients. SRS was negative in all 6 cases. Surgery was as follows: pancreaticoduodenectomy (n=18), central (n=10) or left pancreatectomy (n=8, 6 with splenectomy), or enucleation (n=2). Median size of SPT was 3 cm (1.1-13). There was no sign of malignancy or lymph nodes, and margins were clear in all cases. A peripheral capsule was present in 22 cases (61%). Median follow-up was of 26 months (6-108). No locoregional or distant relapse occurred.

Conclusions: this series suggests that the presentation of SPT has changed with half of patients aged > 30 years and with small lesions (< 2 cm). A third of patients were male. Atypical imaging features (entirely cystic or NET-like lesions) can be encountered as well.
S4-2
IMPACT OF SERVICE CENTRALISATION ON OUTCOMES FOR PATIENTS WITH PANCREATIC CANCER

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Introduction: In 2001 UK guidance was published on best practice advising centralisation of pancreatic cancer services such that centres would demonstrate >200 referrals/year, >10% resection rates and <5% postoperative mortality.

Objective: To assess the impact of centralisation we have studied changes in service delivery and outcomes within a tertiary pancreatic centre.

Methods: A prospectively maintained database of all suspected pancreatic cancer cases referred to the Supra-Regional Pancreas Centre in Liverpool was interrogated from 2001 to 2010 inclusive. Data were analysed using x 2 for trend and log rank for survival data.

Results: 2076 patients with malignancy were referred, rising from 73 in 2001 to 364 in 2010. 710 patients underwent planned operation for malignancy, rising from 41 procedures in 2001 to 88 in 2010 (97 in 2008, 94 in 2009). The percentage of successful planned resections increased from 51% (21/41) in 2001 to 90% (79/88) by 2010 (p<0.001). Mortality from resection was 9/567(2%) and from all surgery was 5% (37/710). The 1 year survival rates following successful resection improved from 65% (13/20) in 2001 to 76% (69/91) by 2009 (p=0.02).

Conclusion: Over the last ten years centralisation has had a positive impact on service provision in the centre studied, with an increase in the number of referrals with both resectable and irresectable disease, as seen in relatively constant successful resection rates >20%. There have been improvements in case selection, reductions in bypass procedure rates and increases in 1 year survival following resection.

S4-3
SERUM IgG4 POSITIVITY IN PATIENTS WITH PANCREATIC CANCER

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Introduction: Elevated serum IgG4 level is typical for IgG4 related diseases, including autoimmune pancreatitis (AIP). Its sensitivity and specificity over 90 % for AIP type 1 is generally accepted. Clinical presentation of AIP and pancreatic cancer (PC) is often similar (abdominal discomfort, icterus, pancreatic head enlargement on imaging) and differentiating factors are needed. IgG4 positivity was believed to be potentially useful but case reports describing elevated serum IgG4 in PC patients have been published.

Aims: To determine IgG4 levels in serum of PC patients and healthy controls.

Patients and Methods: IgG4 serum levels were evaluated in 85 patients with histologically verified PC and in 60 healthy subjects. Levels higher than 135 mg/dl were considered.

Results: In PC group, 8 out of 85 (9.8%) patients had a serum IgG4 level higher than 135 mg/dl. Nobody in the control group scored positive. The mean value among patients with elevated IgG4 was 173 mg/dl, which is 12.9% higher than the normal value. Five of the 8 patients had underlying chronic pancreatitis. None of the patients filled any other criteria for AIP.

Conclusion: Elevated IgG4 serum levels can be found in PC patients and therefore IgG4 positivity alone is not an ideal differentiating factor between AIP and PC, as was presented in the past. However, IgG4 in PC patients is usually mildly elevated (up to 20% over the upper limit) and more than doubled elevation IgG4 is highly suggestive of AIP.

GENETICS IN PANCREATIC DISEASES

S5-1
GENETIC SUSCEPTIBILITY TO PANCREATIC CANCER AND ITS FUNCTIONAL CHARACTERIZATION: THE PANCREATIC DISEASE RESEARCH (PANDORA) CONSORTIUM

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Introduction: Pancreatic cancer is the fourth leading cause of cancer deaths in the European Union and in the USA. In spite of this little is known about the genetic susceptibility to this deadly disease.

Aims: We have established the Pancreatic Disease ReaseArch (PANDoRA) consortium with the driving idea of joining the efforts of different research groups and creating a large bio- and databank aimed at uncovering: 1) new genetic risk factors for pancreatic cancer; 2) genetic factors that influence the outcome of treatment of pancreatic cancer patients; 3) genetic factors that influence the survival of pancreatic cancer patients.

Patients and Methods: The consortium currently includes 13 groups across Europe. So far 1436 cases of exocrine pancreatic cancer and 2581 healthy controls from the same regions of the cases have been collected. When a positive case and controls a DNA sample is available, as well as a minimal set of covariates.
Results: We have replicated the hits from the three published genome-wide association studies on pancreatic cancer, performed in the Caucasian (PanScan), Japanese and Chinese populations. We have also explored the genetic variability of the ABO, TERT and CDKN2A/p16 loci with encouraging results. For all the loci we have also investigated whether genetic polymorphisms influence the survival of the patients.

Conclusion: This consortial effort is particularly important for pancreatic cancer because it is a disease which is poorly understood from the point of view of etiopathogenesis and risk factors. The recruitment of additional collaborators and partner institutions is continuously ongoing.

S5-2
RESTRICTED HETEROCHROMATIN FORMATION LINKS NFATC2 REPRESSOR FUNCTION WITH GROWTH PROMOTION IN PANCREATIC CANCER

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Introduction: NFATc2 emerged as a powerful regulatory transcription factor governing pancreatic cancer cell growth by inducing cell cycle progression. Inactivation of the cell cycle inhibitor and tumor suppressor p15 Ink4b by genetic alterations or epigenetic changes appears in many malignant tumor diseases, including pancreatic cancer.

Objectives: This study aimed to characterize a prospective functional link between NFATc2 overexpression and p15 Ink4b master tumor suppressor pathway inactivation in pancreatic cancer.

Material & Methods: Immunoblotting, immunohistochemistry, real-time PCR and immunofluorescence microscopy were used for expression studies. Protein-protein-interactions, promoter regulation and local histone modifications were analyzed by immunoprecipitation, reporter assays, sequential chromatin immunoprecipitation and DNA pulldown experiments. Cancer growth was assessed in vitro and in vivo by 3 H-thymidine incorporation and xenograft tumor models.

Results: Upon activation and translocation into the nucleus NFATc2 binds to the proximal p15 Ink4b promoter and targets the histone methyltransferase Suv39H1 for local trimethylation of lysine 9 of histone H3. Subsequent docking of Heterochromatin Protein 1 results in the promoter-restricted transition of accessible euchromatin to compacted and transcriptionally silenced facultative heterochromatin. The disruption of the repressor complex by genetic or pharmacological depletion of NFATc2 reactivated expression of the tumor suppressor p15 Ink4b in pancreatic cancer.

Conclusion: These data describe a novel mechanism of NFATc2-mediated gene regulation which beyond the activating functions reveals a previously unappreciated repressor function in pancreatic cancer. Therefore, disruption of the repression complex on the p15 Ink4b promoter by inactivation of NFATc2 presents an attractive strategy to restore anti-tumoral defense mechanisms in pancreatic cancer.

S5-3
RARE CATIONIC TRYSPINOGEN MUTATIONS FOUND IN SUBJECT WITH PANCREATITIS ARE NEUTRAL VARIANTS OR MAY EVEN BE PROTECTIVE.

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Introduction: Mutations in the PRSS1 gene encoding human cationic trypsinogen cause hereditary pancreatitis. Disease-associated trypsinogen mutations increase activation or impair degradation and thereby lead to the development of intrapancreatic trypsin activity. Recently, numerous novel rare PRSS1 mutations with unknown clinical significance were identified in subjects with idiopathic chronic pancreatitis. Despite lack of evidence, some of these variants have been described as pancreatitis-associated.

Objectives: The aim of this study was to characterize published novel trypsinogen variants functionally, in order to judge their possible pathogenic impact.

Methods: Wild type and 10 mutant trypsinogens were expressed recombinantly and purified. Trypsinogen activation, trypsinogen/trypsin degradation by chymotrypsin C and enzyme kinetic parameters were studied by activity assays and gel electrophoresis. Cellular expression of trypsinogens was assessed by SDS-PAGE and trypsin activity assays of conditioned media from transfected HEK 293T cells.

Results: None of the investigated mutants exhibited increased activation or impaired degradation; the gain of function phenotypes typical of disease-associated mutations. Surprisingly, 6 of 10 mutants showed loss of function either due to reduced secretion and/or increased degradation by chymotrypsin C.

Conclusions: Rare cationic trypsinogen mutations found in subjects with chronic pancreatitis are harmless variants, most likely not associated with the disease. The loss-of-function trypsinogen variants may even have a protective effect. These results emphasize that classification of novel PRSS1 variants should be based on functional evidence.

PANCREATIC DISEASES-HOST INTERACTION

S6-1
REPLICATION OF SEVEN PANCREATIC CANCER LOCI IDENTIFIED IN TWO ASIAN POPULATIONS - RESULTS FROM THE PANDORA CONSORTIUM

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Background: Two recent genome-wide association studies (GWAS) of pancreatic ductal adenocarcinoma (PDAC), conducted respectively in a Japanese and in a Chinese population identified eight novel loci affecting PDAC risk.

Aims: We attempted to replicate the novel loci in a series of PDAC and healthy controls of European ancestry in the context of the newly formed PANcreatic Disease ReseAch (PANDoRA) consortium.

Methods: We genotyped seven single nucleotide polymorphisms (SNP): rs12413624, rs1543747, rs372883, rs5768709, rs6464375, rs708224, rs9502893 (one SNP identified in the Chinese GWAS is not polymorphic in Caucasians) in 1034 PDAC cases and 2443 controls in the context of the PANDoRA consortium. We tested each SNP for association with PDAC risk and also assessed whether the risk SNPs have an impact on survival of the patients.

Results: None of the SNPs were significantly associated with PDAC risk or with survival if considering the overall population of the consortium. When stratifying for country of origin we found that in the Polish subgroup rs372883 was statistically significantly associated with increased risk (OR=6.40; CI 95%:2.87-17.91; Pvalue=0.0004) and in the German subgroup with better survival (HR=0.80, 95%CI=0.69-0.92; Pvalue=0.002). However the sample size of the subgroups was rather small, therefore these results have to be taken with caution because they can be due to chance finding.

Conclusions: None of the SNPs associated with PDAC risk in two Asian populations were also associated with PDAC risk or survival in individuals of European descent. This study illustrates the importance of evaluation of PDAC risk markers across ethnic groups.

S6-2

A REAL-WORLD ANALYSIS OF THE OUTCOME OF PATIENTS WITH IPMN AND INDICATION FOR SURGERY ACCORDING TO IAP CRITERIA IN WHOM SURGERY IS NOT PERFORMED DUE TO ADVANCED AGE AND/OR COMORBIDITIES.

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Introduction: IPMN are increasingly diagnosed, often in older patients with comorbidity, who may not be fit for surgery, although meeting Sendai criteria. The outcome of such patients, with surgical indication but unresected is unclear.

Aim: to investigate the outcome of IPMN patients with criteria for resection, who were not operated.

Methods: Retrospective analysis of prospectively enrolled patients in two centers, to compare the outcome of patients with surgical indication (Sendai) and resectable IPMN who received surgery or not.

Results: Of 103 patients (64 F, median age 70 yrs), 30 (29,1%) had Sendai surgical indication. 17 were resected (Group 1), only in 29% of them malignancy was confirmed; in 13 patients (Group 2) an observational follow-up was preferred, due to comorbidities (61,53% vs 29% Group 1) and/or advanced age (median 77 yrs vs 71 Group1). More patients in group 2 had incidental diagnosis (68% vs 41%) and branch-duct-IPMN (46% vs 17,6% Group1). Median survival after therapeutic decision (23 months Group 1 vs 19 Group 2) and survival-curves were similar (Kaplan-Meier p=0,30) in the 2 groups. Mortality was 30,76% in Group 2 (4 disease progressions) and 11,76% in Group 1 (2 after surgical complications). Disease recurred in 2 Group 1 patients.

Conclusion: In this series of IPMN, 29% met Sendai criteria for resection. 56% of them were operated with a low malignancy rate: 44% were unresected as asymptomatic, with advanced age and/or major comorbidities. The option not to operate, although not codified, seems reasonable and not associated with a worse outcome.

BASIC SCIENCE IN CHRONIC PANCREATITIS

S7-1

NATURAL KILLER CELLS AMELIORATE PANCREAS FIBROSIS BY KILLING ACTIVATED STELLATE CELLS IN NKG2D-DEPENDENT MANNER ON EXPERIMENTAL CHRONIC PANCREATITIS.

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Introduction: Sustained activation of pancreatic stellate cells (PSCs) has an increasingly appreciated role in the fibrosis that is associated with chronic pancreatitis(CP). Natural killer (NK) cells have anti-fibrotic properties in animal models. The aim was to study the effect of NK cells on experimental CP in mice.

Methods: We treated mice with polyinosinic-polycytidylic acid (poly I:C), which induces interferon-y and enhances NK cell activity in dibutyltin chloride (DBTC)-exposed mice. To deplete NK cells, mice were injected with anti-AsG1 antibody, and divided into 4 groups: DBTC-treated group, poly I:C-treated group, poly I:C/DBTC-treated group and anti-AsG1/ DBTC-treated group. Pancreas tissues and serum were harvested on 7, 14, 21, 28 and 35 days, and evaluated for expression of α-SMA, collagen type I, IFN-γ, IL-2, IL-6, TGF-β, TNF-α, H60 and Rae-1 via RT-PCR and immunohistochemical characterization assays. The apoptosis of PSCs was detected by TUNEL and GFAP double staining method. NK cells and NKG2D expression was analyzed by flow cytometry.

Results: NK cell activation by poly I:C induced cell death to activated PSCs and attenuated the severity of pancreatic fibrosis in a mouse model of CP. Treatment with poly I:C enhanced the cytotoxicity of NK cells against activated PSCs and the expression levels of NKG2D on NK cells were upregulated. Rae-1 was found on activated PSCs, and more susceptible to NK cell killing, which is enhanced by poly I:C treatment.

Conclusions: Our findings demonstrated that poly I:C treatment inhibits pancreatic fibrosis on experimental CP via immune clearance of activated PSCs results from the cytotoxic action of NK cells in NKG2D-dependent manner.

S7-2

NA+/H+ EXCHANGER REGULATORY FACTOR-1 IS INVOLVED IN PANCREATIC DUCTAL FLUID AND HC03− SECRETION IN MICE

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Background: Na^+H^+ exchanger regulatory factor-1 (NHERF-1) is a scaffolding protein which is responsible for the apical localization of cystic fibrosis transmembrane conductance regulator (CFTR), a key player in pancreatic ductal bicarbonate secretion.

The aim of this study was to evaluate the role of NHERF-1 in pancreatic ductal localization of CFTR, and in bicarbonate and fluid secretion.

Methods: The expression of CFTR was analysed by immunohistochemistry. Pancreatic juice was collected from anesthetized wild-type (WT) and NHERF-1 knock-out (KO) mice in basal and secretin-stimulated conditions. We isolated intra/interlobular ducts from the pancreas of WT and NHERF-1 KO mice. Fluid secretion into the closed luminal space of the ducts was analysed using a swelling technique. Luminal amion exchange activity was determined by microfluorometry.

Results: Pancreatic ductal CFTR staining was more diffuse and less apical in the NHERF-1 KO vs. WT mice. The volume of pancreatic juice was significantly reduced in NHERF-1 KO vs. WT mice under both basal and secretin-stimulated conditions in vivo. Accordingly, the forskolin-stimulated fluid secretory rate was significantly lower in ducts from KO vs. WT mice in standard HCO_3^-/CO_2 solution in vitro. The reduction of ductal bicarbonate secretion in the NHERF-1 KO mice was confirmed by the alkali load and the inhibitor stop methods on basolaterally perfused ducts and by the luminal Cl^- removal technique on time-perfused ducts.

Conclusion: Our results suggest that NHERF-1 is involved in pancreatic ductal CFTR localization and is essential for fluid and bicarbonate secretion.

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

S7-3

A NOVEL TWO-STEP STRATEGY FOR LONG-TERM IN VITRO CULTURE OF HUMAN PANCREATIC ACINAR CELLS

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Objectives. Culture models permitting long-term experimentation on human pancreatic acinar cells in vitro are currently lacking. Recently we described a method for long-term maintenance of human pancreatic acinar cells in vitro. The aim of this study was to develop new approaches for long-term maintenance of functionally competent human pancreatic acinar cells in vitro.

Materials and Methods. Pancreatic tissue specimens were obtained from patients undergoing pancreatic surgery. The specimens were subjected to collagenase digestion and the resulting acini and acinar clusters were collected, embedded in soft Matrigel and placed in tissue culture inserts for primary culture. After three days the clusters were dissociated into single cell suspension and passed onto regular tissue culture plastic. After four days in secondary culture the responsiveness of the cells to stimulation with caerulein and carbachol was determined.

Results. Human pancreatic acinar cells were maintained for a minimum of 7 days in vitro. Acinar clusters showed excellent morphology throughout the three-day period in primary culture and little decline in their basal amylase secretion was observed. Acinar cells in secondary culture, arranged into monolayers of tightly adjoining cells. Carbachol stimulated amylase secretion in secondary cultures, but no stimulatory effect was evoked by caerulein.

Conclusions. The secretory phenotype of human pancreatic acinar cells can be maintained for a minimum of 7 days in the present culture conditions. This versatile two-step system of primary and secondary culture phases enables long-term studies on human acini/acinar clusters and on isolated acinar cells in vitro.


S8-1

SERUM MARKERS FOR THE DIAGNOSIS OF AUTOIMMUNE PANCREATITIS AND IN DISTINGUISHING IT FROM PANCREATIC CANCER

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Background: Autoimmune pancreatitis (AIP) is defined by a characteristic lymphoplasmacytic infiltrate, ductal strictures and pancreatic enlargement or mass that can mimic pancreatic cancer (PaCa). The distinction between this benign disease and pancreatic cancer can be challenging. However, an accurate diagnosis may pre-empt the misdiagnosis of cancer, allowing the appropriate treatment and decrease the number of unnecessary pancreatic resections.

Methods: Mass spectrometry (MS) and two-dimensional differential gel electrophoresis (2D-DIGE) have been applied to analyze serum protein alterations associated with AIP and PaCa, and to identify biomarkers indicative for the diseases. Patients sera were immunodepleted from the 20 most prominent serum proteins prior 2D-DIGE and MS analysis. Identification of autoantigens with 2D-DIGE/immunoblots was performed using pancreatic tissue homogenate and autologous sera. The identity of the biomarkers was determined by a combination of protein-fractionation techniques, chromatographic purification, gel electrophoresis, and MS.

Results: Serum profiling analysis with 2D-DIGE revealed 39 protein-peaks able to discriminate between AIP and PaCa. Proteins were purified and further analysed by MALDI-TOF-MS. Peptide mass fingerprinting led to identification of eleven proteins. Among them apolipoprotein-A-I, transthyretin, and tetracine were identified and found as 3.8 and 1.6 fold decreased whereas haptoglobin and apolipoprotein E were found 3.8 and 1.6 fold elevated in PaCa sera. Identification of proteins that emerged from 2D-DIGE/immunoblot and MS-based analysis revealed 71 different AIP and 42 PaCa autoantigens.

Conclusions: Integration of the here identified proteins as AIP markers enhance the possibility of appropriate disease treatment and are qualified to ensure that PaCa is not misdiagnosed.

S8-2

CONTRIBUTION OF HLA-DRB1*044 ALLELE TO THE GENETIC SUSCEPTIBILITY OF AUTOIMMUNE PANCREATITIS: PRELIMINARY DATA.

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Background: Ductal and periductal inflammatory infiltration, predominantly composed of lymphocytes, plasma cells, and granulocytes, is the histopathological hallmark of autoimmune pancreatitis (AIP). Extension of the inflammatory process to the acinar tissue leads to diffuse fibrosis.
The inflammatory infiltrate consists mainly of CD4+ and CD8+ positive T lymphocytes with fewer B lymphocytes, plasma cells, but also macrophages, and neutrophilic and eosinophilic granulocytes.

**Aim** of the proposed study was to investigate the role of HLA in the development of autoimmune pancreatitis in order to contribute to the understanding of the pathophysiology.

**Methods:** Allelic polymorphisms at the DNA level were investigated in the genes of MHC region (HLA B, DRB, DQB) with PCR based methodologies (PCR-SSP: PCR-RFLP) in 57 AIP patients (38 males, 19 females) and 183 healthy normal controls (78 males, 105 females) of the same ethnic group. All patients and controls gave their informed consent.

**Results:** Among HLA-DRB1 genes, we found a trend to significativity for DRB1*04. PCR reactions were performed to determine the DRB1*04 specificities in the DRB1*04 positive patients: a trend to significativity for HLA DRB1*0408 allele was found. Neither HLA-B nor HLA-DQB1 associations with the disease were found.

**Conclusions:** This study supports a role of HLA-DRB1*04 as susceptibility factor for AIP. T cells may be triggered in the pancreatic tissue upon exposure to foreign peptides similar enough to crossreact and to break immunological tolerance.

**S8-3**

**BLOCKAGE OF CTLA-4 SUGGESTS THAT AUTOIMMUNE PANCREATICITIS IS A T-CELL MEDIATED DISEASE RESPONSIVE TO CICLOSPORIN A AND RAPAMYCIN TREATMENT**

**Methods:** MRL/Mp mice received polyinosinic: polycytidylic acid for 4 weeks to trigger AIP. Mice also received daily dexamethasone injections (two weeks) in parallel poly I:C. In subsequent experiments ciclosporin A or rapamycin were given for 4 weeks. CTLA-4 was blocked by i.p. antibody (2 μg/g) with IgG1 dilution. Treg cells were expanded by CD28-superagonist fusion protein (LTßRIg) directed against LTßR dampened autoimmune pancreatitis (AIP) and abrogated systemic autoimmunity.

**Results:** Neutralization of LTßR type 1 by LTßRIg reduced the number of granulocytes, but also macrophages, and neutrophilic and eosinophilic granulocytes. HLA DRB1*04 positive Treg were expanded by CD28-superagonist fusion protein (LTßRIg) targeted against LTßR.

**Conclusions:** LTßRIg is superior in the prevention of AIP compared to anti-autoimmune responses upon LTßR-Ig treatment. Therefore, inhibition of the LTßR-signaling pathway could become an alternative or supplementary approach for AIP treatment.
**EXPERIMENTAL ACUTE PANCREATITIS**

**S9-1**

**THE EFFECT OF PANCREATITIS-INDUCING FACTORS ON THE EXPRESSION AND FUNCTION OF AQPS IN A PANCREATIC DUCTAL CELL LINE**

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**Background.** Acute pancreatitis (AP) is a multifocal disease in which pancreatic ductal cells play an important role. Toxic agents inducing AP inhibit pancreatic ductal bicarbonate secretion, however, no information is available concerning their effects on the regulation of aquaporins (AQPs). Therefore, the 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.** CAPAN-1 cells were treated with ethanol (EOH; 1-100 mM), chenodeoxycholate (CDC; 0.1-0.5 mM), glycochenodeoxycholate (GCDC; 0.1-0.5 mM) or TNF-α (0.2, 20 ng/ml) for 6, 12, 24 and 48 hours and the expression of AQP isoforms (AQP1-12) was examined by real-time RT-PCR and immunocytochemistry. Water transport was characterized by the dye dilution technique.

**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 and GCDC-treated group, the expression of AQPs decreased both at mRNA and protein levels dose-and time-dependently. 24-hour incubation with EOH, increased, whereas TNF-α did not affect significantly the expression of AQPs. Notably, a 72-hour incubation in culture media restored the expression of AQPs in the 6- and 12-hour CDC- and GCDC-treated groups and in the 24-hour EOH-treated group. Functional investigation of AQPs showed, that CDC inhibited the water transport.

**Conclusion.** The role of AQP in the pathogenesis of AP needs further investigations.

Supported by OTKA, NKTH-TAMP and MTA.

**S9-2**

**EARLY ZYMOSGEN ACTIVATION IN CAERULEIN PANCREATITIS OCCURS IN A LYSOSONAL COMPARTMENT OUTSIDE OF AUTOPHAGOSOMES**

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Autophagolysosomes were recently identified as a compartment of trypsinogen activation. We found that an early extra-autophagosomalzymogen activation also occurs. Here, we characterized this activation compartment.

**Methods.** Caerulein pancreatitis was induced in NMRI mice by up to 3 hourly i.p.-injections of caerulein. At 15, 30, 60 and 180min pancreata were homogenized following incubation for 5 min at 37°C in the presence or absence of 10mM LeuLeuOMe to permeabilize lysosomes. Subcellular fractionation was performed by Percoll gradient centrifugation. Activities of trypsinogen, chymotrypsinogen, cathepsin B (CTSB) were measured, and cathepsin L, LAMP1 and other markers of subcellular compartments were identified by Western blots.

**Results:** After caerulein hyperstimulation trypsin and chymotrypsin activities were detected in fractions of 1.133 to 1.101 g/ml density, which represents the range between maturezymogen granules (1.152 g/ml) and dense lysosomes (1.090 g/ml). Markers of autophagolysosomes (LC3-II, ATG 16) were found at much lower densities. Permeabilization of lysosomes with LeuLeuOMe resulted in a shift of CTSB and CTSI into the soluble fraction. The lysosomal membrane marker LAMP1 shifted from heavy to light fractions. These changes were paralleled by the release of trypsin and chymotrypsin activities into the soluble fraction. However, granule enzymes like amylase, lipase, trypsinogen, SPINK, and granule membrane marker Itmap-1 remained in high density fractions.

**Conclusion:** We conclude that earlyzymogen activation occurs in a compartment that is generated by interaction or fusion of distinct vesicles with dense lysosomes. Our results do not give evidence thatzymogen activation results from missorting of CTSB into zymogen granules.

**S9-3**

**DA-CHENG-QI DECOCTION PROTECTS AGAINST PANCREATIC DAMAGE IN MURINE EXPERIMENTAL ACUTE PANCREATITIS**

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**Introduction:** Da-Cheng-Qi decoction (DCQD) is a traditional Chinese medicine made from Rheum palmatum, Fructus aurantii, Magnolia officinalis and sodium sulphate. This mixture is widely used in China for treating patients with acute pancreatitis (AP), but not elsewhere. Objective: To investigate whether DCQD can ameliorate pancreatic damage in two murine AP models and to optimise its dose for future studies.

**Methods:** AP was induced in C57Bl/6 mice by either hourly intraperitoneal injections of caerulein (50 μg/kg × 7, CER-AP) or L-Aarginine (4.0 g/kg × 2, ARG-AP). In the CER-AP group, DCQD was administered at a dose of 2.5, 10, 20 or 25 g/kg by gavage simultaneously with the 3rd, 5th and 7th injection of caerulein, and mice were sacrificed 12 h after the first injection. In the ARG-AP, mice received DCQD gavage (3 times, 2 hourly) at 24 and 48 h after the first injection of L-Arginine, and sacrificed 72 h after the first injection. The severity of AP was assessed using biochemical markers and histopathology.

**Results:** After caerulein hyperstimulation trypsinogen and chymotrypsinogen activities were detected in fractions of 1.133 to 1.101 g/ml density, which represents the range between maturezymogen granules (1.152 g/ml) and dense lysosomes (1.090 g/ml). Markers of autophagolysosomes (LC3-II, ATG 16) were found at much lower densities. Permeabilization of lysosomes with LeuLeuOMe resulted in a shift of CTSB and CTSI into the soluble fraction. The lysosomal membrane marker LAMP1 shifted from heavy to light fractions. These changes were paralleled by the release of trypsin and chymotrypsin activities into the soluble fraction. However, granule enzymes like amylase, lipase, trypsinogen, SPINK, and granule membrane marker Itmap-1 remained in high density fractions.

**Conclusion:** We conclude that earlyzymogen activation occurs in a compartment that is generated by interaction or fusion of distinct vesicles with dense lysosomes. Our results do not give evidence thatzymogen activation results from missorting of CTSB into zymogen granules.

**44th European Pancreatic Club (EPC) Meeting**
S10-1

CHANGES IN CORTICAL THICKNESS IN PATIENTS WITH CHRONIC PANCREATITIS: A USEFUL INDICATOR OF A REORGANIZED PAIN SYSTEM?

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Introduction: There is increasing evidence of abnormal brain function in patients with painful chronic pancreatitis (CP).

Objectives: To explore brain morphology we assessed cortical thickness in brain areas involved in visceral pain processing.

Patients/methods: Nineteen patients with painful CP and 15 healthy controls were studied in a 3T magnetic resonance scanner. Using an automated method with surface based cortical segmentation, cortical thickness was assessed in the primary (SI) and secondary (SII) somatosensory cortex, prefrontal cortex (PFC), frontal cortex (FC), anterior (ACC), mid (MCC), and posterior (PCC) cingulate cortex, and insula. The occipital middle sulcus served as control area. Dairy pain score was collected assessing average daily pain for one week.

Results: Compared to controls the overall cortical thickness was reduced in CP patients (P=0.0012), without effect modifications from diabetes, alcoholic etiology or opioid treatment (all P-values >0.05). In CP patients decreased cortical thickness was seen in: SI (P=0.002), PFC (P=0.046), FC (P=0.0003), MCC (P=0.001) and insula (P=0.002). No difference in cortical thickness between CP patients and controls was seen in: SII (P=0.20), SI (P=0.06), ACC (P=0.95) and PCC (P=0.42). A positive correlation was seen between cortical thickness in the affected areas and dairy pain score (r=0.47, P=0.003).

Conclusions: In patients with CP brain areas known to be essential in pain processing show reduced cortical thickness. Cortical thickness may, as the end result of longstanding ongoing pain input to the neuromatrix, serve as a measure for overall pain system dysfunction, as also seen in other diseases characterized by chronic pain.

S10-2

CEREBRAL CORTICAL EXCITABILITY IS ABNORMAL IN PATIENTS WITH PAINFUL 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.

Objectives: To further elucidate these abnormalities, we investigated the cerebral response to experimental pain stimuli in CP patients.

Methods: Contact heat evoked potentials (CHEPS) were recorded in 15 patients with CP and in 15 healthy volunteers during repetitive stimulation of the upper abdominal region (pancreatic “viscerotome”) and the right forearm (heterologous area). Three sequences of painful stimuli were applied at each site. Subjective pain scores were assessed by a visual analogue scale. Habituation was calculated as the relative change in CHEPS amplitudes between the first and the third stimulation sequence.

Results: As expected pain scores decreased in healthy volunteers during successive stimulations at both sites (i.e. habituation), while in the CP group they remained unchanged. The cerebral response consisted of an early-latency, low-amplitude response (N1, contralateral temporal region) followed by a late, high-amplitude, negative–positive complex (N2/P2, vertex). During successive stimulation of the pancreatic area N2/P2 amplitude increased 25% in CP patients, while it decreased 20% in healthy volunteers (P=0.006). After stimulation of the forearm N2/P2 amplitudes increased 3% in CP patients compared to a decrease of 20% in healthy volunteers (P=0.06).

Conclusions: Taken together, CP patients had an abnormal cerebral response to repetitive thermal stimuli. This was most prominent after stimulation of the upper abdominal area. As this area share spinal innervation with the pancreatic gland, these findings likely mirror distinctive abnormalities in cerebral cortical pain processing.

S10-3

RADIOTherAPY FOR PAIN CONTROL IN CHRONIC PANCREATITIS. A FOLLOW-UP REPORT.

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Recurrent pancreatitis and unrelenting pain may complicate chronic pancreatitis. Management is limited to analgesics and surgery. Since radiotherapy is useful in painful inflammatory disorders we evaluated its use for painful chronic pancreatitis (Am J Gastroenterol 2009;104:349-55) and concluded it was an effective therapeutic choice. We now present a follow-up report including data from 6 additional patients.

Methods: Chronic pancreatitis patients having two bouts of pancreatitis in 6 months or continuous pain for previous 3 months were assessed. After ruling out malignancy, we selected 21 (5 female) poor candidates for surgery. We administered a single 8 Gy radiation dose and assessed pancreatic function, quality of life (EuroQol), and clinical outcome. No further pain or pancreatitis for 12 months designated good response.

Results: Mean follow-up is now 6.6 years (1.7-10.2). Eighteen patients achieved good response (1 after two radiation doses), and 1 a partial response. Thirteen patients experienced no further pancreatitis despite having 8.9±1.3 bouts for the previous 7.9±1.1 years. Six patients relapsed 3.6±0.7 years later, but remained well thereafter. Patients with good response increased weight at 6 months (mean 6.28 Kg; 1-20), diabetes remained even thereafter. EuroQol improved from 0.57±0.11 to 0.86±0.13. Previous normal exocrine function (11) deteriorated in 5 patients and normal endocrine function (16) in 2. Treatment failed in 2 patients who underwent surgery. Three patients died from advanced lung disease, peritoneal carcinomatosis (no pancreatic mass) and lung cancer 0.5, 2.5 and 8 years later.

Conclusion: Radiotherapy can be useful in compromised patients with painful chronic pancreatitis.
S10-4
PAIN AND NEURAL REMODELLING IN PANCREATIC NEUROPATHY ARE CHARACTERIZED BY INCREASED UNMYELINATED NERVE FIBER CONTENT AND SELECTIVE GLIAL ACTIVATION

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Introduction: Pancreatic neuropathy and pain in pancreatic adenocarcinoma (PCa) and chronic pancreatitis (CP) are associated with decreased sympathetic innervation of the pancreas and “neural remodelling”.
Aims/Objectives: To complete the characterization of pancreatic neuropathy, the degree of myelination and glial content were investigated in intrapancreatic nerves in PCa and CP.

Patients and Methods: Intrapancreatic nerves of patients with PCa (n=20), CP (n=20) and normal human pancreas (n=10) were immunolabeled with the neural myelination marker neurofilament-H (NFH), and the glial activation markers Glial-Fibrillary-Acidic-Protein (GFAP) und p75 receptor (p75NTR). The neural immunoreactivity of each marker was correlated to the neuropathic pain sensation, the degree of neural invasion (NI) in PCa and to the degree of pancreatic neuritis in PCa and CP.

Results: PCa, and not CP, is associated with decreased neural immunoreactivity of GFAP, p75 and NFH. PCa patients with neurofibromatosis had the highest number of their intrapancreatic nerves when compared to those without pain. Intrapancreatic nerves with increasing degree of pancreatic neuritis in PCa and NI harbour higher amounts of NFH and p75. Contrastingly, pancreatic neuritis in CP is mostly encountered around nerves with small NFH content.

Conclusion: Pain in PCa is associated with increased appearance of unmyelinated intrapancreatic nerve fibers and a relative decrease of glia cells. However, pancreatic neuritis and NI in PCa are directed towards myelinated nerve fibers which are accompanied by activated glia cells. Therefore, pancreatic neuropathy in PCa induces a selective – non-global – glial activation and the dominance of unmyelinated and thus pain-transmitting intrapancreatic nerve fibers.

ENDOSCOPY IN PANCREATIC DISEASES

S11-1
PERSONAL CONSULTATION ON ENDOSCOPY AND CYTOLOGY COULD INCREASE EFFECTIVITY OF INTRADUCTAL BRUSHING AT ERCP EVEN IN EARLY CASES OF BILIARY AND PANCREATIC CANCER

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Background: Intraductal brush cytology (IBC) can be effective even in early cases of biliary and pancreatic cancers because the stenosis indicates optimal place of sampling at ERCP increasing sensitivity. During 40 months, 125 IBCs in 113 pts were performed by our oncoem. Mean age of 61 females and 52 males was 65 years (34-85); 43 biliary and 57 pancreatic cancers were diagnosed by ERCP, ultrasonography, CT and/or MR.

Method: For biliary cancers we performed papillotomy at ERCP and the cytological brush was introduced into the bile duct to the level of the sticture and several brushing were made. For pancreatic cancer IBC was performed alongside a guidewire without papillotomy. Samples were fixed and stained by routine methods. ERCP pictures and personal consultation were supplied in all cases to increase efficacy. All patients were followed-up in the clinical records until death or end of March, 2011.

Results: ERCP was negative in 13 cases and positive in 100 patients with 57 pancreatic and 43 biliary strictures. Intraductal sampling from the strictured pancreatic (46) and biliary (47) ducts resulted in positive cytology. Sensitivities were calculated in patients with definitive diagnosis confirmed by histology, surgery or progression during chemotherapy in 98 patients (86.7%); they proved to be 89.3%vs 97.6% at ERCP and 90.4% vs 86.7% with IBC from the pancreatic and biliary strictures, respectively. Decompression of bile duct and chemotherapy could be applied immediately without surgery in these mostly advanced cases, but resection rate remained low even in patients with early cancer because of technical reasons. No complication occurred after the combined ERCP and IBC except a moderate pancreatitis after removal of the nasopancreatic drain at Day 5 and 1 death in a patient with COPD and mild pancreatitis 3 days after ERCP due to pancreatic cancer. In 5 cases>3x normal amylase elevation occurred.

Conclusion: IBC can be performed with almost 90% sensitivity and 100% specificity by expert endoscopists and cytologists if detailed consultation on both morphological and histological techniques is assured in the every-day practice. Surgeons have to be involved in the personal consultation to increase resection-rate in early cases.

S11-2
HOW TO IMPROVE THE DIFFERENTIAL DIAGNOSIS OF SOLID PANCREATIC MASSES? A PROSPECTIVE COMPARATIVE STUDY OF CONTRAST-ENHANCED HARMONIC ENDOSCOPIC ULTRASOUND VS QUANTITATIVE ELASTOGRAPHY

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Contrast-enhanced harmonic endoscopic ultrasound (CE-HUES) and quantitative-elastography endoscopic ultrasound (QE-EUS) are considered useful tools for the evaluation of solid pancreatic tumors (SPT).

Aim of our study was to evaluate the diagnostic accuracy of CE-HUES, QE-EUS and the combination of both for the differential diagnosis of SPT.

Methods: 62 consecutive patients (mean age 64.3 years, ranging 89 years, 44 male) who underwent EUS for the evaluation of SPT were prospectively included. EUS was performed with linear Pentax-EUS and Hitachi-Preirus processor. The mass (area A) and a reference area B were selected during QE-EUS, and results expressed as B/A (strain ratio). Microvascularization of the tumor was evaluated over two minutes during CEHEUS after i.v. injection of 4.8ml Sonovue®. Final diagnosis was based on histopathology of surgical specimens or imaging assessment and clinical follow-up in non-operated cases. Data are shown as mean±SD. Diagnostic accuracy of CE-HUES, QE-EUS, and their combination (either both or at least one positive) was calculated.

Results: Size of the masses was 36±16mm. Final diagnosis was pancreatic adenocarcinoma (n=47), neuroendocrine tumor (n=3), inflammatory mass (n=10), pancreatic metastasis (n=1), and autoimmune pancreatitis (n=1). Overall diagnostic accuracy of QE-EUS, CE-HUES, and their combination is shown in the table.
S11-4

ANATOMIC ANOMALIES OF PANCREATIC DUCT IN CHILDREN WITH CHRONIC PANCREATITIS.

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Objectives: The etiology of CP in children is varied and includes gene mutations, anatomic anomalies and others. The aim of our study was to evaluate frequency of anatomic anomalies of pancreatic duct (PD) and their role as a cause of CP in children.

Methods: 204 children with CP, hospitalized since 1995 to 2011, were enrolled into the study. The medical records of these patients were reviewed for data on the presentation, diagnostic findings and endoscopic treatment.

Results: Anatomic anomalies of PD were found in 39 patients (19%) (18 girls and 21 boys; mean age 9.9 years, range: 2.8-17). We detected pancreas divisum in 25, aorta pancreatic in 2, a long common pancreatico-biliary tract in 5. There was no difference in age of disease onset between children with PD anomalies and patients without anomalies (8.4 vs. 9.0 years; NS). In children with anatomic anomalies ERCP had mean 2.2o Cambridge grade, vs. 1.45o in group without anomalies; p<0.05. Calculifications in the imagine were found more frequently in the group with anomalies of PD (46% vs. 32%; p<0.05). PD stenting was done more frequent in children with PD anomalies (56% vs. 25%; p<0.05).

Conclusions: CP associated with anomalies of PD in children has worse clinical course than CP in group without PD anomalies, despite similar age of the disease onset.

S12-1

TOTAL DUODENOPANCREATECTOMY WITH SUPERIOR MESENTERIC ARTERY RESECTION, EXCISION OF COMMON AND PROPER HEPATIC ARTERIES, HEPATIC ARTERIES RESECTION AND RIGHT ADRENALECTOMY FOR MULTIPLE PANCREATIC NEUROENDOCRINE TUMORS. CASE REPORT.

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Extensive multorgan resections with arterial reconstructions are justified for locally advanced pancreatic neuroendocrine tumors (pNET). The data published suggest that radical resection may be associated with increased survival.

Patient: A 33 year old woman presented with a history of progressive upper abdominal discomfort, paroxysmal abdominal pain attacks and intermittent vomiting. CT, MRI and endoUS showed three wellvascularized pancreatic tumors in the head (7cm), body (2cm) and tail (1.5cm) of the pancreas, and two 3-cm tumors of the right adrenal gland. CTA revealed unfavorable arterial anatomy: common hepatic artery (CHA), originated from the SMA, circularly surrounded with pancreatic artery. The SMA, CHA, proper hepatic artery (PHA) and hepatic arteries bifurcation were involved in the pancreatic head tumor.

Results: After multidisciplinary consensus meeting total duodenopancreatectomy with SMA resection, excision of CHA
and PHA, hepatic arteries resection and right adrenalectomy was performed. The SMA was reconstructed by the direct arterial anastomosis, reversed splenic artery was sutured in the newly-formed hepatic artery bifurcation. Uneventful postoperative course and discharge after adjustment of insulin dosage. Pathohistological examination revealed head and body neuroendocrine carcinomas (proliferative index 40% and 3%, tail pNET and cystic adrenal tumor. After one-year postoperative treatment with octreotide analogues there were no recurrence on the follow-up, patient did well and continued working.

Conclusion: Complex aggressive procedure with vascular reconstruction can be done safely and may be the only possibility for radical tumor resection in locally advanced pNETs. Integrated multidisciplinary approach may prolong survival with acceptable quality of life, supplied by substitution therapy

12-2

PATTERN AND CLINICAL PREDICTORS OF LYMPH NODE INVOLVEMENT IN NEUROENDOCRINE NEOPLASMS OF THE PANCREAS

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Introduction: Well differentiated pancreatic neuroendocrine tumors (PanNETs) are often indolent neoplasms without pathological lymph node metastasis (pN1).

Aim: To construct a model for predicting the risk of pN1 prior to surgical resection.

Methods: The databases from the Surgical Department of the University of Verona and the Beaujon Hospital were queried. Clinicopathological data of all patients with resected (R0 or R1), non-functioning PanNET between 1993 and 2009 were reviewed. Multiple logistic regression analysis was performed.

Results: Data were analyzed for 214 patients. 72 patients were N1 (34%). The 5-year disease free survival for patients with pN1 was significantly lower than for pN0 patients (62% vs 88%, P<0.0001). Multivariable analysis suggested the significant independent factors associated with pN1 were radiological nodal status (rN) (odds ratio 4.7, P<0.0001) and the degree of differentiation (G2 vs G1 odds ratio 4.4, P<0.0001). Overall, the 94% of patients with rN0 PanNET-G1 were pN0. When the degree of differentiation was excluded, on multivariable analysis rN1 (odds ratio 4.1, P=0.001) and radiological size > 4 cm (odds ratio 2.5, P=0.012) were independent predictors of pN1.

Discussion: Patients with PanNET-G1, in the absence of pathological node involvement, have a very low risk of pN1. In patients with PanNET-G2, lymph node dissection should be performed. When a preoperative cytological diagnosis is not achieved, the radiological size of the lesion is a powerful alternative predictor of pN1. The analyses demonstrate that the risk of pathological nodal involvement in PanNET patients can be estimated by a clinical predictive model.

S12-3

PENG’S BINDING PANCREATICOJEJUNOSTOMY: RESULTS OF A MULTICENTRIC ITALIAN PILOT STUDY.

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Background: Peng’s binding pancreaticojejunosmy has been proposed in eastern countries as a safe technique that avoids anastomotic leakage after pancreaticoduodenectomy (PD).

Aim: To evaluate the rate of pancreatic fistula in an Italian population underwent Peng’s binding pancreaticojejunosmy after PD.

Patients and Methods: From January 2009 to December 2010, data regarding 69 consecutives patients underwent PD in three high volume centres were collected. For each patients we registered sex, age, co-morbidities, ASA score, type of resection, characteristics of pancreatic remnant, pathological diagnosis, morbidity and mortality. The primary end-point was postoperative pancreatic fistula (POPF). The secondary end-points were overall complications, postoperative pancreatic haemorrhage (PPH), reoperation and mortality rate. Univariate and multivariate analysis were carried out to evaluate the factors predicting POPF.

Results: Mean age of patients was 64.5 ± 12.4 years. There were 27 (39.1%) female and 42 (60.9%) male. One or more co-morbidities were present in 39 (56.5%) patients; 5 patients (7.2%) were ASA I, 27 (39.1%) ASA II, 35 (50.7%) ASA III and 2 (2.9%) ASA IV. A pancreaticoduodenectomy according Whipple was carried out in 42 (60.9%) patients. An extended resection was performed in 5 (7.2%) cases. Pancreatic stump was hard in 36 (52.2 %) cases and Wirsung duct was dilated in 31 cases (44.9%). Malignant disease was present in 65 (94.1%) cases. Thirteen patients (18.8%) had POPF (8.7% grade A, 8.7% grade B, and 1.4% grade C). Overall complications, PPH, reoperation and mortality rate were 52.2 %, 18.8%, 9.0% and 5.8%, respectively. The univariate analysis showed that the only factor related to POPF was the presence of a soft pancreatic stump (34.4% versus 5.4% of hard pancreatic stump; P=0.004). Multivariate analysis confirmed the soft pancreatic stump as the only independent factor related to POPF (OR 9; CI 95% 2-44; P=0.007).

Conclusion: In Italian population, performing Peng’s binding pancreaticojejunosmy after PD do not reduce the risk of POPF, which is related only to the texture of the pancreas remnant.

FROM CHRONIC INFLAMMATION TO PANCREATIC CANCER

S13-1

GSK-3 B INHIBITION DELAYS INFLAMMATION AND KRAS-DEPENDENT PANCREATIC CARCINOGENESIS IN A TRANSGENIC MOUSE MODEL

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**Introduction:** Chronic pancreatitis, a main risk factor for pancreatic cancer, induces the expression of inflammatory signalling and transcription factors such as NF-κB and nuclear factor of activated T cells (NFAT). Recent evidence has shown that glycogen synthase kinase-3 (GSK-3) β regulates NFAT-mediated pancreatic cancer cell survival and proliferation in vitro. Here, we analysed the role of GSK-3β in NF-κB and NFAT pathway activation in inflammation triggered carcinogenesis in a Kras transgenic mouse model.

**Methods:** Kras transgenic mice (Kras G12D) were randomly assigned to receive either caerulein or a combination of caerulein and GSK-3β inhibition for various treatment periods. Histopathological analyses, immunohistochemistry RT-PCR and Western blot were performed to define carcinogenesis in early and late stages.

**Results:** GSK-3β inhibition caused a dramatic inhibition in development and progression of acinar-ductal metaplasia, mPaniNs and invasive cancers in caerulein-treated Kras transgenic mice. In addition, we found inhibition and downregulation of NFAT and NF-κB pathways and target genes in Western blot analyses and immunohistochemical staining.

**Conclusion:** Our data strongly indicate involvement of GSK-3β in pancreatic carcinogenesis in response to inflammation, and in addition, suggest that specific targeting of this kinase offers therapeutic options.

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**S13-3**

**ROLE OF THE PROTEIN KINASE C SIGNALING PATHWAY IN THE REGULATION OF CLAUDIN-4 IN NORMAL HUMAN PANCREATIC DUCT EPITHELIAL CELLS AND CANCER CELLS.**


**Introduction:** Claudin-4 is a member of the claudin family, which is responsible for forming tight junction strands, and it is frequently overexpressed in pancreatic cancer. Claudin-4 is also a high-affinity receptor for Clostridium perfringens enterotoxin (CPE) and a promising target for diagnosis and novel therapies using CPE in pancreatic cancer. We previously reported that tight junctions in normal human pancreatic duct epithelial (HPDE) cells were regulated by the protein kinase C (PKC) signaling pathway.

**Objective:** We compared the role of the PKC signaling pathway in the regulation of claudin-4 and the effects of CPE treatment, using normal HPDE cells and cancer cells.

**Method:** We used human telomerase reverse transcriptase (hTERT)-transfected HPDE cells (hTERT-HPDE cells) as normal HPDE cells and pancreatic cancer cell lines. Fetal bovine serum (FBS) and 12-O-tetradecanoylphorbol 13-acetate (TPA) were used to activate PKC.

**Result:** In normal HPDE cells, expression of claudin-4 was markedly up-regulated by PKC activation. In FBS-treated normal HPDE cells, claudin-4 was expressed at the apicalmost tight junction area, but cytotoxic effects of CPE were not observed. In pancreatic cancer cells, claudin-4 was expressed at both apical and basolateral cell membranes and dose-dependent cytotoxic effects of CPE were observed. In TPA-treated pancreatic cancer cells, epithelial to mesenchymal transition-like changes were seen and claudin-4 disappeared at cell membranes, attenuating cytotoxic effects of CPE.

**Conclusion:** The PKC signaling pathway regulates expression of claudin-4 in normal HPDE cells, and cancer cells in differential manners and is an important factor for developing novel therapies targeting claudin-4 in pancreatic cancer.

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**S13-4**

**CYTOLOGY, CEL AND K-RAS ANALYSIS OF CYSTIC FLUID ASPIRATE OBTAINED BY EUS-FNA IN DIAGNOSING PANCREATIC CYSTIC NEOPLASIA - A PROSPECTIVE STUDY**

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**Introduction:** Based on imaging, it is difficult to differentiate benign, preneoplastic and malignant pancreatic cysts.

**Objectives:** To investigate the yield of cytological, biochemical and molecular analysis of cyst fluid aspirate obtained by EUS-FNA in diagnosing pancreatic cystic neoplasia (PCN).

**Patients & Methods:** Patients referred for evaluation of pancreatic cystic lesion (PCL) or endoscopic treatment, using normal HPDE cells and cancer cells in differential manners and is an important factor for developing novel therapies targeting claudin-4 in pancreatic cancer.

**Results:** In normal HPDE cells, expression of claudin-4 was markedly up-regulated by PKC activation. In FBS-treated normal HPDE cells, claudin-4 was expressed at the apicalmost tight junction area, but cytotoxic effects of CPE were not observed. In pancreatic cancer cells, claudin-4 was expressed at both apical and basolateral cell membranes and dose-dependent cytotoxic effects of CPE were observed. In TPA-treated pancreatic cancer cells, epithelial to mesenchymal transition-like changes were seen and claudin-4 disappeared at cell membranes, attenuating cytotoxic effects of CPE.

**Conclusion:** The PKC signaling pathway regulates expression of claudin-4 in normal HPDE cells, and cancer cells in differential manners and is an important factor for developing novel therapies targeting claudin-4 in pancreatic cancer.

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**S13-2**

**EPITHELIAL TO STROMAL REDISTRIBUTION OF PRIMARY CILIA DURING PANCREATIC CARCINOSISNOSIS.**

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**Introduction:** The Hedgehog (Hh) pathway is a mediator in pancreatic ductal adenocarcinoma (PDAC). Surprisingly, previous studies suggested that Primary Cilia (PC), the essential organelles for Hh signal transduction, are lost in PDAC. However PC were identified in paraffin sections by double immunofluorescence for acetylated tubulin and gamma tubulin. Co-staining for the Hh receptor Ptch was performed.

**Results:** PC were identified in paraffin sections by double immunofluorescence for acetylated tubulin and gamma tubulin. Co-staining for the Hh receptor Pch was performed.

**Conclusion:** PC are not lost during pancreatic carcinogenesis but their formation is redistributed from the epithelium to the stroma. This redistribution may be the explanation for a redirection of Hh signalling towards the stroma during pancreatic carcinogenesis.
Results: A total of 86 patients (mean age 59.3±13 years, 56.9% male) with PCL were analysed. Final diagnosis revealed carcinoma in 33 (38.4%), mucinous cyst low-grade (MCLG) in 9 (10.5%), serous cystadenoma (SCA) in 9 (10.5%) and inflammatory pseudocyst in 35 (40.6%) patients. The median(IQR) CEA level in pseudocyst, SCA, MCLG and carcinoma were 20(7-51), 4.9(0.4-12.6), 246(171-277) and 2133(807-10349)ng/ml, respectively. Operating characteristics of CEA, CEA>192ng/ml and K-RAS in diagnosing neoplastic PCL were: sensitivity 76%, 85% and 61%, respectively; specificity: 100%, 97% and 100%, respectively. Neither pseudocyst nor SCA were K-RAS positive. Combination of CEA and K-RAS had sensitivity 93% and specificity 97%.

Conclusion: EUS-FNA cytology is insufficient in diagnosing PCN, while CEA is more accurate. Addition of K-ras to CEA analysis increases sensitivity of EUS-FNA. Combination of both tests may select candidates for surgical treatment of PCN.

SURGICAL THERAPY IN CHRONIC PANCREATITIS AND PANCREATIC CANCER

S15-1
OUTCOMES AND PROGNOSTIC FACTORS FOLLOWING PANCREATEO-DUODENECTOMY FOR CHOLANGIOCARCINOMA

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Introduction: Distal cholangiocarcinoma has a UK incidence of approximately 200 cases/year. There are limited small studies identifying clinicopathological prognostic factors following pancreaticoduodenectomy for distal cholangiocarcinoma which report a 5-year survival of around 24%.

Objectives: To identify clinicopathological prognostic factors following pancreaticoduodenectomy for distal cholangiocarcinoma.

Methods: Patients with a histological diagnosis of cholangiocarcinoma following pancreaticoduodenectomy from 1997-2011 were identified from a prospectively maintained database. Perioperative blood tests, pathological findings and survival data were collected. Kaplan-Meier survival curves were produced, and differences assessed using the Log-Rank test for univariate analysis. Multivariate analysis was performed using a Cox Proportional Hazard model.

Results: 104 patients (60 male, 44 female) were identified with a median age of 65 years (IQR 57-70 years). There were 3 perioperative deaths (2.9%). Median overall survival was 17.9 months (95%CI 14.6-21.3 months) and 5-year survival was 18%. Univariate analysis revealed positive post-operative CA19-9 (p=0.014), tumour differentiation (p<0.001), tumour stage (p=0.002), lymph node involvement (p=0.002), positive resection margin (p=0.001) and number of positive margins (p=0.001) to be significant predictors of survival. On multivariate analysis, positive resection margin status (HR=2.27, 95%CI 1.32-3.85, p=0.003), raised post-operative CA19-9 (HR=1.93, 95%CI 1.13-3.25, p=0.013) and tumour differentiation (HR=2.04, 95%CI 1.20-3.50, p=0.009) remained significant independent prognostic factors.

Conclusion: This study is the largest of its kind in a European population and concurs with previous studies regarding the prognostic significance of resection margin status and tumour differentiation. These data suggest for the first time that post-operative CA19-9 levels are useful in predicting outcome following pancreaticoduodenectomy for distal cholangiocarcinoma.

S15-2
DECREASE IN CLINICALLY RELEVANT PANCREATIC FISTULA BY COVERAGE OF THE PANCREATIC REMNANT AFTER DISTAL PANCREATECTOMY

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Introduction: Pancreatic fistulas after distal pancreatectomy (DP) occur in up to 60%. Several techniques for closure of the pancreatic stump have been advocated, but the best management of stump closure remains controversial.

Objectives: Our aim was to evaluate clinical benefits of coverage of the pancreatic resection margin by autologous tissue.

Patients and Methods: 117 consecutive patients underwent a DP at the University hospital in Heidelberg between 05/2009 and 09/2010. A coverage procedure was performed in 73 of these patients. All patients were recorded prospectively, and the clinical course was evaluated focusing on the occurrence of pancreatic fistula (ISGPF-definition). Treatment cost analysis was performed.

Results: The rate of clinically relevant pancreatic fistulas (type B and C) was decreased in patients with coverage compared to the standard controls (type B: 7% vs. 9%; type C: 7% vs. 25%; p<0.002). Patients with a coverage procedure had a lesser (p<0.02) hospital duration of stay, and treatment costs were less (p=0.001) compared to patients without coverage.

Conclusion: Coverage of the pancreatic remnant after DP decreases the rate of clinically relevant pancreatic fistulas, duration of stay, and treatment costs. A randomized trial is needed to verify these results.

S15-3
RADIOFREQUENCY ABLATION OF PANCREATIC CANCER

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Introduction: Radiofrequency ablation (RFA) was suggested to be the therapeutic alternative in locally advanced pancreatic cancer.

Aims: The prospective clinical phase III study evaluating morbidity, mortality, survival and quality of life after intraoperative RFA of locally advanced pancreatic cancer.

Patients and methods: The patients with histologically verified unresectable or inoperable (solitary hepatic metastasis or high operatio risk) pancreatic cancer were included. In RFA group, (n=24), 16 (67%) males, median age 68.5 (min 48, max 77), stage IIIb 4/24 (17%), stage III 15/24 (63%), stage IV 5/24 (21%), intraoperative RFA with or without bypass operation was performed. Thirteen patients (54%) received adjuvant chemotherapy (CHT). The patients in control group (n=24),
12 (50%) males, median age 64 (min 50, max 79), stage IB 4/24 (17%), stage III 14/24 (58%), stage IV 6/24 (25%) underwent only bypass procedures. Seventeen of them (71%) received adjuvant CHT. Three months after surgery quality of life (QoL) using QLQ C30, pan 26 questionaire was evaluated.

**Results:** RFA related 30 day mortality and morbidity were 16 % (4/24) and 0% (0/24) respectively. Two patients were reoperated due to subfascial abscess. In one patient, subfascial abscess was drained spontaneously through laparotomy. Once wound dehiscence had occurred. All patients were discharged and discharged to home care. RFA related 30 days mortality was 0%. Median survival in RFA group: stage IB (n=4) 4.3 months, Stage III (n=15) 12.1 months, stage IV (n=5) 5.8 months, with adjuvant CHT (n=13) 12.1 months, without CHT (n=11) 6.6 months. Median survival control group: stage IB (n=4) 6.5 months, stage III (n=14) 10.7 months, stage IV (n=6) 2.5 months, with adjuvant CHT (n=17) 11 months, without CHT (n=7) 4.8 months. Significant QoL improvement was not apparent 3 moths after surgery in RFA group. There was no pain progression in RFA group 3 months after surgery.

**Conclusion:** Intraoperative RFA of unresectable pancreatic cancer is feasible and safe palliative treatment modality, which can prolong survival especially at stage III patients. Improvement of QoL is not significant.

**S15-4**

**INDIVIDUALIZATION OF PANCREATIC CANCER THERAPY BASED ON PRE- AND POSTOPERATIVE CA19-9 LEVELS**

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**Introduction:** In pancreatic cancer, the serum marker carbohydrate antigen 19-9 (CA19-9) has recently gained growing attention, since genetic markers to aid clinical decision making are still lacking.

**Objectives:** The present study aimed to determine the prognostic role of perioperative CA19-9 in pancreatic adenocarcinoma, with a focus on implications for pre- and postoperative therapeutic consequences.

**Patients and Methods:** Of a total of 1627 consecutive patients who underwent surgery for primary pancreatic adenocarcinoma, data from 1543 patients with preoperative serum levels of CA19-9 were evaluated for tumor stage, resectability, and prognosis. Pre-to-postoperative CA19-9 changes were analyzed for long-term survival. A control cohort of 706 patients with chronic pancreatitis was used to assess the predictability of malignancy by CA19-9 and the effects of hyperbilirubinemia on CA19-9 levels.

**Results:** The more that preoperative CA19-9 increased, the lower were tumor resectability and survival rates. Resectability and 5-year survival varied from 80% to 38% and from 27% to 0% for CA19-9<37U/ml vs. >4000U/ml, respectively. CA19-9 increased with the stage of the disease and was highest in AJCC stage IV. Patients with a postoperative CA19-9 decrease of ≥75% had a superior prognosis. Hyperbilirubinemia did not critically affect CA19-9 levels, neither in cancer nor in chronic pancreatitis (correlation coefficient <0.135).

**Conclusion:** In patients with pancreatic adenocarcinoma, CA19-9 predicts resectability, stage of disease, as well as prognosis, and is not affected by hyperbilirubinemia. Utmost attention should be paid to pre- and postoperative CA19-9 levels in the management of pancreatic cancer patients because they may allow an individualized adaptation of therapy.

**S16-1**

**A MULTICENTER, PROSPECTIVE, COMPARATIVE, RANDOMIZED OPEN-TRIAL OF ENDOSCOPIC ULTRASOUND CYTOLOGIC BRUSHING VS FINE-NEEDLE ASPIRATION (FNA) FOR THE PATHOLOGICAL DIAGNOSIS OF CYSTIC PANCREATIC LESIONS**

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Diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) for cystic pancreatic lesions (CPL) is hampered by the low cellularity of samples obtained. A new system (EchoBrush; Cook-Medical) has been developed to improve the quality of the samples.

**AIM:** To evaluate diagnostic accuracy of Echobrush versus FNA for cytopathological diagnosis of CPL.

**Methods:** Prospective, randomized, multicenter, open and comparative trial of Echobrush versus FNA for the cytological diagnosis of CPL (>15 mm in diameter). Patients were randomized to standard EUS-FNA (group I) or Echobrush (group II). Main outcome was the percentage of correct diagnosis by Echobrush versus FNA. Complication rate was also evaluated. Data were compared by chi-square test.

**Results:** 65 patients (median age 64 years, range 31-84, 33 male) were included (34 in group-I and 31 in group-II). Three of the patients allocated to group II with the lesion in the head of the pancreas had to be changed to group I since Echobrush was technically unfeasible. CPL mean size was 20mm (range 16-60mm). Final diagnosis was IPMN (n=32), serous cystadenoma (n=10), pseudocyst (n=11), mucinous cystadenoma/cystoadenocarcinoma (n=5), pancreatic adenocarcinoma (n=5), Panin lesion (n=1), and inconclusive diagnosis (n=1). A correct diagnosis was achieved in 19/37 cases from group I (50.1%) and in 11/27 cases from group II (40.7%) (p=0.28). There were two mild complications in group I and one in group II (mild bleeding).

**Conclusions:** The use of Echobrush does not improve the diagnostic accuracy of standard EUS-FNA for the differential diagnosis of CPL.

**S16-2**

**BRANCH DUCT INTRADUCTAL PAPILLARY-MUCINOUS NEOPLASIA: THIN RED LINE WALKING BETWEEN SURGERY AND SURVEILLANCE**

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**Introduction:** Performing pancreatic resection or surveillance in patients affected by branch duct intraductal papillary mucinous neoplasms (BD-IPMN) is mainly based on radiological features.
Aim: To identify whether different subgroups of BD-IPMN display a characteristic clinical behavior and to investigate clinical and radiologic predictors of dysplasia/invasiveness.

Patients and Methods: 52 specimens of resected BD-IPMN were reviewed by a pathologist. A correlation between histologic subtypes (gastric, intestinal, pancreato-biliary and oncocytic) and degree of dysplasia (mild, moderate, severe dysplasia and invasive carcinoma) was made. Histologic subtypes were dichotomized into gastric and non-gastric, and the degrees of dysplasia into adenomas and borderline-to-invasive IPMN. Symptoms, tumor markers and magnetic resonance choangiopancreatography (MRCP) features were correlated with pathological findings.

Results: A non-gastric subtype was associated with borderline-to-invasive BD-IPMN (p<0.01). Adenomas arose only from the gastric subtype, in borderline-to-invasive BD-IPMN arisen from a gastric epithelium a correlation with tumor diameter (>3cm) was found. A dilated main pancreatic duct, the presence of mural nodules and thickness of the cystic wall on MRCP were associated with borderline to invasive BD-IPMN (p <0.05). The dilation of the main pancreatic duct (MPD) is highly correlated to the risk of degeneration at the multivariate analysis (p < 0.05).

Conclusion: BD-IPMNs encompass a group of neoplasms with different biological behaviors. Gastric type IPMNs show a more indolent behavior and the risk of malignancy increases with the diameter. We confirm the role played by the radiological features as predictors of malignancy. The dilation of the MPD is highly related to the risk of degeneration.

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S16-3

THREE DIMENSIONAL CONTRAST ENHANCED ULTRASONOGRAPHY VS. MAGNETIC RESONANCE IMAGING IN THE DIAGNOSIS OF IPMN OF THE PANCREAS

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Background: The IPMNs of the pancreas represent a challenge for the imaging.

Aim: To prospectively compare the diagnostic accuracy of three-dimensional contrast enhanced ultrasonography (3D-CEUS) vs. magnetic resonance imaging plus cholangiopancreatography RM (MRI) in the diagnosis of IPMNs.

Methods: Thirty consecutive IPMN patients (22 F, 8 M, age 67±12.2 years, mean±SD; MRI lesion size 13.8±8.3 mm, mean±SD) were studied. The kappa, McNemar and Wilcoxon statistics were applied.

Results: Three patients (10%) had no diagnostic 3D-CEUS for technical problems. 3D-CEUS was judged to improve the two-dimensional ultrasonography (2D-US) findings in evaluating the pancreatic lesions in 14 patients (51.9%). Twelve (44.4%) IPMN type 1 cases were identified by 3DCEUS vs. no cases by RM (p<0.001). IPMN localization showed a poor agreement between 3D-CEUS and MRI (kappa=0.058), whereas the agreement related to the risk of degeneration was highly correlated to the risk of degeneration.

Conclusion: The 3D-CEUS compared to 2D-US improves the IPMN diagnosis. It may be utilized to better evaluate these patients after 2D-US examination. MRI remains the gold standard technique.

S16-4

节约

PARANTIC RESECTIONS FOR CYSTIC NEOPLASMS: FROM THE SURGEON’S PRESUMPTION TO THE PATHOLOGIST’S REALITY


Background: Current guidelines for the management of pancreatic cystic neoplasms are based on the assumption that these lesions can be classified correctly on the basis of features of cross-sectional imaging. But a certain degree of overlap between different lesions exists, and little is known about the rate of inaccurate preoperative diagnoses.

Objective: Preoperative and final pathologic diagnoses of patients resected for a pancreatic cystic lesion presumed to be neoplastic were compared to identify diagnostic pitfalls and potential risk factors for incorrect preoperative characterization.

Methods: Retrospective analysis of patients managed operatively between 2000 and 2010. Univariate and multivariate models were used.

Results: 476 patients were analyzed. Final pathologic diagnosis matched the preoperative diagnosis in 78% of cases. The highest accuracy was reached for solid pseudopapillary neoplasms (95%) and for main duct/mixed duct intraductal papillary mucinous neoplasms (81%). Surprisingly, 23 cysts (5%) were found to be ducal adenocarcinoma, while 45 patients (9%) underwent a pancreatic resection for a non-neoplastic condition. The use of a routine radiologic work-up, including contrast-enhanced ultrasonography and magnetic resonance imaging, was associated with a favorably correct characterization of the cystic lesion. Endoscopic ultrasonography did not seem to improve diagnostic accuracy. Increased levels of serum CA19-9 resulted as risk factors for an incorrect diagnosis as well as for a final diagnosis of a ductal adenocarcinoma.

Conclusion: Overall rate of inaccurate preoperative diagnoses in a tertiary care center with a broad experience in pancreatolgy approached 22%. Serum Ca 19-9 is an important complementar tool within the context of preoperative investigation of cystic neoplasms of the pancreas.
PANCREATIC STEM CELL PLASTICITY

S18-1

THE USE OF ALLOGENEIC MESENCHYMAL BONE MARROW STEM CELLS IN EXPERIMENTAL ACUTE AND CHRONIC PANCREATITIS IN RATS

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Aims: Under the experimental conditions to establish safe doses and optimal timing of stem cell transplantation.

Material and method: 50 white rats, an experimental model of acute and chronic pancreatitis. Allogeneic stem cells transplantation: a dose 5x10⁶, a single intraperitoneal injection of 2 ml of saline; 2x10⁶ in 2 ml of saline once or double injection

Results: Animals are parted in the groups: first group - the injection on the third day after reproduction 5x10⁶; the second group- first introduction to the 6th day 2x10⁶ cells and the second injection the 12th day, 3rd group - the first introduction to the seventh day 2x10⁶ cells at 14th day of the second injection, fourth group - injection a single dose the 2x10⁶ cells on the 10th day. 5th and 6th groups - the introduction of cells in different doses to intact animals. Autopsy. First group: the place of introduction of damaging agent in the pancreatic tissue necrotic, the interintestinal abscesses. Second group of double injection in doses 2x10⁶ cells the all pancreas were “shrouded” fatty tissue. 3rd group of data are similar to data obtained in the second group. 4th group of single injection at a dose of 2x10⁶ ineffective. 5th and 6th groups autopsy - damage is not The level of pro-and anti-inflammatory cytokine change in the 2nd and 3rd groups: IL-1β., IFN,TNF decreasing proinflammatory cytokines. Increased antinflammatorie-IL-4.

Conclusion: Allogenic mesenchymal stem cells of a marrow reduce inflammatory reaction. Unitary introduction noneffectively, most effectively double introductions of stem cells.

S18-2

HYPOXIA ACTIVATES PANCREATIC STELLATE CELLS: DEVELOPMENT OF AN ORGANOTYPIC CULTURE MODEL OF THICK SLICES OF NORMAL HUMAN PANCREAS

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Pancreatic stellate cells (PSC) are involved in the modulation of fibrosis in chronic pancreatitis and promote oncogenesis by modulating the extracellular matrix, cell proliferation and migration.

Aim: To evaluate the early activation of PSC in case of hypoxia and oxidative stress in normal human pancreas.

Methods: An organotypic culture model of thick sections of human pancreas has been developed and validated. Slices of pancreas (300μm) were prepared from surgical specimens and cultured in hypoxia conditions. Half of the samples underwent an initial phase of culture in normoxia (21% O2) to reproduce hypoxia. The total duration of culture was 72 hours. Cell viability, hypoxia, apoptosis and activation were monitored.

Results: 30 sections per specimen were cultured,(50% under conditions of hypoxia). Analysis of sections was performed at baseline, 24h, 48h and 72h. Morphological analysis showed gradual appearance of ductal/acinar dedifferentiation. At 72h, foci of necrosis were identified. Hypoxia was confirmed by the expression of HIF1 and CA9 at 48h (10% and 50% of labeled cells). Apoptosis was limited, acinar cells expressed caspase 3 at 48 and 72h. Analysis of proliferation using Ki67 index showed significant activation of PSC at 48h (x5 / baseline) and at 72h (x6/baseline). Activation of PSC was confirmed by smooth muscle actin immunohistochemistry.

Conclusion: Organotypic culture of normal human pancreas is possible with optimized cell viability at 72 hours. Hypoxia-induced activation of PSC occurs very early. Our model suggests that inflammation and cell stress can participate in the early stages of oncogenesis by activating PSC.

EARLY PANCREATIC CANCER

S19-1

A THREE-MICRORNA SIGNATURE FOR PREDICTING SURVIVAL IN PANCREATIC CANCER

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Introduction: microRNAs (miRNAs) play a role in post-transcriptional gene regulation and are important in pancreatic tumorigenesis. Combined analysis of miRNA and mRNA expression has revealed important functional interactions in many human cancers.

Aims/Objectives: To perform integrated analysis of miRNA:mRNA expression in pancreatic ductal adenocarcinoma (PDAC) / normal pancreas in order to reveal miRNAs targeting transcripts involved in PDAC progression and to establish a prognostic miRNA signature for PDAC.

Patients and Methods: miRNA and mRNA expression arrays were performed on fresh patient samples (PDAC and normal, both n=9) to identify significant interactions. Candidate miRNAs were investigated in vitro and in vivo. Finally, samples from an independent cohort of PDAC patients (n=40) were used to confirm the clinical relevance and prognostic ability of the miRNAs.

Results: Crossed analysis of miRNA expression, gene and mRNA seed data revealed 15 upregulated miRNAs and 148 downregulated genes in PDAC. miR-21, 23a and 27a are highly upregulated in PDAC. miR-21 alone. Multivariate logistic regression analysis showed that inflammation and cell stress can participate in the early stages of oncogenesis by activating PSC.

Conclusion: Organotypic culture of normal human pancreas is possible with optimized cell viability at 72 hours. Hypoxia-induced activation of PSC occurs very early. Our model suggests that inflammation and cell stress can participate in the early stages of oncogenesis by activating PSC.
S19-2
AUTOPHagy IS INDUCED IN PANcreATIC DUCTAL ADENOCARCINOMA (PDA) IN PATients cORRESPONDING TO THE IN-VITRO AUTOPHAGic STATUS OF PANcreATIC CANcer CELLS (PANC-1)
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Objectives: Studies with PANC-1 imply that autophagy may be induced in pancreatic ductal adenocarcinoma (PDA). Investigating the role of autophagy in patients is challenging as the induction of autophagy in pancreatic tissue may be affected by cell death mechanisms taking place after the tissue specimens have been harvested. Eliminating this post-harvesting distraction would be crucial when investigating this phenomenon. No such study about autophagy in PDA in patients exists. Our aim was to study, whether autophagy is 1) induced in PDA compared to healthy pancreatic tissue in patients, and 2) correspondent to the autophagic status of PANC-1 cells in vitro.

Patients and Methods: Pancreatic samples were retrieved in laparotomy from patients undergoing pancreateoduodenectomy. Core-needle biopsies from the center of histologically-confirmed PDA tumors and from healthy pancreas (within the area to be resected) were immediately snap-frozen and proteins were extracted by repeated freeze-thaw cycles. The degree of autophagy was analysed by Western blotting of LC3-II, and compared to the degree of autophagy in PANC-1 cells (in basal conditions and when treated with anticancer drugs (gemcitabine and 5-FU) +/- autophagy inhibitor chloroquine).

Results: Autophagy was significantly induced in PDA compared to healthy pancreatic tissue in patients. This resembled the autophagic status of PANC-1 cells under basal culture conditions.

Conclusions: Autophagy is induced in PDA in patients similarly to PANC-1 cells. In PANC-1 cells chloroquine increases the cytotoxicity of 5-FU and gemcitabine by inhibiting autophagy. Thus patients with PDA may benefit from therapy where anticancer drugs are combined with an autophagy inhibitor.

S19-3
ROLE OF S100A8/A9 IN THE CROSS-TALK BETWEEN CANcer CELLS AND STROMA-ASSOCIATED CELLS
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Introduction: Pancreatic cancer is characterized by the presence of dense desmoplastic stroma harbouring a variety of cells including S100A8 and S100A9-secreting monocytes. We previously reported that exogenous S100A8/A9 proteins increase cancer cell proliferation and migration. In other cancers, these proteins are known to contribute to the formation of a pre-metastatic niche at distant sites. The aim of the current study was to further characterize the influence of S100A8 and S100A9 on pancreatic cancer cells and tumour-derived stellate cells.

Methods: Profiling of 27 cytokines secreted into cell-culture medium by pancreatic cancer cell lines and tumour-derived primary stellate cells was performed using LumineX-based Multiplex assays. Reporter assays and Western blotting were undertaken to unravel signaling mechanisms involved in S100A8/S100A9-mediated effects on pancreatic cancer cells.

Results: Recombinant S100A8 and S100A9 proteins stimulated secretion of specific cytokines (e.g. IL-8, FGF and TNF-alpha), whereas, PDGF secretion was stimulated by S100A8 only. S100A8/A9 activated phospho-p38 and phospho-p44/p42 MAPK and enhanced NF-κB activity through RAGE. S100A8 and S100A9 also induced Smad4 signaling as evidenced by phosphorylation of Smad2/3 and activation of the Smad4 luciferase. Baseline cytokine profiles for pancreatic stellate cells have been obtained, and the effects of S100A8 and S100A9 are currently under assessment.

Conclusion: S100A8 and S100A9 promote specific cytokine secretion from pancreatic cancer cells. Interestingly, a number of these cytokines, in turn, induce the secretion of S100A8 and S100A9 from monocytes cells, creating a paracrine loop. These events may create a favorable environment for tumour development and metastases.

S19-4
MICRONuRNA-142-3P, A NOVEL REGULATOR OF HEAT SHOCK PROTEIN 70, MODULATES TRiptolIDE-INDUCED PANcreATIC CANcer CEll DEATH
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Introduction: Triptolide inhibits pancreatic cancer cell growth in vitro and blocks growth and metastatic spread in vivo. Our lab has shown that triptolide triggers apoptosis via inhibition of heat shock protein 70 (HSP70) expression. Triptolide is hypothesized to decrease HSP70 expression via inhibition of heat shock factor 1 (HSF1).

Aim: We are testing whether triptolide inhibits HSP70 via a novel mechanism of inducing the expression of miR-142-3p, which is predicted to target the 3'UTR of the HSPA1B isoform of HSP70. Further, we sought to characterize the biological function of miR-142-3p overexpression.

Methods and Results: MicroRNA-142-3p was found by miRNA microarray and qPCR to increase after triptolide treatment in MiaPaCa-2, Capan-1 and S2-013 cells. Triptolide induces the expression of miR-142-3p in vivo in human pancreatic cancer xenografts grown in SCID mice. Triptolide-induced expression of miR-142-3p inversely correlates with decreasing HSP70 levels. Overexpression of miR-142-3p inhibits cell proliferation, decreases HSP70 mRNA and protein levels, and sensitizes cells to triptolide treatment. We observe a significant rescue of miR-142-3p mimic-induced sensitization when cells are co-transfected with miR-142-3p inhibitor. The mRNA of neither HSF1 nor its transcriptional target, HSP27, changes following miR-142-3p overexpression. We have demonstrated direct binding between miR-142-3p and HSP70 using a luciferase reporter assay in HEK-293 cells transfected with a HSP70 3'UTR reporter vector.

Conclusion: This demonstrates a novel miRNA mechanism of regulating HSP70 expression in cancer. Further, we show a proof-of-principle of miR-142-3p overexpression as a promising therapeutic strategy for inhibiting cell proliferation and inducing chemosensitization of pancreatic cancer cells.
DIABETES AS A RISK FACTOR FOR PanCREATIC CANCER

S22-1
PREOPERATIVE DIABETES MELLITUS DOES NOT IMPACT ON POSTOPERATIVE MORBIDITY AFTER PanCREATIC RESECTIONS FOR ductAL ADENOCARCINOMA

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Introduction: The prevalence of diabetes mellitus (DM) in patients with pancreatic ductal adenocarcinoma (PDAC) ranges from 20% to 80%. In patients undergoing resection, it is unclear whether DM impacts on postoperative morbidity.

Objective: To address whether preoperative DM is a risk factor for increased morbidity after resection for PDAC.

Methods: Data from 631 consecutive patients were analyzed using univariate and multivariate models.

Results: 130 patients were diabetics. 91 had longstanding DM and 39 a new-onset DM. Diabetics were older, had a greater BMI, and lost more weight preoperatively (all p=0.001). Postoperative morbidity was similar in the two groups, but the incidence of pancreatic fistula (PF) was greater in non-diabetics (16.6% versus 8.3%, p=0.033), who were also more likely to have a soft pancreatic texture (79.5% versus 46.0%, p=0.001). All these variables did not differ when stratifying by DM type. Univariate analysis of patients who did and did not develop PF showed that sex (p=0.029), BMI (p=0.015), preoperative weight loss (p=0.001), DM (p=0.033), pancreatic texture (p=0.001), abdominal collections (p=0.001), delayed gastric emptying (p=0.002), acute pancreatitis (p=0.001), and post-pancreatectomy haemorrhage (p=0.016) were associated with PF. In multivariate analysis DM maintained an independent association with PF (odds ratio=0.460, 95% CI 0.21-0.95, p=0.04). Additional variables associated with an increased probability of PF formation were sex (p=0.037), BMI (p=0.043), preoperative weight loss (p=0.003), soft pancreatic texture (p=0.004), and abdominal collections (p=0.001).

Conclusion: DM is not a risk factor for increased postoperative morbidity after resection of PDAC. The decreased incidence of PF in diabetics is likely to be a consequence of a hard pancreatic texture.

S22-2
AUTOLOGOUS ISLET TRANSPLANTATION TO IMPROVE GLYCEMICAL CONTROL FOLLOWING EXTENDED PANCREATECTOMY: INDICATIONS AND OUTCOME

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Introduction: Autologous Islet Transplantation (AIT) is performed to improve glycaemic control after extended pancreatectomy. In such cases, islet cells are isolated from non-neoplastic pancreatic parenchyma (reseected for technical reason) and then re-infused.

Methods: From November 2008 to present, 31 patients (out of 36 candidates) underwent AIT. Indications for AIT were: completion pancreatectomy (CP) for fistula after pancreaticoduodenectomy (13 pts, Group A); CP as an alternative to high-risk anastomosis during pancreaticoduodenectomy (14 pts, Group B); distal pancreatectomy for benign lesion of pancreatic neck (9 pts, Group C), near-total pancreatectomy for chronic pancreatitis (1 pt).

Results: 5 out of 36 candidates did not receive transplantation for: inadequate islet mass (2 pts), patient instability (2 pts), high contamination of islet culture (1 pt). In 27 patients islet were infused into the portal vein, in 4 patients into the bone marrow. Median islet equivalents per kilogram (IE/Kg) was 2060 (534-4780). Complications occurred in six pts (19%): 2 bleeding, 1 sepsis, 3 portal thrombosis (1 complete, 2 partial). After a median follow up of 18 months, 24% of patients with total pancreatectomy (group A-B) are insulin-independent, 52% developed diabetes (non biliartedabetes); 24% had loss of graft function (C-peptide <0.3 ng/mL). This event was associated with poor islet mass (3/4 patients with <1500 IE/Kg had function loss). 9/10 patient with residual pancreas are insulin-independent.

Conclusions: AIT allowed insulin independency in 24% of patients with total pancreatectomy and 90% of patients with distal or near-total pancreatectomy. Islet mass (IE/Kg) could be a criterium to select patients for transplantation.

S22-3
ROLE OF ADIPOKINES AND ITS CORRELATION WITH ENDOCRINE PANCREATIC FUNCTION IN PATIENTS WITH PanCREATIC CANCER

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Introduction: Some authors suggest that adipokines contribute to the induction of pancreatic carcinogenesis but also to the development of endocrine insufficiency.

Aims: We evaluate the circulating concentrations of leptin, resistin and visfatin in patients with pancreatic cancer (PC) and relationship between the serum adipokines level and various clinicopathologic characteristics of PC. We also analyzed whether these adipokines are related to the development of diabetes in patients with PC.

Patients and Methods: The study group consisted of 45 individuals with PC (mean age 65.5±11.5 years) and 13 healthy individuals. Among PC patients 18 (40%) had recently diagnosed diabetes. Fasting plasma leptin, resistin, visfatin concentrations were determined by ELISA (R&D Systems, Phoenix Pharmaceuticals) and insulin by RIA (DakoCytomation).

Results: Patients with PC as compared with controls had significantly lower plasma leptin (44,58±21,03 versus 63,15±16,26 pg/mL; p<0.007) and visfatin (2,72±1,61 versus 3,77±1,19 pg/mL; p<0,04) levels. In contrast PC patients showed significant greater level of resistin (116,68±169,08 versus 18,9±7,23 ng/mL; p<0,04) than controls. Otherwise in PC patients mean fasting plasma insulin level was significantly lower than in controls (3,42±1,91 versus 10,23±7,94; p=0,0001). When PC patients with and without diabetes were considered separately, plasma leptin concentrations among nondiabetic patients were slightly higher (44,58±21,03) as compared with diabetic patients (34,53±20,73), but the difference was not statistically significant. Moreover there was no difference between visfatin and resistin level in PC with and without diabetes.

Conclusion: Individuals with newly diagnosed pancreatic cancer and diabetes present insulin deficiency and insulin resistance probably mainly due to high resistin level. There were significant differences in the fasting circulating adipokines concentration among patients with PC as compared with healthy controls. This probably suggests that adipokines may have clinical significance in PC pathogenesis and possibly endocrine pancreatic dysfunction.
Macroamylasemia is not a manifestation of chronic CP. This is a biochemical aberration, which occurs in 1% of healthy persons. However, macroamylasemia frequency increases in various inflammatory diseases, including pancreatitis. Macroamylasemia frequency in patients with different etiology of hyperamylasemia is more than 8% (J. E. Berk, 1995).

Aim: To determine the macroamylasemia frequency in CP.

Materials and methods: We examined 64 patients with CP and 30 healthy volunteers. Magnesium blood level was determined by Lachema (Czech Republic) kits with ABXk-02'-NPP-TM' (Russia) biochemical photometric kinetic analyzer in both patients with CP and healthy volunteers. Magnesium hair level was determined by atomic absorption spectrometry with THERMO ELECTRON (USA) analyzer.

Results: Magnesium blood level was similar in both — patients with CP and healthy volunteers. Magnesium level in patients with CP was 0.85±0.14 mol/l versus 0.82±0.11 mol/l in healthy volunteers (p<0.05). We obtained more information by determination of magnesium in hair. Its level was significantly decreased in patients with CP to 218.7±20.9 µg/g, while healthy volunteers had level of 293.5±29.6 µg/g (p<0.05).

After correlation analysis we revealed dependence between magnesium level in hair and clinical, laboratory and instrumental data in examined patients. It was revealed that magnesium deficiency, which occurs in patients with CP, results in aggravation of clinical manifestations of CP (negative correlation between magnesium level in hair with pain, dyspeptic and asthenic syndromes intensity). In addition, magnesium deficiency, probably, is a result of pancreatic exocrine insufficiency (positive correlation between magnesium levels in hair with results of fecal elastase test).

Conclusion: Patients with CP have magnesium deficiency, which influences severity of clinical manifestation and pancreatic deficiency.

Glutathione system in acute pancreatitis

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Introduction: Excessive production of inflammatory mediators and reactive oxygen species, failure of protective mechanisms are lead to progressive damage to cells and tissues, including pancreas. The purpose of this study was to

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P1

THE FREQUENCY OF MACROAMYLASEMIA IN CHRONIC PANCREATITIS (CP)

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SBO is one of the reasons for the lack of effectiveness of substitution enzyme therapy in chronic pancreatitis.

Aim: To identify features of SBO in relationship to pancreatic insufficiency in chronic pancreatitis.

Materials and methods: We examined 64 patients with chronic pancreatitis and 18 healthy persons. Samples of secretory chymus from initial part of jejunum were aspirated with the help of jejunal probe and bacteriological testing of these samples was conducted. Fecal elastase test was performed (Schebo, Germany).

Results: By results of fecal elastase test severe pancreatic insufficiency identified in 5 (7.8%), moderate — in 26 (40.6%), mild — in 33 (51.6%) patients. SBO was diagnosed in 45 (70.3%) patients. Number of microorganisms in 1 mL of jejunal content in healthy persons amounted 160.0±51.0 Colony Forming Units, while in chronic pancreatitis patients —169.8±103±33.5x103 Colony Forming Units (p<0.05). Number of bacterial species amounted 0.14±0.09 and 1.12±0.17 correspondingly (p<0.05). 29 (43.7%) patients had 1 bacterial species, 6 (9.4%) patients — 2 species, 11 (17.2%) patients — 3 bacterial species. Enterococcus was revealed in 16.3%, B. fecalis — in 3.5%, E. coli — in 39.8%, E. paracolica — in 3.6%, Staphylococcus — in 18.3% of cases. The correlation between Colony Forming Units and fecal elastase-1 was developed (r = +0.47).

Conclusion: SBO develops in 70.3% of patients suffering from chronic pancreatitis. The SBO severity depends on the pancreatic insufficiency severity.

P2

SYNDROME OF BACTERIAL OVERGROWTH (SBO) IN PATIENTS WITH CHRONIC PANCREATITIS WITH EXOCRINE PANCREATIC INSUFFICIENCY

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Materials and methods: A total of 186 patients with CP was included into the study. Diagnosis of macroamylasemia was performed according to the three-stage algorithm J. E. Berk (1995). In the first stage blood lipase activity and the ratio of amylase and creatinine clearances were determined, in the second - precipitation with polyethyleneglycol was performed, and chromatography - in the third. A total of 85 healthy persons were included in the study.

Results: Macroamylasemia was diagnosed in 20 (10.75%) patients with CP and in 1 (1.8%) healthy. At the first stage of diagnosis macroamylasemia was identified in 14 (70.0%) patients, in 5 (25.0%) patients - on the second stage. And only 1 (5.0%) patient necessitated all three stages of diagnosis for confirmation of macroamylasemia. Hyperamylasemia occurred in 15 (75.0%) patients with macroamylasemia, and in 5 (25.0%) patients — blood amylase was normal. Only 4 (20.0%) patients with macroamylasemia had clinical symptoms of CP exacerbation, the remaining 16 (80.0%) patients with CP experienced a remission.

Conclusion: It is necessary to consider the possibility of macroamylasemia in CP (10.75%) in cases of stable hyperamylasemia and the absence of clinical signs of exacerbation of the background disease.
Poster Sessions

P6
SONOGRAPHIC EXAMINATION OF HAEMODYNAMICS IN ODD VISCERAL VESSELS IN PATIENTS WITH PANCREATITIS


Introduction: One of the reasons of pancreatitis is blood flow disorders in odd visceral vessels of a.mesenterica sup., truncus celiacus, a.lienalis, v.portae, v.lienalis.

Purpose of research: To find out influence of various factors on haemodynamics in patients with acute and chronic pancreatitis.

Materials and methods: Doppler examinations of patients with chronic pancreatitis were analysed. 258 patients in 1-st group with average age 53,0±2,4 years. 156 patients with acute pancreatitis, - 2-nd group, average age 55,8±3,5 years. Control group includes 25 patients 30-45 years old with healthy pancreas.

Results: In 58 patients (37,1%) with oedematous form of acute pancreatitis increased vascularization was found. Statistically valid increasing of blood flow in truncus celiacus, a mesenterica sup., a.lienalis was found: +85,3±7,55 systolic and +101,3±5,7 systolic. In patients with destructive form of acute pancreatitis amplification of parenchymatic vessels vascular pattern was found in 35.3% of cases with signs of arteriovenous bypass. PI decreased up to 60,2±5,6%, RI - 27,8 ±3,5%. Lowering of systolic blood flow on 47,8±8,5%, PI on 56,4 ±5,5%, RI on 32,1±3,1%. were found in a.lienalis. Special attention was paid to the junction of vv. lienalis and porta. When acute pancreatitis located in pancreas head, extravasal compression of a mesenterica sup. was found in 23,5%, v.porta in 16,7% of cases. When located in tail of pancreas, compression of v.lienalis was found in 24,5% of cases.

Conclusion: Pancreatitis aggravation causes diffuse blood flow increase in odd visceral blood vessels. In patients with destructive forms of acute pancreatitis deterioration of peripheral blood flow resistance occurred.

P7
CHRONIC PANCREATITIS IN COMBINATION WITH CORONARY HEART DISEASE: HOW SUFFERS LEFT VENTRICLE CONTRACTILE FUNCTION?

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The purpose - to study the structural and functional parameters of the left ventricle (LV) in patients with chronic pancreatitis (CP) in combination with coronary artery disease (CAD).

Materials and Methods: The study included 15 patients (9 men and 6 women), mean age 48,3 ± 3,2 years. Myocardial contractility was assessed by ejection fraction (EF) and the degree of shortening of the anterior-posterior size of the left ventricle in systole (Δ S, %). Dysfunction of the left ventricle (LV DF) was investigated by studying transmural flow. Recorded a maximum flow velocity of early diastolic filling (E), the maximum flow velocity of atrial systole during (A), deceleration time (DT) of early diastolic filling flow left ventricular, isovolumic relaxation time (IVRT), ratio E/A.
**Poster Sessions**

We calculated the relative thickness of the left ventricle walls (LV UTS), myocardial mass index (LV MMI).

**Results:** All surveyed EF was 55.8±2.3%, systolic SAPS LV size was 31.9±0.6%. 9 people have increased LV UTS and 6 - increased LV UTS and IMM LV. A correlation between the IMM and LV IVRT (r=0.45; p=0.034) was found, and E/A ratio (r=0.51; p=0.04), indicating increased rigidity of the myocardium and diastolic dysfunction LV myocardium according to the type of abnormal relaxation.

**Conclusion:** In patients with CP in combination with CAD in middle age, there are signs of diastolic dysfunction of the pancreas, which indicate a violation of the relaxation of the myocardium with preserved LV function, which is necessary to consider the appointment of therapy.

**P8**

**SERUM PROINFLAMMATORY CYTOKINE LEVELS AND WHITE BLOOD CELL (WBC) DIFFERENTIAL COUNT IN PATIENTS WITH DIFFERENT DEGREES OF SEVERITY OF ACUTE ALCOHOLIC PANCREATITIS (AAP).**

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**Introduction:** Several studies suggest that cytokines and neutrophils play an important role in the pathogenesis of acute pancreatitis (AP).

The aim of the study was to assess the systemic release of proinflammatory cytokines and WBC count with differential in patients with AAP and to characterize the differences between patients with mild and severe forms of the disease.

**Patients and methods:** Thirty-five patients with the mild form of AAP (MAAP) were compared to 11 with severe AAP (SAAP). Serum levels of IL-6, IL-8, IL-12p40 and WBC differential count were measured every other day during the first week after admission.

**Results:** During the course of the study, the average level of IL-6 was significantly (p<0.05) higher in SAAP than in MAAP. Serum levels of IL-8 and IL-12p40 on admission were higher in SAAP than with MAAP but the difference was not statistically significant. Of all the types of WBCs, only neutrophils were significantly (p<0.05) elevated the entire time in SAAP patients when compared to MAAP.

**Conclusion:** Patients with SAAP had significantly higher IL-6 levels and neutrophil counts than patients with MAAP.

The results suggest that proliferation and overstimulation of this subset of leukocytes might contribute to the development of the systemic inflammatory response in patients with SAAP.

**P9**

**HYPERGLYCEMIA-INDUCED S100A8 AND S100A9 EXPRESSION TARGET AKT, MTOR AND NF-KB SIGNALLING IN PANCREATIC CANCER CELLS.**

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**Introduction:** S100A8/S100A9 inflammatory proteins are suggested to be involved in pancreatic cancer (PaCa) progression and in cancer-associated diabetes mellitus (DM).

**Aims:** to analyze S100A8/S100A9 expression levels in PBMC of patients with PaCa, chronic pancreatitis (ChrPa) or pancreatobiliary tract tumors (PBT) and ascertain whether they differently affect Akt, mTOR and NF-kB signalling in PaCa cells with different aggressiveness.

**Methods:** S100A8 and S100A9 mRNA was quantified by RT-PCR in 55 PaCa, 12 ChrPa, 15 PBT. S100A8, S100A9 and S100A9/A9 effects on Akt (Ser473, Thr308), mTOR (Ser2448) and NF-kB (p-ikB-a) were WB analyzed using BxPC3, Capan1 and MiaPaCa2.

**Results:** S100A8 and S100A9 mRNA did not vary between groups (F=0.65, p:ns and F=2.75, p:ns), but correlated with plasma glucose (r=0.22, p=0.05; r=0.46, p<0.0001), Hba1c (r=0.11, p:ns; r=0.37, p=0.002) and insulin (0.37, p=0.008; r=0.46, p=0.001). In BxPC3 Akt was Thr308 phosphorylated by S100A8/A9, while in Capan1 and MiaPaCa2 S100A8/A9, S100A8 and S100A9 phosphorylated both Akt sites. In BxPC3 mTOR was phosphorylated (Ser2448) by S100A8. In Capan1 and MiaPaCa2 S100A8, S100A9 and S100A9/A9 caused significant Ser2448 phosphorylation. S6RP, downstream effecter of mTORC1, was phosphorylated (Ser235/236) only in S100A8 treated MiaPaCa2. A strong NF-kB activation was induced by S100A8 in BxPC3, by S100A9 and S100A8/A9 in Capan1; NF-kB was inhibited by both molecules in MiaPaCa2.

**Conclusions:** In PaCa-associated DM high expression levels of these proteins might favour cancer cell growth by inducing Akt, mTOR and NF-kB. In the less invasive BxPC3 cells S100A8 activates NF-kB. In more aggressive Capan1 and MiaPaCa2 cells S100A8, S100A9 and S100A8/A9 activate mainly Akt and mTORC1, not NF-kB pathways.

**P10**

**THE INFLAMMATORY CALCIUM BINDING PROTEIN S100A8 AND ITS N-TERMINAL PROTEOLYTIC FRAGMENT INTERACT WITH TRANSFORMING GROWTH FACTOR-BETA1 (TGF-B1) AND ALTER AKT, MTOR AND NF-KB CANCER CELL SIGNALLING.**

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**Introduction:** in pancreatic cancer S100A8 is highly expressed by stromal cells when SMAD4 is not mutated or by cancer cells when SMAD4 is mutated, suggesting a link between TGF-b1 and S100A8 pathways. The proteolytic fragment of S100A8, NT-S100A8, highly abundant in pancreatic cancer, is involved in altering insulin secretion and action.

**Aim:** to ascertain whether S100A8 and NT-S100A8 interacts with TGF-b1 in altering intracellular calcium, NF-kB, Akt and mTOR signalling.

**Methods:** BxPC3 cells were stimulated with S100A8 (10nM), NT-S100A8 (50nM) alone or combined with TGF-b1 (0.02ng/mL). Intracellular calcium was monitored by Fluo4 (epifluorescence). Akt (Ser473, Thr308), mTOR (Ser2448), NF-kB (p-ikB-a) were WB analyzed.

**Results:** NT-S100A8 evoked a train of intracellular calcium fluxes after 150 seconds lag time, which was reduced to few
RESULTS: In 22/81 (27.2%) PCa and in 2/32 (6.2%) GC Apo-A1 values were found to be part of clusterin, human apolipoprotein A1 (Apo-A1), while values in this order of magnitude were never found in the other groups (100% specificity). Apo-A1, C3 and CA 19-9 were correlated with PCa diagnosis at univariate analysis: in 172/187 sera and in an additional series of 69 new samples yielding 30 controls, 81 PCa, 37 chronic pancreatitis (ChrPa), 24 DM, 29 gastric cancer (GC), 24 chronic gastritis (CG).

Aim: to validate new serum biomarkers identified by MALDI-TOF/MS analysis as emerging serum biomarkers for PCa diagnosis.

Patients and methods: MALDI-TOF/MS analysis was performed in sera from 22 controls, 51 PCa, 37 chronic pancreatitis (ChrpA), 24 DM, 29 gastric cancer (GC), 24 chronic gastritis (CG).

Results: 11/160 selected features (m/z range 1200-5000) were highly correlated with pancreatic diseases (univariate and binary recursive partitioning tree analyses). By MALDI-TOF/TOF analysis three features (1530, 1550, 1778 m/z) were found to be part of clusterin, human apolipoprotein A1 (Apo-A1), human complement C3. Apo-A1 and C3 were measured in 172/187 sera and in an additional series of 69 new samples yielding 30 controls, 81 PCa, 26 ChrPa, 51 DM, 32 GC, 21 CG. Apo-A1 was reduced in PCa and in GC (F=10.49, p<0.0001). In 22/81 (27.2%) PCa and in 2/32 (6.2%) GC Apo-A1 values were below 0.6 g/L, while values in this order of magnitude were never found in the other groups (100% specificity). Apo-A1, C3 and CA 19-9 were correlated with PCa diagnosis at univariate logistic regression analysis; at multivariate logistic regression only Apo-A1 (OR=0.38, 95% CI=0.17-0.86, p=0.020) and C3 (OR=4.75, 95% CI=2.33-9.67, p<0.001) were confirmed to be strictly correlated with PCa.

Conclusion: reduced serum levels of the anti-inflammatory and antioxidant protein Apo-A1, major protein in HDL, and increased serum levels of the inflammatory mediator C3 are potential biomarkers for PCa.

**P12**

**SENESCENCE LIMITS THE PROFIBROGENIC ACTIVITY OF RAT PANCREATIC STELLATE CELLS**

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Introduction: Pancreatic stellate cells (PSC) play a key role in the development of fibrosis associated with chronic pancreatitis (CP). While PSC activation has been extensively studied, the mechanisms to terminate pancreatic wound healing are largely unknown.

Objectives: We aimed to test the hypothesis that PSC senescence limits fibrogenesis and completes tissue repair, and were interested in mechanisms of PSC ageing.

Methods: Susceptibility of PSC to undergo senescence was analyzed by long-term culture and exposure to triggers, using senescence-associated β galactosidase (SA-β-Gal) as surrogate marker. The role of intracellular mediators in PSC senescence was studied employing pharmacological inhibitors and a siRNA approach. The model of dibutylin dichloride-induced CP in rats was used to investigate senescence in vivo.

Results: Long-term culture and exposure of PSC to stressors (doxorubicin, H2O2) diminished growth and induced senescence. Senescent PSC highly expressed CDKN1A/p21, mdm2 and interleukin 6, but displayed low levels of α-smooth muscle actin (α-SMA) mRNA. Inhibition of p38 MAP kinase and Jun kinase was associated with reduced proliferation and increased expression of SA-β-Gal. Downregulation of CDKN1A/p21 expression inhibited doxorubicin-induced senescence. In CP tissue, areas staining positive for SA-β-Gal overlapped with fibrotic regions and dense infiltrates of immune cells. The number of senescent cells was linked to the severity of inflammation and followed its time course.

Conclusion: Senescent PSC are present in the fibrotic pancreas. Like quiescent PSC, they do not proliferate and express less α-SMA than fully activated PSC. PSC senescence represents an integral component of pancreatic wound healing and may contribute to its termination.

**P13**

**GROWTH FACTORS AND MMPs IN THE PANCREATIC CANCER MICROENVIRONMENT**

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Background: Pancreatic cancer remains the most aggressive malignancy of all human cancers. Patients have an extremely poor prognosis, with less than 5% surviving for 5 years and a median survival period of 6 months. Pancreatic cancer is characterized by infiltrating tubular units embedded in desmoplastic stroma, which is rich in immune cells, endothelial cells and fibroblasts. This heterogeneous microenvironment provides excellent conditions for tumor development. The question arises which factors may be responsible for cancer cell detachment and metastasis formation.

Aim: To evaluate enzymatic activity and expression of growth factors in pancreatic cancer tissue.

**44th European Pancreatic Club (EPC) Meeting**
**P14**

**ANTIPROTEASE STRATEGY IN COMBINATION WITH GEMCITABINE AS A PUTATIVE NOVEL THERAPEUTIC APPROACH FOR PANCREATIC CANCER TREATMENT.**

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**Introduction:** Gabexate mesylate (GM), a protease inhibitor, has been shown to exert a significant antitumoral activity in pancreatic cancer (PC) cells.

**Aim:** To evaluate whether pre-treatment with GM could improve PC cells response toward gemcitabine (GEM).

**Methods:** Studies have been performed on PANC-1, SW1990 PC cells and EA.hy926 endothelial cells. Treatment consisted in pancreatic cancer (PC) cells. GM significantly enhanced GEM anti-invasive and anti-angiogenic efficacy by inhibition of GEM-induced signalling (Western Blotting), VEGF and IL-8 levels (endothelial tube formation assay), NF-kB activation (NF-kB chemoinvasion and chemotaxis assay), angiogenesis assay), cell invasiveness and migration (Boyden chambers in culture medium. Aspects studied included: cell viability (MTT assay), cell invasiveness and migration (Boyden chambers chemoinvasion and chemotaxis assay), angiogenesis (endothelial tube formation assay), NF-kB activation (NF-kB luciferase assay, Western Blotting), VEGF and IL-8 levels (ELISA), MMP-2 and MMP-9 activity (gelatin zymography), Ras signalling (Western Blotting).

**Results:** Post-thaw recovery of cells was approximately 55%. The recovered cells were of excellent quality their viability being over 95%. Cellular amylase content was similar before and after cryopreservation. The cells maintained their ability to secrete amylase and to respond to secretory stimuli after thawing. Cryopreserved cells were able to form amylase-expressing glandular structures in three dimensional cultures in Matrigel.

**Conclusion:** Functional properties of mouse primary pancreatic acinar cells obtained by explant outgrowth method are largely maintained during cryopreservation and thawing. [1] Eur J Cell Biol 90:1052-60, 2011

**P15**

**CRYOPRESERVATION OF MOUSE PANCREATIC ACINAR CELLS OBTAINED BY EXPLANT OUTGROWTH CULTURE METHOD FOR LONG-TERM IN VITRO PURPOSES: POST-THAW MAINTENANCE OF FUNCTIONAL CHARACTERISTICS**

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**Objectives:** We recently described a culture method for obtaining functionally competent mouse pancreatic acinar cells for long-term in vitro purposes [1]. Cryopreservation of acinar cells with long-term culturing capacity would improve standardization of experiments by enabling the use of the same cell preparation at different times and by different laboratories. Our aim was to investigate the effect of cryopreservation on the viability and function of mouse primary pancreatic acinar cells.

**Materials and Methods:** Acinar cells were prepared by the explant outgrowth method [1]. Each batch was divided into two aliquots and cell viability was determined. One aliquot of each batch was processed for cryopreservation with 10% DMSO as cryoprotectant and cells of the remaining aliquot were placed in culture. The following characteristics were compared in cryopreserved-thawed and non-cryopreserved cell preparations: cell recovery, viability, amylase content in 10 000 viable cells before culture, basal and stimulated amylase release in culture and the ability of the cells to form glandular structures in Matrigel.

**Results:** Post-thaw recovery of cells was approximately 55%. The recovered cells were of excellent quality their viability being over 95%. Cellular amylase content was similar before and after cryopreservation. The cells maintained their ability to secrete amylase and to respond to secretory stimuli after thawing. Cryopreserved cells were able to form amylase-expressing glandular structures in three dimensional cultures in Matrigel.

**Conclusions:** Functional properties of mouse primary pancreatic acinar cells obtained by explant outgrowth method are largely maintained during cryopreservation and thawing. [1] Eur J Cell Biol 90:1052-60, 2011
Objectives: The use of chemotherapy to treat pancreatic cancer is limited by the development of cancer cell resistance. ATP-Binding Cassette (ABC) transporters play a crucial role in the development of resistance by the efflux of anticancer agents outside of cancer cells. On the other hand, ABC transporters play physiological roles whose importance for cancer progression is virtually unknown. We evaluated the differences in the expression levels of all 49 human ABC transporters between the tumor and non-neoplastic tissues of pancreatic adenocarcinoma patients.

Methods: Tissue specimens were obtained from 30 histologically verified pancreatic adenocarcinoma patients. The transcript profile of ABCs was assessed using real-time PCR with a relative standard curve.

Results: The observed significant upregulation of ABCB2, ABCB3, ABCB4, ABCC1, ABCC3, ABCC5, ABCG2 (p<0.005) in tumors compared with non-neoplastic controls is in line with their already established multi-drug resistance phenotype. Downregulation of ABCA3, ABCA5, ABCA8, ABCC6, ABCC7, ABCC8 and ABCC9 in pancreatic adenocarcinoma was not reported so far and may have rather physiological consequences.

Conclusion: In conclusion, our pilot study brings a new and interesting data. Transcript levels of all known human ABC transporter genes were assessed in a series of tumor and control tissue samples from well-characterized homogeneous group of patients with pancreatic adenocarcinoma. The observed upregulation of genes associated with MDR phenotype seems the most interesting for the subsequent validation studies including comparison of transcript levels with the therapy outcome.

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P17

AUTOPHAGY IN PANCREATIC CANCER CELLS (PANC-1) TREATED WITH ANTICANCER DRUGS AND INHIBITORS OF AUTOPHAGY

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Objectives: Autophagy is a regulated process of degradation and recycling of cellular constituents, participating also in cell-death mechanisms. Previous studies have shown controversy about the effect of autophagy in pancreatic cancer cell lines both with and without anticancer treatment. The aim of this study is to investigate the role of autophagy in pancreatic cancer cells, and to provide insights into new strategies for treating pancreas cancer.

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

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

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

P18

ALCOHOLIC CHRONIC PANCREATITIS AND LIVER CIRRHOSIS: DIFFERENCES IN LIFESTYLE AND RARE COINCIDENCE

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Introduction: Alcoholic chronic pancreatitis (ACP) and liver cirrhosis (ALC) are sequels of excessive alcohol intake. They develop in a minority of long-term alcohol consumers. The organ selection of alcohol-induced damage remains unknown. The aim of study was to compare patients with ACP and ALC with respect to their lifestyle.

Methods: Sixty-six patients with ACP and 80 with ALC were personally interviewed about lifestyle, drinking and eating habits.

Results: The groups of ACP (60 males, 6 females) and ALC (64 males, 16 females) did not differ in the amount of alcohol intake (58g/day vs. 64g/d). Significantly more patients with ACP reported first alcohol intake before the age of 15 (p=0.03). The ACP patients were more likely to consume most alcohol between 20 to 30 years of age (43.6% vs. 20.3%, p<0,01), were more likely to smoke (92.4% vs. 78.7%, p=0,02) and were more likely to start smoking before the age of 15 (16.7% vs. 3.7%, p=0,04). Patients with ACP had a lower level of education (p<0,01). We did not observe significant differences in dietary habits between the groups. The incidence of cirrhosis in patients with ACP was 16.7%. The incidence of pancreatitis in the ACL group was 2.5%.

Conclusion: Sociobehavioral factors influencing development of liver and pancreas impairments differed in our patients. The development of ACP was associated with an early onset of drinking and smoking, a young age of highest alcohol intake and lower education. Simultaneous occurrence of ACP and ALP was rare.

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INCREASE OF INTRAABDOMINAL PRESSURE WORSENS PROGRESS OF ACUTE PANCREATITIS

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Introduction: Most cases of acute pancreatitis (AP) are mild, but in up to 25% of patients the condition is graded as severe, especially in case of presence of pancreatic infection. Disorders of gut barrier function has been demonstrated to play major role in it occurrence and increased intraabdominal pressure (IP) is supposed to be one of the important aggravating factor.

Aim/Objectives: To investigate the influence of elevated IP on progress of AP, blood supply and barrier function of small intestine.

Methods: AP was induced in 90 Wistar rats by intraperitoneal injection of 250 mg/100 g of L-arginine solution. IP has been measured after initiation of AP (1-st group) or elevated to the level of 15 mm Hg (2-nd group), 20 mm Hg (3-rd group) and 25 mm Hg (4-th group) during 3 hours. Changes of level of lactic acid, malonedialdehyde and diene conjugates were measured after initiation of AP (1-st group) or elevated to the level of 15 mm Hg (2-nd group), 20 mm Hg (3-rd group) and 25 mm Hg (4-th group) during 3 hours. Changes of level of elevation of IP to the level of 20 – 25 mm Hg pancreonecrosis appeared at 73,4% of experimental animals, translocation of E. coli and other Enterobacteria sp. occurred to mesenteric lymph nodes and pancreas.

Results: Increase of IP to the level of 15 mm Hg was followed with ischemia of mucosal layer of small bowel. In case of elevation of IP to the level of 20 – 25 mm Hg pancreatic necrosis appeared at 73,4% of experimental animals, translocation of E. coli and other Enterobacteria sp. occurred to mesenteric lymph nodes and pancreas.

Conclusion: Increased intraabdominal pressure has harmful effects on progression of acute pancreatitis in rats due to disorders of intestinal wall metabolism and enhancing of bacterial translocation to pancreatic tissue.

P20

EFFECT OF L-LYSINE AESCINATE ON STRUCTURE AND PERMEABILITY OF INTESTINAL BARRIER DURING ACUTE PANCREATITIS

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Introduction: Gastrointestinal tract barrier disruption is involved in the development of systemic septic complications of acute pancreatitis (AP). Still there is no effective treatment of such unfavorable event of pathogenesis of AP.

Aim/Objectives: To investigate the effect of lysosomal ferments inhibitor L-lysine aescinate on structure of small intestinal barrier (glycoproteins and proteoglycans of mucus and extracellular matrix) and permeability during AP.

Methods: AP was induced in 90 Wistar rats by intraperitoneal injection of 250 mg/100 g of L-arginine solution twice during 1 hour. L-lysine aescinate has been infused intraperitoneal 0,015 mg/100 g twice per day in 1 group or normal saline - in 2 group. Changes of level of hydroxyproline, hexosamine, fucose, sialic and hexuronic acids were investigated in small intestinal mucus and mucosal layer and in serum during 6-48 h after induction of AP. Intestinal permeability was evaluated by lactulose/mannitol ratio.

Results: In animal of 2 group induction of AP was followed by disorders of structure of intestinal barrier: concentration of free hydroxyproline, hexosamine, fucose, sialic and hexuronic acids increased on 33,6-56,8% (p<0,05) during 6-48 h both in small intestine and blood which was followed with elevation of lactulose/mannitol ratio on 3,5-5,2 times. L-lysine aescinate infusion significantly decreased concentration of free connective tissue markers and normalized intestinal permeability in 2 group rats.

Conclusion: Infusion of L-lysine aescinate to rats with AP defends small intestinal mucosal glycoproteins and proteoglycans from lysosomal ferments activity and normalizes intestinal permeability.

P21

PANCREATITIS ASSOCIATED CHYMOTRYSIN C (CTRC) MUTATIONS SHOW DISTINCT LOSS-OF-FUNCTION PHENOTYPES

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Background and Aim: The digestive enzyme chymotrypsin C (CTRC) protects against pancreatitis by promoting degradation of potentially harmful trypsinogen and trypsin. Loss-of-function mutations in CTRC increase the risk for chronic pancreatitis. In addition, CTRC mutations may elicit endoplasmatic reticulum (ER) stress due to mutation-induced misfolding. The aim of the present study was to perform a comprehensive functional analysis of all known CTRC missense mutants and identify phenotypic changes associated with chronic pancreatitis.

Methods: We investigated secretion of 24 published and 8 novel CTRC missense mutants in transiently transfected HEK 293T cells. Peculiar mutations were purified for investigation of enzyme kinetics and degradation by trypsin. We assessed the effect of 5 mutants on ER stress in AR42J cells transfected with recombinant adenovirus.

Results: Seventeen of 32 mutants exhibited essentially normal secretion and activity, whereas 15 mutants showed one or more functional deficiencies: 7 mutants were secreted poorly, 9 mutants showed diminished catalytic activity and 5 mutants were subject to degradation by trypsin. Mutants with considerable secretion defect caused ER stress.

Conclusion: Fifteen of 32 known CTRC variants exhibit some form of functional impairment and therefore are likely to be pathogenic. We identified three distinct but mutually non-exclusive loss of function mechanisms: secretion defect, catalytic defect and degradation by trypsin. ER stress is associated with a secretion defect but not with other loss-of-function phenotypes. This phenotypic dataset should aid in the classification of the clinical relevance of CTRC mutations identified in patients with chronic pancreatitis.
P22

NOTCH INHIBITION BY γ-SECRETASE INHIBITOR IX ATTENUATES EPITHELIAL MESENCHYMAL TRANSITION AND INHIBITS PANCREATIC TUMOR INITIATING CD44+/EPCAM+ CELLS

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Introduction: Pancreatic ductal adenocarcinoma (PDAC) is an aggressive disease with a high rate of metastasis. Early diagnosis is rare and treatment options are limited. The Notch pathway has recently emerged as a candidate drug target. Notch signalling is important in PDAC initiation and maintenance. This provides a rationale for further analysis of Notch signalling in PDAC carcinogenesis.

Aims: Based on the known roles of Notch in development and stem cell biology, we investigated the effects of GSI IX on epithelial mesenchymal transition (EMT) and on pancreatic tumor initiating CD44+/EPCAM+ cells.

Methods: We analyzed the effect of the GSI IX on growth and epithelial plasticity of human pancreatic cancer cell lines, and on the tumorigenicity of pancreatic tumor initiating CD44+/EPCAM+ cells. In addition, sorted CD44+/EPCAM+ cells were subcutaneously injected into the nude mice (NMRI-nu/nu) and treated with vehicle or with GSI IX. The effect of GSI on Xenograft tumors, EMT markers, and cell proliferation was evaluated.

Results: GSI IX inhibited pancreatic cancer cell proliferation, migration and invasion in a dose-dependent manner. Apoptosis was induced after GSI IX treatment and EMT markers reversed partially. GSI IX significantly inhibited the growth of pancreatic tumor initiating CD44+/EPCAM+ cells in vitro and in a xenograft mouse model.

Conclusion: Our data support the central role of Notch signalling pathway in pancreatic cancer pathogenesis and identifies an effective approach to inhibit EMT and suppress tumorigenesis by eliminating pancreatic tumor initiating CD44+/EPCAM+ cells.

Keywords: Cancer Stem Cells; EMT; GSI; Pancreatic cancer

P23

THERAPEUTIC EFFECT OF OBESTATIN IN ISCHEMIA/REPERFUSION-INDUCED ACUTE PANCREATITIS

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Introduction: Pretreatment with obestatin inhibits the development of edematous acute experimental pancreatitis, as well as obestatin promotes survival of pancreatic islets and administration of this peptide exhibits therapeutic effect in the course of mild acute pancreatitis evoked by cerulein.

Objectives: Aim of the study was to determine the influence of treatment with obestatin on the course of severe necrotizing pancreatitis.

Methods: Acute pancreatitis was induced in rats by severe pancreatic ischemia followed by reperfusion. Obestatin was administered twice a day at the dose of 8 nmol/kg/dose, starting 24 h after the beginning of reperfusion. Rats were sacrificed 2, 5, 9, or 14 days after the start of reperfusion.

Results: Administration of obestatin after the development of acute ischemia/reperfusion-induced pancreatitis has accelerated normalization of pancreatic histology in this disease. It was manifested as a faster reduction of pancreatic necrosis, edema and hemorrhages. This effect has been accompanied with an improvement of pancreatic blood flow and partial reversion of the pancreatitis-evoked increase in serum activity of lipase. Moreover administration of obestatin has reduced local and systemic inflammation, what was found as a decrease in inflammatory infiltration of pancreatic tissue, reduction of myeloperoxidase activity in the pancreas, as well as a decrease in serum concentration of pro-inflammatory interleukin 1β.

Conclusions: Obestatin exhibits therapeutic effect in severe necrotizing acute pancreatitis evoked by ischemia followed by reperfusion. This observation suggests that therapeutic effect of obestatin in the course of acute pancreatitis has an anti-inflammatory nature and is independent to the primary cause of this disease.

P24

ACENOCOUMAROL INCREASES THE SEVERITY OF CERULEIN-INDUCED ACUTE PANCREATITIS IN RATS

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Introduction: Inflammation and coagulation are closely linked processes. Inflammatory cytokines activate coagulation and coagulation stimulates development of inflammation. Previous studies have shown that pretreatment with heparin inhibits the development of acute pancreatitis, as well as treatment with heparin exhibits therapeutic effect in the course of this disease.

Objectives: Aim of the present study was to determine the influence of treatment with acenocoumarol, a vitamin K antagonist, on the development of acute pancreatitis.

Material & methods: Acute pancreatitis was induced by cerulein given i.p. Acenocoumarol at the dose of 1, 2 or 5 mg/kg/dose or vehicle were administered once a day for 7 days before induction of acute pancreatitis. Severity of acute pancreatitis was examined immediately after the last injection of cerulein.

Results: Treatment with acenocoumarol alone increased serum level of pancreatic digestive enzymes. D-dimer concentration and increased aPTT. Administration of cerulein led to induction of acute edematous pancreatitis in all rats. Pretreatment with acenocoumarol increased the severity of cerulein-induced acute pancreatitis. It was manifested as an additional increase in serum amylase and lipase levels, and D-dimer concentration. These results were accompanied by reduction in pancreatic DNA synthesis, an index of pancreatic cell proliferation. Morphological examination showed that pretreatment with acenocoumarol increased histological signs of acute pancreatitis such as pancreatic edema, leukocyte infiltration and vacuolization of acinar cells.

Conclusions: Administration of acenocoumarol increases the severity of acute pancreatitis.
P25

THE EFFECTS OF KYNURENINE ON PANCREATIC AMYLASE SECRETION IN THE RATS

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Introduction: Tryptophan, an essential amino acid can be metabolized through different pathways, a major route being the kynurenine pathway. Kynurenines are involved in physiological functions such as behavior, sleep, thermoregulation, also in mechanisms associated with several inflammatory processes in organisms. Tryptophan as well as its derived substances (melatonin or serotonin) have been involved in the regulation of pancreatic exocrine function but the role of kynurenines on pancreatic enzyme secretion has not been investigated yet.

Aim: To assess the effects of L-kynurenine, on pancreatic enzyme secretion in the rat. Material and methods: The study was performed on Wistar rats weighing 350 g. Under pentobarbital anesthesia the animals were surgically equipped with silicone catheters, one of them was inserted into pancreatico-biliary duct, the other one - into duodenum. The experiment started 2 hours after surgery. L-kynurenine at doses of 50 or 250 mg/kg was given as intraduodenal bolus after stabilization of amylase basal secretion. The samples of pancreatic-biliary juice were collected in 15 minutes aliquots to measure the enzyme output. The blood specimens were taken for determination of CCK employing ELISA.

Results: Intraduodenal administration of L-kynurenine in dose of 50 mg/kg i.d. resulted in augmentation of pancreatic amylase secretion about 50%. The higher dose of tryptophan metabolite when applied directly into duodenal lumen manifested also in the significant increase of amylase output, reaching the level of 823 IU/15 min. These changes were accompanied by increase of CCK plasma levels.

Conclusion: Kynuramines, the metabolite of tryptophan are able to stimulate the exocrine pancreatic secretion.

P26

INTRACELLULAR CALCIUM LEVELS AND ENZYME SECRETION IN RESPONSE TO TOBACCO VS ETHANOL IN PANCREATIC ACINAR CELLS.

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Alterations in intracellular calcium levels and enzyme secretion in acinar cells are involved in the pathophysiology of chronic pancreatitis (CP). It has been previously shown that alcohol induces an increase of intracellular calcium, but its effect in enzyme secretion is controversial. The effect of tobacco in this context is unknown.

Hypothesis: Tobacco, similarly to alcohol, promotes the development of CP by altering intracellular calcium levels and enzyme secretion in acinar cells.
CAERULEIN MODULATES THE GHERLIN SYSTEM IN THE PANCREATIC ACINI

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**Introduction:** Ghrelin, an endogenous ligand for the growth hormone (GH) secretagogue receptor (GHS-R) was originally isolated from the stomach and identified in the pancreas. Ghrelin protects the pancreas from the damage caused by caerulein-induced pancreatitis, but the implication of GHS-R and its endogenous ligand in the pancreatic protection is unclear.

**Aim:** To determine the effect of ghrelin and caerulein on mRNA and protein levels of GHS-R1a subtype and of acylated ghrelin in isolated pancreatic acini.

**Material & Methods:** Wistar rats were injected with ghrelin (12.5; 25.0 or 50.0 μg/kg i.p.) or with physiological saline. 48h later pancreatic acini were isolated and subjected to caerulein stimulation (10–12, 10–10 or 10–8M) for: 0 h, 20’, 1, 3 or 5h at 370C. The most effective time of incubation was 3h. High doses of ghrelin and caerulein were selected for further experiments. RT-PCR and Western blot methods were used to determine mRNA and protein levels.

**Results:** GHS-R1a and acylated ghrelin were identified in the pancreatic acini isolated from control rats. Pretreatment of the rats with ghrelin resulted in the significant and dose-dependent upregulation of both investigated parameters. On the contrary, application of caerulein to the acini significantly downregulated GHS-R1a, but failed to affect the signal for ghrelin. Pretreatment of the rats with ghrelin prevented from caerulein-induced downregulation of GHS-R1a.

**Conclusions:** Caerulein is able to modify the GHS-R1a subtype in the pancreatic acini. This effect could be prevented by pretreatment with ghrelin and perhaps might be implicated in the mechanism of pancreatic damage induced by caerulein overstimulation.

CHANGES OF HEMORHEOLOGICAL LABORATORY PARAMETERS AND COURSE OF MEDICATION IN EXPERIMENTAL ACUTE Pancreatitis.

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**Introduction:** The role of microcirculatory disturbance in severe acute pancreatitis is generally accepted.

**Objectives:** Effectiveness of Pentoxiphyllin, Enoxaparine and Flunixin was analysed in experimental cerulein pancreatitis.

**Methods:** Fifty female Sprague-Dawley rats divided into 5 groups (n=10). In general anaesthesia 2 hours after acute pancreatitis was induced tissue microcirculation was examined, cupping, was performed in all group. Controll group (C): no pancreatitis. Acute pancreatitis group (AP): 10 µg/kg cerulien was injected s.c. AP+Flunixin group (AP+Fl): 2.5 mg/kg Flunixin was also administered. AP+Pentoxifyllin group (AP+Pe): 50 mg/kg Pentoxifyllin i.p. was also administered. AP+Clexan group (AP+C): 2 mg/kg Exonaparine s.c. was also administered. Tissue blood exitus flow unit (BFU), rectal temperature, blood acidity and hemorheological parameters were measured.

**Results:** The rectal temperature was significantly elevated in AP, it was moderate in AP+Fl and AP+E and high in AP+Pe. The decrease of BFU was lower in AP+Pe and AP+Fl. The blood pH level decrease was moderate in all treated groups. The elevation of hematocrit level was was moderate in AP+Fl. The maximal elongation index values decrease in AP+Fl was not noticed. The osmoscan confirmed the best result also in AP+Fl. The M and M1 indices were elevated in all AP, it was moderate in AP+Fl and significant in AP+Pe. The changes of the RBC aggregation parameters were resemble.

**Conclusion:** The measured drugs had good effects on microcirculation, pH levels and microrheologic parameters in cerulein induced acute pancreatitis in rats.
P30

EUS-FNA (ENDOSCOPIC ULTRASONOGRAPHY DIRECTED FINE NEEDLE ASPIRATION BIOPSY) AND DIAGNOSTIC PITFALLS IN DIAGNOSTIC CYTOTOLOGY OF CYSTIC LESIONS OF THE PANCREAS

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Introduction: Endoscopic ultrasound-directed (EUS) fine needle aspiration (FNA) biopsy is a gold standard in diagnostics of focal and cystic lesions of the pancreas.

Objectives: From March 2007 to January 2012 we performed 670 cytological examinations of the pancreatic lesions (mean age 61 years, 56% male). From the total 15.4% (n = 76) were diagnosed by imaging methods (CT, ultrasonography) as cystic lesions of the pancreas.

Patients and Methods: We present diagnostic structure of our set (n=76) diagnosed by imaging methods as cystic lesions of the pancreas. From this was confirmed by 25% of malignant lesions, 17% of undetermined lesions biological behaviour, 6.5% intraductal papillary mucinous neoplasm, 5.2% serous cysts as benign lesions, 25% postinflammatory changes and pseudocysts and 21% with others diagnostic limitations.

Results: EUS FNA is a powerful method in diagnosing cystic pancreatic lesions. However, it brings a higher portion of different diagnostic limitations, of which the most common are low cellularity of the samples and frequent cytolytic damage of the diagnostic features. This can be partially resolved through the preparation of cytospin or cytoblock samples directly from aspirated content of the cysts.

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P31

CYTOTOXICITY, PREMATURE ENZYME ACTIVATION AND REACTIVE OXYGEN SPECIES PRODUCTION IN PANCREATIC ACINAR CELLS IN RESPONSE TO TOBACCO VS ALCOHOL

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Intracellular enzyme activation, reactive oxygen species (ROS) production and acinar cell death are pathophysiologic events associated with chronic pancreatitis (CP). The effect of alcohol and mainly tobacco in these events is poorly understood, despite the fact that both alcohol and tobacco are accepted etiologic factors of CP.

Aim: To evaluate the cytotoxicity, intracellular enzyme activation and ROS production induced by tobacco compared with alcohol in acinar cells in vitro.

Methods: Experimental in-vitro study in primary acinar cell culture. Acinar cells were isolated by enzymatic and mechanical digestion from Swiss mice pancreas. Cells were stimulated by increasing concentrations of alcohol (0.1-100mM) and tobacco (0.1-0.5mg/ml), and with CCK as positive control. Intracellular elastase activity and ROS production were evaluated by fluorescence assay, with rodamine and DCFDA substrates, respectively. Lactate dehydrogenase activity was quantified as a measure of cytotoxicity and cell death.

Results: Neither alcohol nor tobacco induced the activation of intracellular elastase. Tobacco (0.1-0.4 mg/ml), but not alcohol, produced a significant and dose-dependent cytotoxic effect (from 14% to 45% at 3h compared to negative control, p<0.05), which was associated with a significant and dose-dependent increase of ROS production (up to 3-fold at 3h compared to negative control). High alcohol concentrations (75 and 100mM) induced a non significant increase of ROS production.

Conclusions: Tobacco, but no alcohol, induces cytotoxicity and ROS production in pancreatic acinar cells. These results provide insight into the pathogenic mechanisms by which tobacco is able to cause CP.

P32

CHANGES IN THE EXPRESSION OF PANCREATIC PROGENITOR CELLS DURING ALLOXAN DIABETES IN RATS.

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One of the most common markers for stem cells in pancreas is C-kit - the stem cell factor receptor, important for differentiation of progenitor endocrine cells of pancreas islets. But still the role of C-kit positive cells during the diabetes mellitus type I isn’t clear. That’s why the aim of our work was to evaluate the C-kit expression in Langerhans islets during the experimental alloxan diabetes in rats.

The work was made on 45 rats, which were injected intraperitoneally with alloxan, in dose of 180 mg/kg. Blood glucose levels and morphological changes were analyzed 1,2,3,5,7 days after the injection. Histological sections of the pancreas were studied immunohistochemically with antibodies against insulin, glucagon and C-kit.

The results of the study showed that the expression of C-kit was found after one day of injection and was persisted at all stages of the experiment. We observed the increasing of glucagon-positive cells at the earliest stages of the experiment and the decreasing at the latest. The appearance of C-kit-positive cells in the islets during the alloxan destruction of B-cells shows its main role of progenitor cells differentiation. And the increasing of glucagon-positive cells may say about the similarity of C-kit –positive cells differentiation during prenatal development and diabetes mellitus type I.

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P33

C-KIT EXPRESSION IN PANCREAS AFTER PARTIAL HEPATECTOMY IN RATS.

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Stem cell factor receptor (C-kit) – is one of the most common markers for stem cells. According to some authors, this marker is present in progenitor cells of normal rat pancreas. It is unknown about the behavior of these cells in disorders of carbohydrate metabolism during liver disease.

44th European Pancreatic Club (EPC) Meeting
The aim of our study was to evaluate C-kit expression in pancreas after partial hepectomy in rats. We performed partial hepectomy (PH) for 45 white male rats. Organs were obtained after 1, 2, 3, 5 and 7 days after the surgery. Sections were stained immunohistochemically with commercial monoclonal antibodies to C-kit.

The results showed the absence of C-kit expression in normal islets. In interstitial space we observed rare single triangular C-kit+ cells. The similar pattern persisted at 1 and 2 day of the experiment. After 3 days of experiment, we observed weak expression of C-kit in islets, as well as the increasing number of single interstitial C-kit+ cells. The appearance of C-kit+ cells in the islets and the increasing number of single C-kit+ interstitial cells are observed in pancreas after PH. This may indicate the beginning of the differentiation of islet’s progenitor cells after PH. The source of C-kit+ cells can be progenitor cells of islets or the migrating interstitial C-kit+ cells.

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P34

DOES TOBACCO STIMULATE PROLIFERATION AND MIGRATION OF PANCREATIC STELLATE CELLS (PSC)?

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PSC proliferation and migration are essential in pancreatic fibrogenesis. Alcohol has been associated with activation and survival of activated PSC, but the effect of tobacco in this process is unknown.

Aim: To evaluate the effect of tobacco, ethanol and the combination of both in migration and proliferation of PSC.

Methods: Isolated PSC from rat pancreas were activated in culture after 2-3 passes and exposed to increasing concentrations of tobacco (0.01 to 0.4 mg/ml) ethanol (5 to 100mM) or the combination of both. Lactate dehydrogenase activity was evaluated as a measure of cytotoxicity and cell death. PSC proliferation was determined by WST-1 assay and migration by a wound healing assay (WHA).

Results: Tobacco at 0.1, 0.2 and 0.4 mg/ml had a cytotoxic effect in PSC and produced 28% to 49% cell death (p<0.05).

This cytotoxic effect was associated with a significant decrease of cell proliferation that was not modified by addition of ethanol. Ethanol alone had neither a significant effect in PSC death nor proliferation. In the presence of tobacco at 0.01mg/ml, ethanol at 5, 10 and 50mM increased PSC migration in a dose-dependent manner (p=0.08). Neither alcohol nor tobacco alone did have any effect in PSC migration.

Conclusions: Tobacco at concentrations of 0.1mg/mL or higher induces cell death and decreases PSC proliferation. In the presence of non-cytotoxic concentrations of tobacco, ethanol induces a dose-dependent increase of PSC migration. In this way, combined consumption of alcohol and tobacco is probably involved in the process of fibrogenesis in chronic pancreatitis.

P35

DESMIN-POSITIVE PANCREATIC STELLATE CELLS IN HUMAN ONTOGENESIS

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It is known activated desmin-positive pancreatic stellate cells (PSC) play a major role in pancreatic regeneration and fibrogenesis. However, it isn’t defined cellular sources of PSC development and ways of their differentiation. It is supposed also PSC may be a source of islet cells, particularly insulin-producing cells.

The aim of study was to analyze the dynamic changes of desmin-positive PSC in human pancreas during ontogenesis and to establish the possibility of insulin secretion by these cells.

The study was made on prenatal human pancreas, which were taken from legal abortions, and on the autopsy of different ages. Paraffin sections were stained immunohistochemically with antibodies against desmin and insulin.

Results: Mesenchymal cells surrounding the pancreatic bud of human embryo expressed desmin. Desmin-positive PSC appeared in pancreatic stroma at 12th week of gestation (WG). The most acinar and islet cells expressed desmin in the late prenatal period and after birth, ductular cells were desmin-negative. Single desmin-positive cells were found in the islets, acinuses and interstitium of the adult pancreas. The first insulin-positive cells were detected at 11th WG. In the late prenatal period and after the birth desmin-positive cells attended in the pancreas islets, some of them expressed insulin too. In the adult pancreas number of desmin+/insulin+ cells was significantly reduced.

We conclude the islet and acinar cells of human pancreas can develop not only from the epithelium of the foregut, but from the mesenchymal desmin-positive cells too. Apparently, desmin-positive PSC can be the pancreatic progenitors of B-cells.

P36

GLUCOSE INTOLERANCE IN PATIENTS WITH PANCREATIC TUMOR

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Introduction: Pancreatic cancer is a tumor with a bad prognosis. The only effective treatment is surgery, but a large number of patients undergo surgery when the disease is already advanced and only palliative treatment is possible.

Aim: The aim of this study is to estimate the correlation between glucose intolerance and pancreatic tumor.

Patients and Methods: In the period July 2010- July 2011 we operated on 50 patients with pancreatic tumors. In every case we assessed the clinical stage of the disease and pancreatic endocrine function (C-peptide, glucose profile, glycated hemoglobin level, oral glucose tolerance test).

Results: Out of the whole group 9 patients received previous diabetes treatment and 14 patients had recent-onset diabetes. 15 patients had a glucose intolerance and only 12 patients had normal glucose profiles. All patients had pancreas resection. Histopathology examination revealed ductal adenocarcinoma in 36 patients (72%). In the group with cancer disease only
4 patients had normal glucose profiles before the operation, glucose intolerance was found in 32 patients (89%). Only 6 patients (17%) received previous diabetes treatment, the rest of the patients wasn’t aware of the glucose intolerance.

**Conclusion:** Pancreatic cancer is often connected with different glucose intolerance. Performing simple tests evaluating pancreatic endocrine function may allow preoperative diagnostics and cancer prediction in asymptomatic patients.

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**P37**

**HEMORHEOLOGICAL CHANGES DURING EXPERIMENTAL ACUTE PANCREATITIS IN MALE AND FEMALE RATS**

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**Introduction:** Although microcirculatory disturbances play pivotal role in the pathomechanism of acute pancreatitis (AP), very few papers can be found in which any of hemorheological parameters had been tested.

The aim of our study was to analyze the hemorheological changes in cerulein-induced experimental acute pancreatitis in rat in two doses (5 and 10 µg/kg, s.c.), aiming to analyze the possible gender difference in hemorheological response, too.

**Methods:** Male and female rats were subjected to Control group, or AP with 5 or 10 µg/kg cerulein groups. Blood samplings (lateral caudal vein) were completed before cerulein administration, and 1, 2 and 24 hours later. Hematological parameters, amylase activity, erythrocyte deformability (ektacytometry) and aggregation (light-transmission method) were tested.

**Results:** Subcutaneously administrated cerulein in dosage of 5 and 10 µg/kg resulted in AP in rats, with significant changes in red blood cell deformability and alterations in erythrocyte aggregation. The presence of AP could be confirmed by amylase testing and histological examination. The earliest impairment of the red blood cell deformability could be observed 1 hour after cerulein administration in 10 µg/kg dosage.

**Conclusion:** We found micro-rheological changes in cerulein-induced acute pancreatitis, showing further differences depending on the cerulein dosage and gender. Female animals had the worst rheological results, and the mortality was the highest among them. This model seems to be suitable for further comparative studies.

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**P38**

**MICRORNA EXPRESSION ALTERATION IN PANCREATIC NEUROENDOCRINE TUMOURS**

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**Introduction:** Neuroendocrine pancreatic tumours (PETs) represent a group of rare neoplasms, characterised by a high degree of histological and clinical heterogeneity, whose molecular biology is still under research. MicroRNA (miRNA) deregulation has been well documented in many human malignancies, however it is still poorly investigated in PETs.

**Aims/Objectives:** Here we described the expression levels of 13 miRNAs in matched-pairs of tumour and adjacent non-cancerous tissue samples from 3 patients with MEN1-associated PETs.

**Patients & Methods:** Tissue specimens from PETs were collected from patients with familial history of MEN1, undergoing pancreatic resection.

**Results:** Only 2 out of the 13 miRNAs, miR-151-5p and miR-455-3p, were over-expressed in all PET samples compared to normal tissues. miR-31 and miR-30a were over-expressed in insulinomas, while in glucagonoma sample they were down-regulated compared to normal tissue; conversely, miR-135b and miR-143 were down-expressed in insulinomas and over-expressed in glucagonoma tissue sample. The subset of miRNAs that includes miR-21, miR-23a, miR-145, miR-199a-5p, miR-30c showed over-expression in tissue from Insulinoma with high Ki-67, while in samples from PETs with lower proliferation index all these miRNAs were down-regulated compared to normal tissue; conversely, miR-155 and miR-143 were down-expressed in insulinomas and over-expressed in glucagonoma tissue sample. The subset of miRNAs that includes miR-21, miR-23a, miR-145, miR-199a-5p, miR-30c showed over-expression in tissue from Insulinoma with high Ki-67, while in samples from PETs with lower Ki-67. Finally, miR-let7-i was differentially deregulated in the insulinoma samples and it was over-expressed in glucagonoma compared to normal tissue.

**Conclusion:** This study showed that miRNAs up-regulation is present in PETs and allowed us to associate specific miRNA alterations to the immunostaining of pancreatic cells or to the proliferation index of PETs.

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**P39**

**A NEW BIOMARKER TO ASSESS THE GRADE OF DYSPLASIA IN INTRADUCTAL PANCREATIC MUCINOUS NEOPLASMS (IPMN) BRANCH DUCTS.**

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Preventive surgical resection of branch duct IPMN is proposed according to radiological features suggesting severe dysplasia, but these criteria lack specificity. Moreover, no biomarker strongly correlated to the grade of dysplasia has been hitherto described.

**Aim:** To investigate the proteome of IPMN using MALDI (Matrix-Assisted Laser Desorption/Ionization) imaging and to characterize biomarkers indicating the grade of dysplasia.

**Methods:** Proteomic analyses of frozen IPMN samples were performed by MALDI imaging to obtain mass spectra.

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Identification of the most discriminating peaks was realized using MS/MS, nanoLC and Orbitrap®. Identifications were validated by western Blot on pancreatic mucus and immunochemistry on surgical specimens (tissue-microarrays) and EUS FNA.

**Results:** Branch ducts IPMN samples with low (n = 10) and high (n = 10) grade dysplasia were analyzed. Differential spectra of proteins were found between the two groups with significantly different expression intensity of molecular weight in high grade area (n = 27). One of the most discriminating peaks (m/z 8565) in high grade was characterized as the monomeric ubiquitin (Orbitrap® validation, score = 287).

Immunohistochemical study on tissue microarray confirmed that ubiquitin was overexpressed in high grade dysplasia (p = 0.04). Immunochemistry on EUS FNA samples confirmed a nuclear positivity in high grade dysplasia (94% versus 14%, p = 0.0004). Sensitivity, specificity, positive and negative predictive values were 94, 86, 94 and 86%, respectively.

**Conclusion:** Ubiquitin plays a major role in the oncogenic process regulating the oncogenic/ anti- oncogenic protein degradation. Positive immunochemical staining for ubiquitin on the EUS-FNA material could be a major argument favoring preventive resection.

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**P41**

**MEK INHIBITION BLOCKS S-PHASE ENTRY IN K-RAS MUTATED PANCREATIC CANCER CELL LINES**

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**Background:** Deregulations of the Ras-Raf-MEK-ERK pathway, mainly driven by K-Ras mutations (70%-90%), are frequently observed in pancreatic ductal adenocarcinoma (PDAC) and, thus, kinases involved in this pathway have been considered interesting therapeutic targets. MEK inhibitors (MEKi) are currently evaluated in clinical trials in PAC. Moreover, epithelial-to-mesenchymal transition (EMT) has been suggested to be predictive for response to chemotherapy and MEKi in various cancer types. However, no predictive biomarker is validated for MEKi in PAC.

**Aims/objectives:** To evaluate the effects of MEKi UO126 in K-Ras mutated human PAC cell lines.

**Materials and Methods:** UO126 is an allosteric non-ATP competitive MEKi. Effects of UO126 on proliferation and cell cycle were evaluated in Miapaca-2, Panc-1 and Capan-1 cell lines using MTT assay and flow cytometry, respectively. Protein expression was assessed by Western blot.

**Results:** Miapaca-2 and Panc-1 exhibited a mesenchymal phenotype (low E-cadherin and high vimentin expression) while Capan-1 was epithelial. In addition, Miapaca-2 expressed a higher level of pro-survival protein Bcl-2 than Panc-1 and Capan-1. UO126 blocks S-phase entry. Lower cyclin D1 expression was observed in Miapaca-2 compared to Panc-1 and Capan-1.

**Conclusion:** Miapaca-2 cells that display a very aggressive phenotype (EMT and K-Ras mutated) were remarkably sensitive to MEKI UO126. Cyclin D1 expression is currently investigated as a potential biomarker for PAC response to MEKi.

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**P43**

**PLAC8/ONZIN: A KEY REGULATOR OF PROLIFERATION AND SURVIVAL IN PANCREATIC CANCER CELLS.**

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**Introduction:** Pancreatic ductal adenocarcinoma (PDAC) is the most aggressive pancreatic cancer with an overall 5-year survival rate of <5%. Despite significant advances in treatment of the disease during the past decade, the median survival rate (~6 months) has hardly improved, warranting the need to identify novel targets for therapeutic approaches. Our previous data from microarray analyses of microdissected pancreatic tumor tissues as well as parallelized cell-based assays indicated a previously unknown role for Plac8 in pancreatic cancer initiation and progression. Plac8 is a rather small protein whose physiological functions remain largely unclear.

**Aim:** Main aim of this project is to characterize gene Plac8 with respect to its role in PDAC. The study also intends to dissect out the pathway(s) involved in the functional role.

**Methods:** qPCR, tissue microarrays, RNAi, cell proliferation and viability assays, FACS analysis, Western blot, shRNA inducible clones.

**Results:** qRT-PCR as well as tissue microarray data confirmed that Plac8 has a strong ectopic expression in pancreatic cancer tissues and further demonstrated that this high Plac8 expression is also retained in the majority of pancreatic tumor cell lines in vitro, with negligible expression in non-transformed cell lines. Functional effects of Plac8 were investigated after transient knockdown in a variety of different transformed and non-transformed cell lines. Proliferation and viability were strongly impaired by down-regulation of Plac8. Western blot and flow cytometry did not show any involvement of classical apoptosis pathway (Casapse-3 and PARP cleavage). Flow cytometry analyses and time course experiments with cell cycle inhibitors demonstrated strong attenuation of cell cycle progression after Plac8 knockdown, although intriguingly classical checkpoint mechanisms (p21, p53, Chk1, Cdc25A) were not activated, thereby suggesting involvement of hitherto unknown mechanisms. Generation of stable inducible clones as well as “multiple” transgenic mice (pertinent to human PDAC condition) for further in vivo experiments is in progress.

**Conclusion:** Our experimental data shows that ectopic expression of Plac8 is dispensible for proliferation, viability and cell cycle progression in pancreatic cancer cells. A clear insight into pathophysiological role(s) of Plac8 in the onset and progression of pancreatic cancer is expected to emerge with the generation of transgenic mice.
P44

PROTEOMICS SIGNATURE OF EARLY STAGES IN PANCREATIC CANCER.

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Introduction: Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancer in humans; its diagnosis sounds like a death sentence. PDAC develops from Pancreatic Intraepithelial Neoplasia (PanINs) lesions, graded from PanIN-1A to PanIN-3. Until now, PDAC molecular markers are not suitable to detect who is currently developing or is going to develop PDAC. We made the hypothesis that specific proteomic signatures from each pre-cancerous stage exist and are detectable in plasma.

Aims/objectives: Our aim is to identify biomarkers to detect asymptomatic high-grade precursor neoplasms.

Methods: We explored the peptide profiles of microdissected PanIN cells as well as of plasma samples corresponding to the different stages of PanINs from transgenic Pdx1Cre/KrasG12D mice using proteomics approaches. For that purpose, we used CE-MS, a non invasive technology compatible with diagnosis that combines high resolving power of capillary electrophoresis and high sensitivity of Mass Spectrometry for peptide detection.

Results: By coupling on-line a CE to MS, we successfully characterized differential peptides profiles from PanIN microdissected cells. With the perspective to develop a non invasive screening test, we also determined plasma peptide profiles corresponding to each different pre-cancerous stage characterized by distinct plasma peptide patterns. We thus identified peptide signatures that fully correlate with the pre-neoplastic stages.

Conclusion: These results strongly suggest that benign and advanced PanIN lesions display distinct plasma peptide patterns. This strongly supports the perspectives of clinical strategies for prediction and early detection of PDAC.

P45

SEVERE ACUTE PANCREATITIS : IDENTIFICATION OF CRITICAL FORMS

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INTRODUCTION AND AIMS: Severe Acute Pancreatitis (SAP) is characterized by some degree of severity. The aim of this study is to indentify within severe forms the critical, early severe acute pancreatitis (ESAP).

METHODS AND PATIENTS: Since 1997 to 2011 we have treated 276 acute biliary pancreatitis. SAP was 21.7% (60); ESAP was 21.7% (60); simple organ dysfunction : SAP 47% - ESAP 13%. In a later phase the gravity of severe pancreatitis lies on the septic complications of fluid necrotic collections. In ESAP the mortality is higher : 15.4% because of multilorgan dysfunction (in first phase); in SAP is 4.3% because of septic complications (in later phase).

CONCLUSIONS: Treatment of SAP and ESAP is now more conservative and less invasive than in the past : intensive care, prevention of intestinal failure and assure papillary patency in the first phase of the disease. In the later phase therapeutic procedure for fluid necrotic collections, is US/CT percutaneous catheter drainage.

P46

ASSOCIATION OF KRAS PATHWAY WITH EXPRESSION OF ABC TRANSPORTERS IN PANCREATIC ADENOCARCINOMA

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Objectives: KRAS mutations challenge the use of tyrosine kinase inhibitors (TKIs) in therapy of pancreatic adenocarcinomas (PDAC). TKIs are transported outside of tumor cells by ATP Binding Cassette (ABC) transporters. Our study aims to explore effects of KRAS pathway on ABCs expression and identify patients who could potentially benefit from therapy by TKIs.

Methods: Transcript levels of KRAS pathway genes SOS1,GRB2,SHC1,KRAS,RAF1,RAC1,MAP2K1/2, MAPK1/3 and all human ABC genes were evaluated by real-time PCR with relative quantification in tumors and paired adjacent non-neoplastic control tissues from 21 PDAC patients. Differences in transcript levels between tumor and control tissues, between patients divided by stage, grade and KRAS mutation status, and correlations of all transcript levels were then analyzed.

Results: KRAS transcript level significantly correlated with SHC1,MAP2K1 and MAPK1 in control tissues and with GRB2 and MAPK1 in tumors. MAPK1/3 but not KRAS correlated with fourteen ABCs including ABCB1/PgP and ABCG2/BCRP in control tissues. However, six different ABCs correlated with KRAS level and eight with MAPK1/3 in tumors. Transcript levels of SOST,M APK1,ABC87,ABC6,ABC7,BCG1 and ABCG2 significantly associated with tumor size, stage or grade of PDAC.

Conclusions: Our study identified potential candidates for drug targets modified by the KRAS signaling pathway. MAPK1 associated with the aggressiveness of PDAC and shall be further followed. Moreover, MAPK1/3 levels modified expression of ABC transporters in PDAC and interactions with therapy by TKIs may be expected. We further aim to validate results in an independent set and investigate functional aspects of our findings.

Study was supported by CSF grant no.:P301/12/1734.
P47

**PANCREATIC ACINI DRIVE EARLY PANCREATIC FIBROSIS IN THE PATHOGENESIS OF PANCREATITIS**

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**Background & Aims:** The role of pancreatic acinar cells in the necrosis-fibrosis sequence and in initiating fibrogenesis in the progression from acute to chronic pancreatitis remains unknown.

**Aims:** We investigated whether or not injured acinar cells can generate pro-fibrotic signals and whether or not acinar cell necrosis is required for fibrosis.

**Methods:** Rats were fed either an ethanol-containing or a control diet over 14 weeks and euthanized 3 or 24 hours after a single LPS injection. Pro-fibrotic TGF-β, fibrosis and necrosis of acinar cells were assessed by histology, electron microscopy and immunofluorescence methods. Human pancreatic tissues were also evaluated.

**Results:** LPS-injured acinar cells produce TFG-β after the onset of experimental subclinical acute pancreatitis. Furthermore, mild acute pancreatitis can establish peri-acinar fibrosis 24 hours after endotoxemia. Similar results were found in human acute/recurrent pancreatitis specimens. HMBG1 is reduced at the early stage, it is restored later, indicating rapid restoration of nuclear HMG1. We found no evidence of acinar cell necrosis despite the presence of fibrosis.

**Conclusion:** Our results suggest that acinar cells produce TGF-β and facilitate pancreatic fibrogenesis. Thus, the development of fibrosis in chronic pancreatitis does not require prior acinar cell necrosis in acute pancreatitis.

P48

**PREVALENCE OF CHRONIC AUTOIMMUNE THYROIDITIS IN A GROUP OF ADULTS WITH DIABETES MELLITUS AND OTHER CHANGES IN GLYCEMIC BALANCE**

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**Introduction:** Thyroid disorders are frequently associated with diabetes in clinical practice. In type 1 diabetes, because autoimmune etiology it is often associated with autoimmune thyroid disease (chronic autoimmune thyroiditis, Basedow-Graves disease). In type 2 diabetes and other changes in glycemic balance, they usually occur secondary to excess thyroid hormone or this association is random.

**Objectives:** To study the prevalence of autoimmune chronic thyroiditis (ACT) in a group of adults with diabetes mellitus (DM) and other changes in glycemic balance.

**Methods:** 650 people with diabetes mellitus and other changes in glycemic balance (588 F and 62 M), aged between 18 and 79 years represented the studied group. Depending on glycemic balance, the group was divided into:
- The group with type 1 diabetes (DM type 1) - 60
- The group with type 2 diabetes (DM type 2) - 290
- The group with impaired glucose tolerance (IGT) - 183
- The group with impaired fasting impaired glucose tolerance (IFG) - 117

In all cases were evaluated:
- Lipid profile: total cholesterol (TC), triglycerides (TG), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C);
- Glycemic balance: fasting blood glucose, glycosylated hemoglobin;
- Investigation of the thyroid gland: TSH, FT4, FT3, thyroid antibodies, thyroid ultrasound

**Results:** The prevalence of ACT in the study group was 32% (33.33% F and 19.35% M, p = 0.024, X² = 5.04). ACT prevalence in type 1 diabetic group was 83.33% (85.45% F and 60% M, p = 0.143, X² = 2.14), 26.55% in type 2 diabetic group (27.38% F and 21.05% M, p = 0.41, X² = 0.68), 28.41% in IGT group (29.47% F and 10% M, p = 0.184, X² = 1.76), and 24.78% in IFG group (26.85% F and 0% M, p = 0.07, X² = 3.21). Seminificative differences regarding ACT prevalence were found between the group with diabetes type 1 and type 2 diabetes and other changes in glycemic balance (83.33% vs. 26.55%, p < 0.001, X² = 69.33 for type 1 diabetes and type 2 diabetes, 83.33% vs. 28.41%, p < 0.001, X² = 55.95 for type 1 diabetes and IGT, 83.33% vs. 24.78%, p < 0.001, X² = 55.01 for type 1 diabetes and IFG), but not between type 2 diabetes and other changes in glycemic balance (26.55% vs. 28.41%, p = 0.65, X² = 0.2 for type 2 diabetes and IGT, 26.55% vs. 24.78%, p = 0.21, X² = 0.13 for type 2 diabetes and IFG, 28.41% vs. 24.78%, p = 0.21, X² = 0.48 for IGT and IFG).

**Conclusions:** ACT has prevailed in females and in the group with type 1 diabetes due to autoimmune origin, part of the polyglandular autoimmune syndrome (PAS) type III A. It is useful to determine antithyroid antibodies in patients with type 1 diabetes to detect early ACT because it may progress with hypothyroidism (risk of atherosclerosis and associated cardiovascular diseases).

P49

**INFLUENCE OF ANTITHYROID ANTIBODIES ON GLYCEMIC BALANCE IN A LOT OF CHILDREN WITH TYPE 1 DIABETES AND AUTOIMMUNE CHRONIC THYROIDITIS**

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**Introduction:** If we have an autoimmune endocrine disease, in time we’ll have other autoimmune endocrine disease, the most frequent association were between type 1 diabetes mellitus and thyroid or suprarenal diseases.

**Objectives:** Evaluation of antithyroid antibodies (ATAb) on glycemic balance in a group of children with type 1 diabetes and autoimmune chronic thyroiditis (ACT).

**Methods:** We studied 54 children and teens aged 14.46 ± 2.4 years, 87.03% girls and 12.97% boys (F/M ratio 6.7/1) (X²=59.26, p<0.001). We evaluated:
- glycemic balance: fasting blood glucose, urine glucose, ketonuria, glycosylated hemoglobin
- investigation of thyroid gland: TSH, FT4, FT3, thyroid echography
- antithyroid antibodies: thyroid peroxidase antibody (TPO-Ab) and antithyroglobulin (TgAb) antibodies

**Results:** The antiTPO AB were present in high titers in 85.18% cases (n = 46) and normal titers in 14.81% cases (n = 8). The mean values of these antibodies were 416.1±5319.11 mIU/ml. We noticed significant differences between patients with positive and negative antiTPO antibodies related with the onset age of diabetes (were younger) (4.86 ± 3.94 vs. 8.62 ± 0.51), the duration of diabetes (much longer) (9.23 ± 4.05 vs. 8.12 ± 0.64 years), the values of HbA1c (more elevated) (8.91 ± 2.03 vs.7.55 ± 1.96%) and the TSH levels (more (more elevated) (8.91 ± 2.03 vs.7.55 ± 1.96%).
values (much lower) (12.00 ± 23.7 vs. 14.77 ± 17.03 mIU/ml) than those with negative antiTPO AB. (p<0.001). The incidence of positive titers antiTg AB was the same as for antiTPO antibodies. In 45 cases both antibodies were increased. We also noticed significant differences related with ATAB between the age groups 10-14 years and 15-17 years (p < 0.001), values being higher in the age group 10-14 years (puberty) to age group 15 -17 years (adolescence), but not between another age groups.

Conclusions: Because early age of diabetes mellitus was smaller at patients with positive antiTPO antibodies, it is necessary to determine the possibility of association of autoimmune diseases, especially for thyroid diseases (higher risk for those with autoimmune chronic thyroiditis for hypothyroidism) for all patients with type 1 diabetes mellitus Although it is recommended that antithyroid antibodies, particularly those antiTPO positive to be determinate at children and adolescents with type 1 diabetes at the onset of diabetes, or at the latest before puberty. If the antibodies are positive therapy should be initiated to prevent self-induced hypothyroidism in young patients with type 1 diabetes.

P50
INHIBITORY EFFECTS OF MINOCYCLINE ON MITOCHONDRIAL FUNCTION IN MURINE PANCREATIC ACINAR CELLS: INVOLVEMENT OF THE MPTP
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Introduction: Mitochondrial dysfunction is a feature of pancreatic acinar cell injury in acute pancreatitis. Minocycline and other tetracyclines have been implicated as causes of acute pancreatitis by an unknown mechanism.

Objective: To determine the effects of minocycline on murine pancreatic acinar cell mitochondrial function and its mode of action.

Methods: Confocal and TIRF microscopy were used to evaluate mitochondrial membrane potential (\( \Delta Vm \): TMRM), NAD(P)H (autofluorescence) and cytosolic Ca2+ levels (\( [Ca^{2+}] c \): Fura-2) in freshly isolated pancreatic acinar cells from wild type (Wt, CD1) and \( \text{Ppif}^{-/-} \) (cyclophilin D knockout, which inhibits induction of the mitochondrial permeability transition pore, MPTP ) mice.

Results: Application of minocycline (10 - 100 \( \mu \)M) for 10 min induced rapid and sustained falls of \( \Delta Vm \) (44%), mean F/fo = 0.55, SEM= 0.028) associated with decreases of NAD(P)H in Wt cells, indicating mitochondrial inhibition (\( n = 11 \)). The protonophore CCCP (10 \( \mu \)M) was applied after minocycline to show maximal depolarisation. Comparison of effects of 10 \( \mu \)M minocycline indicated that mitochondrial depolarisation was significantly less pronounced (p<0.05), in the \( \text{Ppif}^{-/-} \)- group (\( n = 16 \)) although some loss of \( \Delta Vm \) (23.4%, mean F/fo = 0.734, SEM = 0.022) was still apparent. Perfusion of cells with minocycline (10 - 100 \( \mu \)M) did not produce an alteration of \( [Ca^{2+}] c \), whereas cholecystokinin (20 \( pM \)) applied after minocycline induced typical oscillatory elevations (\( n = 27 \)).

Conclusion: Minocycline causes mitochondrial inhibition in murine pancreatic acinar cells at least in part via MPTP opening, which may be a mechanism by which tetracyclines induce acute pancreatitis.

P51
LAPAROSCOPIC PanCREATIC RESECTION - THE NEW „GOLD STANDARD” FOR DISTAL PanCREATIC RESECTION
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Laparoscopic pancreatic resection is a new technique increasingly used in the treatment of mostly benign tumors in distal part of the pancreas. However, the use of this technique in the treatment of malignant tumor is more controversial. This technique is more technically demanding on the surgeon than the previous methods.

The aim of the study was to demonstrate its benefits to the patients in both benign and malignant cases.

In the period 2009-2011 we performed 26 such procedures and 40 classic open resections. The patients who underwent the laparoscopic procedure included 19 women and 7 men with an average age of 55 years.

To qualify for this procedure patients required a small benign or malignant tumor in the body or tail of the pancreas, and they could not have previously undergone a laparotomy.

Results: The average hospitalization period for those who underwent a laparoscopy was 4 days, while for those who underwent a classic operation the average period was 7 days. The most frequent histopathology of those who underwent the laparoscopy was cystadenoma (9cases) then neuroendocrine tumors (7cases), ductal adenocarcinoma (4 cases), inflammatory tumors (3 cases) and IPMN (3 cases). In each case of ductal adenocarcinoma an R0 resection was performed.

Those who underwent a laparoscopy required less anti analgesics and intravenous supplements ceased on the second day. There was no hospital mortality and in 4 cases pancreatic fistula was treated conservatively with success.

Conclusions: The laparoscopic technique is a good alternative to open distal pancreatic resection and even in cases of small malignant tumors it allows for radical resection.

P52
RESPONSE EVALUATION USING RECIST AND CHOI CRITERIA IN PATIENTS WITH WELL-DIFFERENTIATED PANCREATIC NEUROENDOCRINE TUMORS (pNET) TREATED WITH SUNITINIB OR EVEROLIMUS.
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Background: Despite low response rate by RECIST, sunitinib and everolimus improved the progression-free survival of patients (pts) with well-differentiated pNET in two large phase III controlled trials. RECIST being a poor surrogate
endpoint for PFS, this study aimed evaluating the value of CHOI criteria in PNET pts.

**Methods:** Data for this analysis were collected from pts with well-differentiated PNET treated consecutively with sunitinib or everolimus in our center between 2006-2010. All pts had tumor progression within 12 months (m) prior to treatment. Pts were considered evaluable if CT-scans were performed within 6 weeks prior treatment and <3 months following treatment initiation. A radiologist blinded for clinical data evaluated responses according to RECIST and CHOI criteria. Best responses were correlated with Kaplan Meier estimates of time-to-progression (TTP) and overall survival (OS).

**Results:** A total of 25 pts were treated with either sunitinib or everolimus. Among them, three pts were evaluated using MRI and thus were not evaluable in this study. Twelve pts received sunitinib and ten pts were treated with everolimus (Male/female: 8/14, median age: 57, range 38-76). All pts had tumor progression within 12 m prior to sunitinib or everolimus. Pts were either treated in 1st line (n=6), 2nd line (n=9), 3rd line (n=7) or 4th line (n=1) after cytotoxic chemotherapy. At the first CT-scan evaluation, 2 pts presented a partial response (PR), 18 pts had a stable disease (SD), and 2 pts had a progressive disease (PD) by RECIST. Using CHOI criteria, 11 PR, 8 SD, and 3 PD were observed. Nine of 18 pts (50%) with SD according to RECIST were reallocated to the responders (PR) using CHOI criteria. Median TTP and OS for all pts were 14.0 m and 35.8 m, respectively. According to RECIST, TTP was higher in pts with PR+SD compared to PD (14.2m vs 3.3m, p<0.0001). According to CHOI criteria, TTP was 26.1m in pts with PR, 8.7m in pts with SD, and 3.5m in pts with PD (p=0.038). Conclusions: Response by CHOI criteria is a prognostic factor for TTP and may identify among SD pts by RECIST those benefiting the most of targeted therapy.

**P52A**

**THE USE OF ALLOGENEIC MESENCHYMAL BONE MARROW STEM CELLS IN EXPERIMENTAL ACUTE AND CHRONIC PANCREATITIS IN RATS**

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**Aims:** Under the experimental conditions to establish safe doses and optimal timing of stem cell transplantation.

**Material and method:** 50 white rats, an experimental model of acute and chronic pancreatitis. Allogeneic stem cells transplantation: a dose 5x106, a single intraperitoneal injection of 2 ml of saline; 2x106 in 2 ml of saline once or double injection.

**Results:** Animals are parted in the groups: first group - the injection on the third day after reproduction 5x106; the second group- first introduction to the 6th day 2x106 cells and the second injection the 12th day, 3rd group - the first introduction to the seventh day 2x106 cells at 14th day of the second injection, fourth group - injection a single dose the 2x106 cells on the 10th day. 5th and 6th groups - the introduction of cells in different doses to intact animals. Autopsy. First group: the place of introduction of damaging agent in the pancreatic tissue necrotic, the interintestinal abscesses. Second group of double injection in doses 2x106 cells the all pancreas were “shrouded” fat+ty tissue. 3rd group of data are similar to data obtained in the second group. Fourth group of single injection at a dose of 2x106 ineffective. 5th and 6th groups autopsy - damage is not The level of pro-and anti-inflammatory cytokine change in the 2nd and 3rd groups:
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P53

METACHRONOUS PRESENTATION OF METASTASES TO THE PANCREAS AND STOMACH FROM A RENAL CELL CARCINOMA; A CASE REPORT

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Introduction: One third of patients undergoing resection of renal cell carcinoma will eventually suffer from disease recurrence. Renal cell carcinoma most commonly metastasizes to the lungs, bones, liver, adrenals and brain; although almost any organ can be involved. To our knowledge, we present the first report of a case of metachronous pancreatic and gastric renal cell carcinoma metastases without evidence of disseminated disease, to be managed with laparoscopic surgery.

Case Report: We report the case of a patient who was found to have a pedunculated polyp in his stomach 17 years after undergoing a left nephrectomy for renal cell carcinoma. Computerized tomography was performed which revealed a rounded lesion involving the stomach wall and the incidental finding of a lesion within the tail of the pancreas. The patient underwent a laparoscopic distal pancreatectomy, splenectomy and laparoscopic resection of the sub-mucosal stomach tumor. Immunohistochemistry confirmed metastatic renal cell carcinoma. The patient made a good recovery following surgery and was subsequently discharged home.

Discussion: In the absence of widely disseminated disease we would support an aggressive surgical approach to management, using laparoscopic surgery where technically feasible, especially with the possibility of combining surgery with immunotherapy and antiangiogenetic agents.

P54

EFFICACY OF THE ANTIHOMOTOXIC DRUG LEPTANDRA COMPOSITUM ON CLINICAL COURSE OF CHRONIC PANCREATITIS (CP)

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Introduction and aim: Different experimental data indicate that severity of pancreatitis decreased in case of including some antihomotoxic preparations in management of patients. The aim was to study dynamics of clinical symptoms (pain and dyspepsia) in patients with CP after add to the treatment antihomotoxic drug Leptandra compositum (Heel, Germany).

Methods: We observed 50 patients with CP. 25 of them (main group) re-ceived traditional therapy in combination with Leptandra compositum in dosage of 10 drops 3 times in day during 1month. Another 25 patients (comparison group) received only traditional treatment (enzymes, spasmolitics etc.). We studied the dynamics of clinical presentation especially pain and dyspepsia (vomiting, meteorism, nausea) in both group after treatment in 1 month. The degree of CP clinical manifestations was evaluated by means of semiquantitative score and average severity index.

Results: At the end of the treatment pain disappeared or became minimal in 84,3% patients of the main group and 63,2% patients of comparison group. Dyspepsia disappeared or became minimal in 86,1% patients of the main group and 67,4% patients of the comparasion group. The most strong effect of treatment in main group explained by antinflammatory, detoxication effect and motility correction by Leptandra compositum components.

Conclusion: Inclusion of antihomotoxic preparation Leptandra compositum to complex therapy of CP improves results of treatment.

P55

SERUM LEPTIN AND GHARELIN LEVELS IN PATIENTS IN THE EARLY STAGES OF ACUTE BILARY PANCREATITIS AND DIFFERENT DEGREES OF SEVERITY

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Introduction: Acute pancreatitis (AP) is a potentially fatal disease. In animal experiments leptin and ghrelin were shown to modulate the course of AP.

Aims: We studied the relationship between the severity of acute biliary pancreatitis (ABP) and serum levels of leptin and ghrelin in nonobese patients in the first seven days of the hospitalization.

Patients & Methods: The study included nine patients with mild ABP (MABP), eleven patients with severe ABP (SABP) and twenty healthy controls, appropriately matched age, sex and weight. Serum concentrations of leptin and ghrelin were measured in patients on the first, third, fifth, and seventh days of hospitalization using leptin and ghrelin RadiolImmonoAssay (RIA) kits.

Results: At admission and throughout the study the mean serum leptin concentration in SABP patients was higher than in the controls but without statistical significance. Serum ghrelin concentrations on admission were significantly lower in patients with ABP than in the controls. We observed steadily increasing serum ghrelin levels in both groups of the patients during the course of ABP.

Conclusion: The results of our study do not support the role of leptin as a marker of the severity of ABP. On the other hand, rising serum ghrelin levels during the course of ABP may be a marker of recovery and an indicator of the healing process.
Oral Sessions

P58
TOTAL ANTIOXIDANT CAPACITY IN ACUTE PANCREATITIS
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Introduction: Defining peculiarities of oxidative stress in acute pancreatitis patients need for targeted prevention and treatment. To assess antioxidant system determines the total antioxidant capacity. Results of total antioxidant capacity (TAC) can provide urgent biological information obtained in comparison with the measurement of individual components, as it takes into account the cumulative effect of all antioxidants present in plasma and body fluids.

Materials and methods: The total antioxidant capacity was measure in 53 patients with acute pancreatitis.

Results: Severe deficiency antioxidant protection correlated significantly in patients with acute necrotizing pancreatitis in the early days of hospital stay with the development of organ dysfunction, including pulmonary, central nervous system, renal, hepatic, metabolic, and with the development of multiple organ dysfunction syndrome (MODS). However, the total antioxidant capacity does not affect the development of necrotic foci of infection, but their failure could be one cause of fatal results for.

Conclusion: In acute pancreatitis, insufficiency of antioxidant capacity may lead to the development of multiple organ dysfunction and death.

P59
PEROXIDES IN ACUTE PANCREATITIS
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Introduction: Oxidative stress is an important factor in the pathogenesis of acute pancreatitis. Defining features of oxidative stress in acute pancreatitis patients is necessary for effective treatment. Investigation of concentration of peroxides in plasma can give to assess oxidative status in general, because there is a direct correlation between the presence of free radicals and circulating biological peroxides.

Materials and methods: The blood plasma peroxides levels were measure in 53 patients with acute pancreatitis.

Results: Concentration of peroxides in plasma in admission significantly increased in patients with severe acute pancreatitis. Average concentrations of peroxides in plasma of patients with acute necrotizing pancreatitis exceeded the levels in patients with acute interstitial pancreatitis in admission at 2.55 times, on the third day - at 2.35 times in seventh - in 2.27 times. It was noted that the concentration of peroxides in plasma of patients during hospitalization significantly correlated with the occurrence of organ dysfunction, including respiratory, renal, hepatic, metabolic, and therefore the MODS.
**Oral Sessions**

**Conclusion:** Thus, in patients with acute necrotizing pancreatitis in circulating plasma increased the number of peroxides, including hydrogen peroxide, peroxides of lipids, proteins and DNA, which can worsen the disease because of its various negative impacts.

**P60**

**CLINICAL CHARACTERISTICS OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM OF THE PANCREAS (IPMN) MANIFESTING AS ACUTE OR ACUTE RECURRENT PANCREATITIS (AP/ARP)**

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**Objectives:** As a premalignant lesion, there have been many reports about malignant potential of IPMN. However, comparatively little is known to date about AP/ARP with IPMN as the causative lesion. We therefore evaluated the clinical characteristics of IPMN which was strongly suspected as a cause of AP/ARP.

**Methods:** From 2000 to 2008, 488 patients were diagnosed with IPMN in a single tertiary referral center. Of these, 33 patients in whom other well-known causes (e.g. alcohol, gallstone, metabolic) of AP were excluded and IPMN was strongly suspected as a cause of AP/ARP, were enrolled. We retrospectively reviewed their clinical, radiologic, endoscopic and pathologic characteristics from these prospectively collected database.

**Results:** AP/ARP caused by IPMN occurred in 33 of 488 (6.8%) patients with IPMN, including 15 of 110 with main-duct or combined type and 18 of 378 with branch-duct type (13.6% (15/110) vs. 4.8% (18/378), P=0.002). The severity of pancreatitis was relatively mild, based on the computed tomography severity index score (median; 2, range, 0–4). Histologic review of 23 patients with surgical resection revealed 3 adenomas (14%), 17 borderline neoplasm (74%), 2 carcinoma in situ (9%) and 1 invasive carcinoma (3%). AP/ARP did not recur in 23 surgically resected patients during follow-up period (median; 49 months, range; 35-112 months).

**Conclusions:** AP/ARP caused by IPMN occurred in 6.8% of patients with IPMN, and prevalence rate of AP/ARP was higher in main-duct or combined type than in branch-duct type. It was mild in severity and benign in histopathology. IPMN should be entertained in the list of potential causes of AP/ARP.

**P62**

**INDICATORS OF ENDOTHELIAL FUNCTION AND SOME CYTOKINES BLOOD LEVELS DURING CHRONIC RECURRENT PANCREATITIS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

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**The purpose** - to determine the parameters of endothelial function and level of some cytokines in the blood of patients with chronic relapsing pancreatitis (CRP) and chronic obstructive pulmonary disease (COPD).

**Materials and Methods:** 32 patients with CRP and COPD (I group), 27 patients with COPD (II group), 24 patients with CRP (III group) and 19 healthy persons (HPs) - IV group. Vascular endothelial growth factor (VEGF) levels, stable metabolites of nitrogen monoxide (NO), interleukin (IL)-1B, IL-6 and IL-10 were been studied.

**Results:** VEGF levels were higher, compared to HPs (76,36±3,21, p<0,001), in the blood of patients group I by 3,4-fold (p<0,001), in group II - 2,2-fold (p<0,001) in group III - 1,7-fold (p=0,001). At the same time, all groups showed a significant (p<0,05) decrease (relative to the indices in HPs (23,17±0,94, p<0,001) of NO by 61,6%, 30,4%, 44,7% respectively.

Higher concentration of IL-1B, IL-6, IL-10, than HPs (1,57±0,13, 1,86±0,16, 8,84±0,34, respectively, p<0,001) in group I - in 3,1, 3,2, 3,4 - fold (p<0,001), in II - in 1,7 (p<0,01), 1,5 and 1,7 times (p<0,001), in III - 1,9, 1,7, 2-fold (p<0,001) was found.

**Conclusions:** It was established reciprocal burdening of CRP and COPD in patients with combination of the diseases and increased systemic inflammatory response compared to corresponding data in patients with CRP without comorbidity.
P63

INDICATORS PROINFLAMMATORY CYTOKINES TNF-Α IN PATIENTS WITH CHRONIC PANCREATITIS AND CORONARY HEART DISEASE

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Introduction: It is known that the production of TNF-α has an activation character and provides data exchange between the cells involved in chronic low-intensity inflammatory response, which is interpreted by us as a chronic inflammatory reaction that occurs in the pathogenesis of chronic pancreatitis (CP) and coronary heart disease (CHD).

The purpose of the study - to examine indicators of TNF-α in the course and progression of CP in conjunction with CHD.

Materials and methods: 23 patients with CP in concomitant with CHD, including 14 men and 9 women were examined. TNF-α was investigated by ELISA using a set of reagents, the company «Immunoenzyme assay-TNF-alpha» production of «Cytokines» (St. Petersburg, Russia).

Analysis of results and discussion: According to the obtained results: TNF-α levels in women were higher than in men. In patients with CP, which was accompanied by CHD a short time period (3-5 years) indicators of TNF-α were 117 ± 14,52 pg / ml, with a combined length of period up to 10 years old - 91,52 ± 26,01 pg / ml and more than 10 years of indicators of TNF-α were 83,12 ± 15,41 pg / ml.

Conclusion: In patients with CP in combination with CHD average level of TNF-α is not stable and decreases depending on the duration of the comorbidity of these pathologies, which appears to be due to inadequacy or inferiority of immune response and may indicate significant morphological and functional changes in the structure of the pancreas and the myocardium.

P64

QUALITY OF LIFE IN PATIENTS WITH CHRONIC PANCREATITIS: AN ANALYSIS OF RESULTS

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Introduction: Quality of life is one of the important indicators of adaptation abilities in patients (including those with chronic pancreatitis (CP)) to the social conditions of life.

The purpose of the study - to study features of the quality of life (QoL) in patients with CP.

Materials and Methods: 36 test «Health Status Survey» which 100 points represents medical history, objective methods of research, laboratory, ELISA and instrumental data. QoL was assessed using the SF-36 test «Health Status Survey» which 100 points represents full health. The results were compared with the control group (20 almost healthy persons).

Results: In patients with CP significantly reduced physical and role functioning (67.5 ± 8.2 points and 32.9 ± 9.2, respectively) compared with the control group (96.3 ± 2.4 and 87.5 ± 7.5). Vital activity was limited to 47.0 ± 10.4 points, while in almost healthy it amounted to 77.5 ± 4.2 points. Sleep disturbance was recorded at 45.6% and 43.7% poor coping with stress.

Conclusion: These data confirm the particular violations of the quality of life during exacerbation of CP that must be considered in therapeutic practice.

P65

LOCORECURRENCE AFTER RESECTION FOR DUCTAL ADENOCARCINOMA OF THE PANCREAS: PREDICTORS AND IMPLICATIONS FOR ADJUVANT CHEMORADIOThERAPY

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Introduction: Loco (regional) recurrence rate after pancreaticoduodenectomy (PD) for pancreatic ductal adenocarcinoma (PDAC) remains high and the efficiency of adjuvant chemoradiotherapy is still debated.

Aims/Objectives: To assess predictors of loco-recurrence, in order to tailor the indications for adjuvant chemoradiotherapy.

Patients and Methods: Prospective data for patients who underwent PD for PDAC (2001-2010) were retrieved. Tumor recurrence was categorized as loco-recurrence or distant recurrence. Clinico-pathological characteristics and survivals were compared between patients with different recurrence patterns. The predictors for loco-recurrence were assessed.

Results: 79 patients were included. Loco-recurrence alone was identified in 22 patients (27.8%), distant recurrence alone in 33 (41.8%), both loco- and distant recurrences in 17 (21.5%) and no recurrence in 7 (8.9%). Median survival after recurrence (SAR) was significantly better in patients with loco-recurrence alone than those with distant recurrence alone (10.4 vs. 5.0 months, P=0.002) or those with both loco- and distant recurrences (10.4 vs. 5.8 months, P=0.044); the survival for patients with distant recurrence alone or with both patterns was identical. Patients with early recurrence had a significantly poorer SAR than those with late recurrence (median, 5.5 vs. 9.0 months, P=0.001). Logistic regression analysis revealed that positive resection margin (P<0.001, HR=14.532; 95%CI 7.399-38.466), early T stage (P=0.018, HR=0.014; 95%CI 0.000-0.475) and large tumor size (P=0.030, HR=4.345; 95%CI 1.152-16.391) were the determinant factors directly related to loco-recurrence alone.

Conclusions: Patients with PDAC loco-recurrence alone had a significantly better SAR than those with distant recurrence. Adjuvant chemoradiotherapy should be considered to reduce loco-recurrence further and improve long-term survival.
TUMOR INFILTRATION IN THE MEDIAL RESECTION MARGIN PREDICTS SURVIVAL AFTER PANCREATICODUODENECTOMY FOR PANCREATIC DUCTAL ADENOCARCINOMA

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Introduction: The relevance of R1 (microscopic tumor involvement) status in different surgical resection margins (RMs) after pancreaticoduodenectomy (PD) for pancreatic ductal adenocarcinoma (PDAC) has been debated.

Aims/Objectives: To assess the rates of R1 resection in different RMs and analyse their prognostic influence on survival.

Patients and Methods: Data for patients who underwent PD (n=258) in our hospital between January 2001-December 2010 were retrieved from a prospective database. Using our standardized pathological reporting protocol, the circumferential resection margin is distinguished as 4 RMs: pancreatic transection, medial, posterior and anterior surfaces.

Results: A total of 84 patients were included with a median age of 63.7 years (range, 40.7–79.5 years). R1 rate was 57.1% (48/84) at all margins, 31.0% (26/84) in anterior margin, 42.9% (36/84) in posterior margin, 29.8% (25/84) in medial margin, and 71.3% (58/84) in pancreatic transection margin. The median overall and disease-free survival for all R1 resections were significantly poorer than those for R0 resection (17.2 vs. 28.7 months, P=0.007; and 12.3 vs. 21.0 months, P=0.019). Only median margin positivity had a significant impact on survival (13.8 vs. 28.0 months, P < 0.001), as opposed to anterior margin (19.7 vs. 23.3 months, P=0.187) and posterior margin (17.5 vs. 24.2 months, P=0.104) involvement. Multivariate analysis showed that median margin R0 status was an independent prognostic factor (P=0.002, HR=0.381; 95% CI 0.207-0.701).

Conclusions: With a standardized pathological reporting protocol, the medial surgical RM is the most important margin in PD for PDAC and a R1 resection here predicts poor survival.

ORAL SESSIONS

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CLINICAL, THERAPEUTICAL AND ECONOMICAL BENEFIT OF EXOCRINE PANCREATIC FUNCTION TESTS

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Introduction: Follow-up of patients with exocrine pancreatic insufficiency can be easily performed with non-invasive test of exocrine pancreatic function - 13C-mixed triglycerides breath test (13C-MTG) and fecal elastase-1 (FELA).

Aim: Methods: 56 patients (25/31 female/male; mean age 51 years) with diagnosed or suspected chronic pancreatitis (CHP) or after severe acute pancreatitis (AP) treated with enzyme substitution were included. 13C-MTG test was performed with 250mg Glyceryl-1,3-dioctadecanoate-2-octanooate-1-13C, standardized test procedure and calculated per 250mg Glyceryl-1,3-dioctadecanoate-2-octanooate-1-13C, standardized test procedure and calculated.

Results: Laboratory verified pancreatic exocrine insufficiency with 13C-MTG lower then 30%, was found only in 3/56 subjects, FELA less than 200 µg/g was found in 11 patients. Substitution therapy, based on these tests, are still continued only in 8/56 i.e 14.28%.

Conclusions: Measurement of fecal elastase 1 is simple, non-invasive, robust test, which well correlates with morphological, static, extent of tissue damage. 13C-MTG breath test is better in evaluation of dynamic and kinetic aspects, real digestive ability and response to stimulation. 13C-MTG breath test is, contrary to FELA, suitable to evaluate pancreatic supplementation therapy. Clinical, therapeutical and economical benefit of exocrine pancreatic function tests is in possibility to exclude pancreatic substitution therapy in more than three-fourths patients with suspected pancreatic insufficiency.

P67

URINARY NEUTROPHIL GELATINASE-ASSOCIATED LIPOCAIN AS A PREDICTOR OF DISEASE SEVERITY AND MORTALITY IN ACUTE PANCREATITIS.

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Introduction: In reference to our earlier publication, laboratory tests that reflect severe intravascular volume depletion (serum creatinine level, eGFR) can be used for predicting the severity of acute pancreatitis (AP).

Aim: The aim of the study was to assess whether urine level of Neutrophil Gelatinase-Associated Lipocain (uNGAL) could represent a useful marker of AP severity.

Patients and Methods: We have observed a cohort of 100 prospectively enrolled patients. The study describes the entity: moderately severe acute pancreatitis (MSAP), characterized by local complications (LCs) without organ failure (OF). Severe acute pancreatitis (SAP) was defined by the presence of infectious (peri)pancreatic complication or an OF for more than 48 h. Urine 24h samples for uNGAL measurement by ARCHITECT assay were collected on 1st, 3rd and 7th hospital day. Utility of uNGAL for the prediction of clinical outcome was evaluated by receiver operator characteristic (ROC) curve analysis.

Results: Usefulness of uNGAL for the prediction of OF and LCs was superior to CRP. Areas under the ROC curve of urinary NGAL for predicting MSAP and SAP were 0.885, 0.955, respectively. The cutoff points of 1st day uNGAL that maximized the combined sensitivity and specificity for predicting MSAP and SAP were 40 ng/mL, 57 ng/mL, respectively.

Conclusion: We strongly suggest using the uNGAL with cutoff value of >40 ng/mL as a simple indicator of severity in patients presenting with AP.
**P69**

**CHRONIC PANCREATITIS AS A CAUSE OF DIABETES**


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**Aim:** evaluation of clinical characteristics of chronic pancreatitis (CP) complicated by diabetes.

**Patients & methods:** 66 patients with CP (55 m & 11 f, age 46.8 ± 9.2 yrs) were investigated. Complications of CP were observed in 47 (71.2%) cases: calcification of the pancreas had 22 patients, 14 patients had undergone pancreatic resection, 11 - drainage surgery. Diabetes diagnosed in 15 (23.1%) cases. Exocrine pancreatic function was assessed by breath ¹³C-trioktanainom test. The content of C-peptide (CCP), antibodies to insulin and secretin were determined in blood samples by ELISA.

**Results:** The most pronounced decrease of exocrine pancreatic function was observed in patients after resection surgery (total share of output labels 18.7% vs. 44.0% in normal, p<0.05) and patients with calcification of the pancreas (20.9±14.4%, p<0.05), as well as decrease of secretin secretion fasting and after food stimulation. In addition, CCP were decreased in patients with uncomplicated CP, p<0.05) and underwent pancreatic resection (0.96±0.19 ng/ml vs. 2.3±0.31 in patients with not complicated CP, p<0.05) and underwent pancreatic resection (0.96±0.19 ng/ml, p<0.05). A direct correlation between the CCP and results of breath test was observed in patients after resection (r=0.84, p=0.03). Antibodies to insulin in patients were not discovered. The leading cause of CP in patients with diabetes was alcohol consumption.

**Conclusion:** Risk factors for diabetes in CP patients are calcification of pancreas and pancreaticoduodenal resection. Exocrine and endocrine insufficiency developed in parallel to the disorder of secretin secretion.

**P70**

**LAPAROSCOPIC PANCREATIC RESECTION: SINGLE-INSTITUTION EXPERIENCE OF 7 PATIENTS.**

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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) 5 cases (MCN3, IPMN1, Insulinoma1), pancreaticoduodenectomy (LPD) 1 case (Cancer of the Papilla), and tumor enucleation 1 case (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, 7days, 6days. (4) Cancer of the Papilla: A 72-years-old woman had the T2 tumor with no involvement of lymph nodes. The operative time, blood loss and hospital stay were 558min, 70ml, 20days.

**Conclusion:** Laparoscopic pancreatic surgery can be performed safely and effectively in patients with benign or low-grade malignant neoplasms of the pancreas.

**P71**

**A PROSPECTIVE NON-RANDOMISED STUDY, COMPARING FREY PROCEDURE WITH PYLORUS-PRESERVING PANCREATEODUODENECTOMY IN THE TREATMENT OF CHRONIC PANCREATITIS**

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**Introduction:** Resection and drainage are the two basic surgical principles in surgical treatment of chronic pancreatitis (CP).

**Aims/Objectives:** The aim of this prospective study was to compare two surgical procedures in the treatment for CP: pylorus-preserving pancreateoduodenectomy (PPPD) to Frey’s procedure (FP), to define the advantages of each procedure with regard to postoperative complications, pain relief, and the quality of life.

**Patients and Methods:** 58 consecutive patients were included into this study. PPPD was chosen when the head pancreatic mass was present or pancreatic cancer could not be ruled out (21 patients); otherwise FP was performed (37 cases). Early postoperative morbidity and mortality were assessed and evaluated in both groups of patients. Quality of life was measured prospectively before surgery and during follow-up (median 12 – 15 months) using the SF-36 v.2 Health Survey Questions (Russian version).

**Results:** In the immediate postoperative period more complications were observed in the PPPD-group (p<0.05). Total pain score decreased and quality of life increased significantly after surgery in both groups of patients, but the differences were not significant.

**Conclusion:** Both surgical procedures led to significant improvement in the quality of life and pain relief after surgery for CP. Under equal conditions, the preference should be given to FP, as more safe operation by result in the early postoperative period.
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LAPAROSCOPIC INTERVENTIONS IN PATIENTS WITH CHRONIC PANCREATITIS

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Background: The usefulness of laparoscopic access in treatment of chronic pancreatitis has to be explored.

Objective: the analysis of laparoscopic operations in treatment of chronic pancreatitis.

Patients and methods: In our clinic there were 26 laparoscopic interventions performed for chronic pancreatitis and its complications.

Results: Laparoscopic interventions were performed in 26 cases: cystogastrostomy 6, cystoduodenostomy 3, cystojejunostomy 8, cysctectomy 1, longitudinal laparoscopic pancreaticojejunostomy 8. In all the cases of laparoscopic procedures the communication of a cyst with the main pancreatic duct were confirmed by preoperative biochemical and cytologic analysis of cystic fluid taken under the ultrasound control puncture. In the patient with a cyst located in the tail of the pancreas, the bleeding from the splenic artery required to convert the operation into open. In another patient laparoscopic longitudinal pancreateovisurgotomy and pancreatic resection were performed due to the impossibility of adequate cyst drainage in the hamulus region of the pancreas which required conversion of the operation into open. All patients who underwent minimally invasive procedures were discharged on the 6th day without any postoperative complications.

Conclusion: Clinical experience in the use of laparoscopic procedures in chronic pancreatitis treatment supports the conclusions of other authors concerning the advantages of laparoscopic techniques which are of better tolerance and which shorten hospital stay. The application of minimally invasive surgery techniques may be effective on condition that there is a thorough selection of patients taking into account the anatomic features of the pancreas and its duct system in every individual case.

P73

DOUBLE DRAINAGE AT TREATMENT OF LARGE PSEUDO CYSTS OF THE PANCREAS

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Objectives: Improved results of surgical treatment of patients with pancreatic pseudocysts larger (more than 10 cm in diameter) using the internal “double drain”.

Methods: 68 patients with pseudocysts of more than 10 cm in diameter were operated on. In 14 (23.3%) patients the method of double drainage was applied. Method of treatment of large pancreatic pseudocysts include external-internal drainage of the cyst through the stomach or duodenum, and an additional cistoejejunostomomas. Transnasal through these anastomoses in the cavity of the cyst drainage is carried out. After surgery, cyst cavity was washed through the drainage tube, control the volume of discharge from the cavity of the cyst. At 4 - 5 days after surgery performed X-ray. With a decrease in the cyst cavity and a good evacuation, drainage removed. At the 12 days after surgery to perform ultrasoundography - study. The results of treatment were analyzed for the following indicators: postoperative complications, mortality, duration of treatment.

Results: In 2 patients for 2-3 days spontaneously evacuated drainage and control X-ray examination was not performed. After applying the method of dual drainage of pseudocysts, postoperative complications and deaths was not observed. Periods of observation from 1 to 4 years. Recurrence of the disease have been not identified. In our work, we identified the indications and contraindications for the implementation of the method of dual drainage of large cysts of the pancreas.

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DISTANT RESULTS OF THE PANCREAS PROXIMAL RESECTION IN PATIENTS WITH CHRONIC PANCREATITIS

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Objectives: To analyze distant results of the pancreas proximal resection and to study the quality of patients, life in the postoperative period.

Methods: 153 patients with chronic pancreatitis (CP) were included in the research in whom pancreas proximal resections were performed (pancreatoduodenal resection in 53 patients; Beger operation in modification of the clinic – in 61 patients; Bern modification – in 39 patients). Criteria of treatment efficacy were the level of distant lethality, frequency of complications and repeated interventions, marked character of exocrine and endocrine insufﬁciency. The pain syndrome level and professional rehabilitation of patients were estimated.

Results: Late lethality related to chronic pancreatitis progressing made up 2,61%. Firstly revealed diabetes mellitus developed in 15 (9,8%) patients after all surgical interventions; reliably smaller number of such cases in patients after Beger operation was noted in comparison with pancreatoduodenal resection. Exocrine insufﬁciency was revealed in 27 (17,65%) patients and it doesnt depend on the operative technique. High level of professional rehabilitation was marked at all techniques which was achieved in 137 (89,54%) patients. There was a reliable improvement of parameters of the pain syndrome elimination after Beger operation in modiﬁcation of the clinic in comparison with pancreatoduodenal resection.

Conclusions: The performed analysis of the distant results of surgical treatment of CP patients demonstrates advantages of the pancreas proximal resection with the duodenum saving.

P75

FEASIBILITY AND EFFICACY OF DISTAL PANCREATECTOMY WITH EN BLOC CELIAC AXIS RESECTION (DP-CAR) FOR LOCALLY ADVANCED PANCREATIC BODY CANCER

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Introduction: The status of surgical margin is an important prognostic factor. DP-CAR has been reported to offer complete curative resection even in patients with locally advanced
cancer of the pancreatic body with the involvement of celiac axis.

**Objectives:** Now, we examine the feasibility and efficacy of DP-CAR.

**Patients and Methods:** Five patients with locally advanced pancreatic body cancer underwent DP-CAR. We performed preoperative coil embolization of the common hepatic artery to facilitate blood flow into the liver through collateral pathways of the pancreatic head. We analyzed the status of resection, postoperative complication, QOL and executing of adjuvant therapy.

**Results:** The majority of the patients accomplished the histological curative resection (R0). The postoperative pancreatic fistula (PF) was observed in three patients, one of which showed from abdominal abscess secondary to PF. Postoperative diarrhea was not found. Any patients did not require intensive nutritional support postoperatively. The postoperative mortality rate was zero. One month after the procedure, most patients could receive adjuvant chemotherapy using S-1.

**Conclusion:** DP-CAR seems to be a feasible procedure, and may offer R0 resection for locally advanced pancreatic body cancer with the involvement of celiac axis.

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**P76**

**CLINICOPATHOLOGIC STUDY ON Pancreatic GROOVE Carcinoma**

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**Introduction:** Pancreatic groove carcinoma, usually presenting with duodenal stenosis, is relatively rare type of pancreatic head cancer.

**Aim:** We report clinicopathologic features of pancreatic groove carcinoma.

**Patients & Methods:** Five patients enrolled in this study. All the clinical and radiological features were reviewed retrospectively and analyzed to identify correlations with the histological findings.

**Results:** Vomiting was an initial symptom in all cases, but obstructive jaundice was not inevitable until the disease progresses. Hypotonic duodenography demonstrated severe postbulbar stenosis. Pathological findings of biopsy specimens showed no evidence of malignancy at the early stage. Computed tomography revealed a hypovascular mass. Magnetic resonance imaging indicated a hypointense mass on T1-weighted images and an isointense to slightly hyperintense mass on T2 images. Macroscopically, the stenosis seemed to be the result of a hard yellowish-white tumor invading the duodenal wall. Histopathologically, an adenocarcinoma arising from the groove infiltrated the submucosal layer of the duodenum circumferentially. No cancer cells were found in the mucosa at the early stage. The intrapancreatic common bile duct was involved at the advanced stage.

**Conclusion:** We believe that these features resulted from the anatomical characteristics of the groove involvement and that the string stricture of the duodenum resulted from invasion of the groove tumor into the submucosal layer around the wall.

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**P77**

**LONG-TERM OUTCOME AFTER FREY PROCEDURES FOR CHRONIC PANCREATITIS WITH INFLAMMATORY MASS OF THE PANCREATIC HEAD: COMPARISON OF PANCREATECODOUDENECTOMY**

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**Introduction:** Frey procedure, combination of the coring out of inflammatory mass and longitudinal pancreaticojejunosotomy, may be an alternative to pancreatectoduodenectomy (PD) for chronic pancreatitis with inflammatory mass.

**Aim:** We examined the long-term outcome after this procedure compared to PD.

**Patients & Methods:** Five patients underwent Frey procedure and 10 patients received PD. The follow up was gained in all patients with a median period of 5 years.

**Results:** Pancreatic fistula was detected in one patient receiving Frey procedure, but could be managed conservatively. Pain control was achieved in all patients of both groups. No significant difference was found in terms of postoperative QOL C30 score and exocrine function. However, two patients with PD suffered from diabetes mellitus postoperatively, requiring insulin injection. In all patients with Frey procedure, there was no evidence of exacerbation of duodenal stenosis and biliary stricture postoperatively.

**Conclusion:** Frey procedure can offer the better long-term outcome for the treatment of chronic pancreatitis with inflammatory mass of the pancreatic head compared to PD.

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**P78**

**LEFT POSTERIOR APPROACH FOR PANCREATECODOUDENECTOMY FOR CANCER OF THE PANCREATIC HEAD**

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**Introduction:** Left posterior approach for pancreatectoduodenectomy (lp-PD) is a modified technique of the standard Whipple procedure (s-PD). The lp-PD leads to an increased number of R0 resections and facilitation of en bloc PV/SMV resection.

**Aim:** We report the technique of the lp-PD and clinical outcomes.

**Patients and Methods:** 14 patients underwent the lp-PD and 22 patients received the s-PD. Demographic characteristics, intraoperative data, pathologic findings and patient outcomes were analyzed in both groups.

**Results:** The technique of the lp-PD is described in details. The mean blood loss was lesser in the lp-PD group (P<0.05). No lethal complications were observed in both groups. Diarrhea occurred in 50% of patients with the lp-PD and required antidiarrheal agents. In the lp-PD group, all patients achieved
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microscopically R0. Moreover, the number of removed lymph node around SMA was larger in lp-PD group than in the s-PD group (P<0.01). Most patients (85%) in the lp-PD group could receive adjuvant chemotherapy as well as in the control group.

**Conclusion:** The lp-PD can offer increase the number of R0 resections by ensuring the circumstantial surgical margins and reduce intraoperative blood loss. In addition, this technique facilitates vascular resection and reconstruction.

**P79**

**PANCREATIC EXOCRINE-ENDOCRINE INTERACTIONS EVALUATED BY THE “PANCREATOGRA” TEST**

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**Introduction:** Between the two “bullets” in the “barrel” of the “pancreatic revolver”: the “pancreon” and Langerhans islets, evolve a subtle interplay that can be evaluated when coupling, to the oral glucose tolerant test (OGTT), the measurement in blood of the exocrine enzymes and calcium.

**Purpose:** The aim of this report is to put into consideration our findings in a control (C) group and in patients classified either as intolerant (I) or diabetics (D).

**Mat. & Meth:** Patients: 31-75 years of age, C(n=38), I(n=32) and D(n=19). Classical OGTT was performed with the additional determination of: amylasemia, pancreatic isoamylasemia, lipasemia and calcium. The main emphasis was put in the cumulative value (CV): (basal+30+60+120min) of each parameter. CV “diagnostic indexes”, resulting of the correlation in the cumulative value (CV): (basal+30+60+120min) of each parameter. CV "diagnostic indexes", resulting of the correlation of glycemia with the different enzymes and calcium gave a useful insight into the patient’s condition.

**Conclusions:** This approach facilitates the insertion of the patient in the appropriate group. It is notoriously easier to differentiate the C from the I group. Sequential testing of the “pancreatogram” accurately establish if the patient under scrutiny keeps a stable functional “insulo-pancreon-axis” condition, or, otherwise, is showing signs of either progressive deterioration or stimulating improvement.

<table>
<thead>
<tr>
<th>C</th>
<th>I</th>
<th>D</th>
<th>C vs I</th>
<th>C vs D</th>
<th>I vs D</th>
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</thead>
<tbody>
<tr>
<td>Glucose (mg/dl)</td>
<td>47±3</td>
<td>63±7</td>
<td>86±138</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Amylase (U/l)</td>
<td>386±173</td>
<td>297±125</td>
<td>228±95</td>
<td>&lt;0.003</td>
<td>&lt;0.05</td>
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<tr>
<td>Lipase (U/l)</td>
<td>344±187</td>
<td>268±128</td>
<td>379±192</td>
<td>&lt;0.04</td>
<td>ns</td>
</tr>
<tr>
<td>Ca (mg/dl)</td>
<td>34.9±6.7</td>
<td>35.8±5.3</td>
<td>33.9±4.9</td>
<td>ns</td>
<td>ns</td>
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<tr>
<td>Insulin(µU/ml)</td>
<td>144±55</td>
<td>242±165</td>
<td>173±141</td>
<td>&lt;0.0004</td>
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</table>

**P80**

**A WIDE VARIATION IN DIAGNOSTIC AND THERAPEUTIC STRATEGIES IN CHRONIC PANCREATITIS: A DUTCH NATIONAL SURVEY**

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**Introduction:** Optimal diagnostic and treatment modalities in chronic pancreatitis (CP) are controversial due to lack of evidence. To evaluate current clinical practice, we conducted a survey in the Netherlands with the primary objective to evaluate decisions regarding the diagnosis, management and screening in CP.

**Methods:** We developed a vignette survey. We surveyed Dutch gastroenterologists (GEs), internists, gastrointestinal surgeons (GIS) and an international expert panel.

**Results:** A total of 110 questionnaires were returned (response percentage 8.3%); 31% GEs, 39% internists and 20% GIS. There was a wide variation in strategies regarding diagnosis, treatment and screening in CP. As a diagnostic test, serum amylase is used frequently by internists, while gastroenterologists and experts often use fecal elastase. Most respondents preferred CT-scanning for diagnosis, while experts preferred transabdominal ultrasound as an initial test. Respondents frequently use pancreatic for treatment of pain in CP. The majority advised to perform an intervention (endoscopic or surgical) in case of morphological changes of the pancreatic duct.

**Conclusion:** The results of our survey identify important differences between physicians in diagnosis and management of CP. This is often due to lack of evidence and consensus in literature. Certain wide-spread practices are in contrast with available evidence, and should be addressed by improved education and adherence to guidelines.

**P81**

**NEOADJUVANT CHEMO-RADIO THERAPY FOR PATIENTS WITH BORDERLINE RESECTABLE PANCREATIC CANCER: A META-ANALYTICAL EVALUATION OF PROSPECTIVE STUDIES.**

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**Introduction and Aims:** For patients with borderline resectable (BR) pancreatic cancer, the benefit of neoadjuvant therapy remains to be defined. We did a systematic search of the literature on this topic.
PATIENTS AND METHODS: Prospective studies, where chemotherapy, irrespective of regimen, in combination with radiotherapy was given before surgery to patients with BR cancer, were analyzed by a meta-analytical method. Primary outcome was tumor response; surgical exploration rate, resection rate, therapy-induced toxicity, and survival were secondary outcomes. Data were expressed as weighted pooled proportions with 95% Confidence Interval (CI).

RESULTS: Eleven studies with 247 participants were included. Three were phase II/III trials, 3 phase II, and 5 prospective cohort studies. The complete/partial response rate was 17.1% (CI 10-26). Stable and progressive disease were 61.4% (CI 51-70) and 24.3% (CI 16-33), respectively. Treatment-related grade 3-4 toxicity was 34.6% (CI 24-46). At restaging following neoadjuvant therapy, 67.5% of patients (CI 54-78) underwent surgery, and 80.3% of them (CI 67-88) underwent resection. R0 resections amounted to 82.1 % (CI 74-88). Estimated 1- and 2-year survival probabilities after resection were 52.1% (CI 33-70) and 44.9 % (CI 21-71).

CONCLUSION: Our data cast some concern on the value of neoadjuvant therapy for patients with BR pancreatic cancers: if the intent of therapy were to induce tumor shrinkage and to allow curative surgery, this is only accomplished in one out of 7 patients; moreover, two thirds of patients could have been explored at their initial presentation, as they underwent surgery despite an unsuccessful response to therapy. The only benefit of this approach seems to be sparing surgery for patients with progressive disease.

P82

PANCREATECTOMY USING A NO-TOUCH ISOLATION TECHNIQUE

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Background and Aims: Pancreatectomy (pancreatodudenectomy: PD and distal pancreatectomy: DP) is the only effective treatments for pancreatic cancer. The recurrence rate after resection has remained high. As one of factors influencing the poor prognosis, intraoperative dissemination of cancer cells by grasping the tumor is proposed. In an effort to overcome this problem, I developed no-touch surgical techniques for both PD (Am J Surg, 2010) and DP (Scand J Surg, in press).

Patients / Methods: From April 2008 through January 2012, 36 invasive pancreatic ductal carcinoma patients have been operated on using a no-touch technique by a single operator. As for the tumor stages in the 36 patients, final pathological stage (I/II/III/IVA/IVB) according to the Japan Pancreas Society (JPS) classification system was 0/1/17/7/11. The International Union against Cancer (UICC) stage according to pTNM pathological classification (IA/IB/IIA/IIIB/IIIV) was 0/1/11/18/2/4. During the procedure, the pancreatic lesion is neither grasped nor squeezed by the surgeon. And all drainage vessels from the pancreatic lesion have been ligated and divided.

Results: In the current series, the post-operative prognosis was not deteriorated with this technique. Overall one-and three-year survival rates were 91.0 and 63.6% with mean follow-up periods of 26 months (range: 2-46 months). The numbers of observations for one- and three- years were 27 and 13. Eight patients with tubular adenocarcinoma were actual three-year survivors.

Conclusion: No-touch pancreatectomy technique may have some theoretical advantages, which merit future investigation in randomized controlled trials.

P83

RISK FACTORS FOR INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (IPMN) OF THE PANCREAS: RESULTS OF THE AISP (ITALIAN ASSOCIATION FOR THE STUDY OF THE PANCREAS) MULTICENTRE CASE-CONTROL STUDY

Capurso G.1, Boccia S.2, Salvia R.3, Del Chiaro M.4, Frulloni L.5, Arcidiacono P.G.6, Zerbi A.2, Manta R.8, Fabbri C.3, Ventriucchi M.10, Tarantino L.1, Picucchi M.1, Carnuccio A.12, Boggi U.4, Leoncini E.7, Costamagna G.12, Delle Fave G.1, Pezzilli R.10, Bassi C.3, Larghi A.12
1Gastroenterology, University of Rome; 2Epidemiology, Catholic University Rome; 3Surgery, University of Verona; 4Surgery, University of Pisa; 5Gastroenterology, University of Verona; 6Gastroenterology & Gastrointestinal Endoscopy, San Raffaele Hospital, Milano; 7Surgery Istituto Humanitas, Milano; 8Gastroenterology, S. Agostino Hospital, Modena; 10Gastroenterology, Bellaria Maggiore Hospital; 11Internal Medicine, Sant’Orsola-Malpighi Hospital, Bologna; 12Endoscopy, Iset, Palermo; 12Digestive Endoscopy Unit, Catholic University Rome. ITALY.

Background and aim: There are no studies specifically investigating risk factors for the occurrence of IPMN. The study aimed at investigating environmental, personal and hereditary risk factors associated with the occurrence of IPMN.

Material and methods: A multicentre case-control study was conducted after power calculation. Risk factors for IPMN recorded throughout a questionnaire regarding family and medical history, and risk factors. Cases were prevalent IPMNs seen at the participating Units between June 2010 and December 2011. Sex and age matched controls enrolled amongst patients seen at GI outpatient-clinics. Cases and controls compared by appropriate statistics.

Results: We enrolled 390 IPMN and 390 controls (166 male, 42.6%, median age 65.2 and 65.3 in cases and in controls); 310 cases had branch duct IPMNs and 80 main duct involvement. Pancreatic ductal adenocarcinoma (PDAC) was the only cancer, were analyzed by a meta-analytical method. Primary outcomes. Data were expressed as weighted pooled proportions with 95% Confidence Interval (CI).

P83

RISK FACTORS FOR INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (IPMN) OF THE PANCREAS: RESULTS OF THE AISP (ITALIAN ASSOCIATION FOR THE STUDY OF THE PANCREAS) MULTICENTRE CASE-CONTROL STUDY

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ADVANTAGES OF LUMBOSCOPY IN SURGERY OF PERIPANCREATIC FAT NECROSIS.

V. Boiko1, O. Pesockiy2, A. Kozachenko2, A. Vasko2, M. Suplichenko2
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Introduction: Retroperitoneal phlegmon is a serious complication of severe acute pancreatitis. It requires draining operations. This is usually carried out by lumbotomy but can be performed by lumboscopy.

Objectives: To compare open and lumboscopic approaches to draining operations.

Patients & Methods: Patients who had surgery for retroperitoneal phlegmon draining between 2006-2011 were identified. 29 patients underwent 45 draining operations-13 lumboscopic (9 patients), 32 open (20 patients). The laparoscopic and open groups were comparable for age (56 vs. 51 years), sex distribution and severity (severe acute pancreatitis was established in all patients). The two approaches were compared on an “intension-to-treat” basis.

Results: There was no difference in operating time between lumboscopic (25min.) and open (21min) groups. Lumboscopic surgery was associated with less operating trauma and complications, had a lower risk of mortality (22% vs.35%) and shorter postoperative stay (20 vs. 28 days).

Conclusion: The lumboscopic approach to draining operations in retroperitoneal peripancreatic fat necrosis is associated with decrease of mortality, more rapid recovery, shorter hospital stay compared with open surgery.

ABSTINENCE AFTER THE FIRST ACUTE ALCOHOL-ASSOCIATED PANCREATITIS PROTECTS FROM RECURRENT PANCREATITIS AND SEEMS TO DECREASE THE RISK FOR PANCREATIC DYSFUNCTION.

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Objectives: Alcohol is a risk factor for acute pancreatitis. In our previous two year follow up abstinenence protected for recurrences. Our aim was to further determine recurrence of pancreatitis and later pancreatic function in patients who quit drinking after the first episode of alcohol-associated pancreatitis.

Materials and Methods: Out of the total of 120 patients with their first alcohol-associated pancreatitis, 23 (20 M, 3 F; age median 47 (27–60) years) met the inclusion criteria for abstinence during the follow up. The criteria for abstinence was alcohol consumption less than 24 grams per two months (self-estimated) which is in line with questionnaires detecting alcohol consumption and dependency (Alcohol Use Disorders Identification Test, AUDIT < 8 and Short Alcohol Dependence Data, SADD < 9). Recurrent attacks of acute pancreatitis were studied. Smoking, body-mass index and laboratory tests detecting heavy use of alcohol were recorded. Blood and fecal tests were studied to assess endocrine and exocrine pancreatic function.

Results: During a mean follow up time of 4.8 (2–9) years and total of 111 patient years there were no recurrent attacks of acute pancreatitis. Two patients had diabetes prior to and two just after the first episode of acute pancreatitis. One patient demonstrated new onset diabetes during the follow up at 1.5 years. One patient showed low elastase activity at 2 and another at 3 years, but no-one later on.

Conclusions: Abstinence after the first acute alcohol-associated pancreatitis protects from recurrent attacks and seems to decrease the risk for pancreatic dysfunction.

THE SIGNIFICANCE OF ENDO-ULTRASONOGRAPHY IN THE PREOPERATIVE MANAGEMENT OF PATIENTS WITH (EARLY) PANCREATIC CANCER.

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Introduction: Pancreatic ductal cancer remains a devastating disease with an urgent need for improved diagnostics and new treatment strategies. It has no early specific symptoms, shows rapid progression and is practically undiagnosable in the early stage. Survival of radically operated patients is very unsatisfactory. Nonetheless, only radical surgical resection offers potentially curative treatment.

Aim: To present the importance and usefulness of endo-ultrasonography in the diagnostic algorithm, particularly in patients with early stage of disease.

Patients and Methods: Set of consecutive 70 patients (2009-2011) with ductal cancer of the head of the pancreas that underwent radical resection- pancreaticoduodenectomy. Retrospectively were evaluated diagnostic methods leading to final decision about surgical therapy.

Results: Fifty-seven patients had obstructive jaundice and underwent ERCP (81%). In twenty-one (30%) CT did not show the cause of jaundice. Endo-ultrasonography subsequently revealed the actual cause of jaundice in 15 of them. Correlation between preoperative CT and operative and histological findings was seen in 67%, while correlation between EUS and operative and histological findings was observed in 96% of the operated patients.

Conclusion: Ductal cancer of the head of the pancreas usually present with obstructive jaundice. CT diagnosis of tumors classified as T1 often fails. Subsequent EUS in cases of negative CT findings usually significantly contributes to definitive diagnosis and thus leads to indication for surgical treatment. Correlation of preoperative EUS staging is much higher than CT when comparing with the resulting histological findings in our set.
P85B

THE SURGICAL RESECTABILITY FOLLOWING NEOADJUVANT THERAPY IN PANCREATIC HEAD CANCER.

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Background: Surgical radical resection is only curative therapy with potential of prolonged survival. Because pancreatic cancer rarely causes any symptoms early in its development, it is locally advanced in approximately 20-30% and has already metastasized in 50-60% by the time it is diagnosed. The rate of radical resection is 10-20%. Relative one year survival rate is 24% and overall 5 year rate is 5%, .

Patients, material, methods: The authors present their experience with resectability of primarily borderline resectable or unresectable tumors following neoadjuvant radiochemotherapy. Surgical procedure is technically rather difficult due post radiation changes of vascular structure, but it is possible and safe. Sometimes is necessary to plan vascular resection and reconstruction or extention of the procedure to total pancreatectomy. Small set of patients contains five patients (2009-2011), who underwent neoadjuvant radiochemotherapy to achieve the downstaging of the tumor and subsequent resectability. Successful resection was performed in two patients, in two was no response for therapy and last patient is waiting for surgical resection.

Conclusion: Based on studies approximately one-third of initially staged non-resectable tumor patients would be expected to have resectable tumors following neoadjuvant therapy. Survival rate following primary resection is 23.3 months, survival rate following neoadjuvancy and subsequent resection is 20.5 months. For primarily non-resectable patients neoadjuvancy can offer improved prognosis for longer survival. The overall resectability of pancreatic cancer could be increased by 10% approximately.
P86

ENDOSCOPIC TRANSLUMINAL NECROSECTOMY IN INFECTED NECROTIZING PANCREATITIS: A SYSTEMATIC REVIEW

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Introduction: Infected necrotizing pancreatitis almost always requires intervention. Endoscopic transluminal necrosectomy (ETN) is a promising minimal invasive technique. We performed a systematic review of the literature on ETN in (infected) necrotizing pancreatitis.

Methods: We conducted a systematic literature search from January 1980 to October 2011. Inclusion criteria were: 1) cohorts of patients undergoing ETN as primary treatment for (infected) necrotizing pancreatitis; 2) essential outcomes reported: percentage of infected necrosis, number of ETN sessions, complications and mortality. Exclusion criteria were: 1) cohorts <5 patients; 2) cohorts also including sterile necrosis, chronic pancreatitis, ‘pseudocysts’, ‘pancreatic abscesses’ unless results of these subgroups were reported separately. Outcomes were number of ETN procedures, definitive treatment with ETN alone, complications and death.

Results: 11 studies including 401 patients fulfilled the eligibility criteria. Six studies reported on ICU admission before ETN; this occurred in 60/185 patients (32%). Three studies reported on organ failure before ETN, which occurred in 10/34 patients (29%). Average APACHE-II and CTSI scores before ETN varied from 6 to 11 and 4 to 8 respectively. Infected necrosis was present in 216/401 patients (54%). With ETN alone, definitive treatment was achieved in 328/401 patients (82%). On average 4.2 ETN procedures were needed per patient. Complications occurred in 177/401 patients (44%) and 22/401 patients (6%) died.

Conclusion: This systematic review suggest that ETN is a promising treatment in infected necrotizing pancreatitis. However, the number of infected necrosis in these cohorts is relatively low and complication rates are comparable to surgical series.
examination is needed, either by fine-needle aspiration (FNA) or surgical exploration.

**Objectives:** Authors present a case of laparoscopic distal pancreatectomy for an IPAS.

**Patients and methods:** 56-year old man was investigated because of 20 kilogram weight loss within a few months. In addition contrast enhanced CT scan showed a 32x28 mm well-demarcated, heterogenous, enhancing, hypodens mass in the pancreatic tail. No suspicious lymph nodes were detected. Because of unfavourable localisation of the mass CT-guided FNA could not be performed. Possible malignancy could not be excluded therefore laparoscopic exploration was arranged. On the basis of intraoperative histological findings distal pancreas resection with splenectomy was performed.

**Results:** In the postoperative course the patient had fever caused by a fluid collection in the operative site. CT guided percutaneous drainage was performed successfully. The patient was discharged home on the 28th postoperative day. The final histology revealed intrapancreatic accessory spleen. Seven months after surgery the patient is free of complaints.

**Conclusion:** In case of an uncertain intrapancreatic lesion the possibility of an IPAS should be considered. Laparoscopic resection is safe and provides definitive diagnosis. Excellent view of the pancreas, safe and precise handling of the tissues, fast recovery, less postoperative pain was experienced.

**P89**

**FERRITIN AS AN INDEPENDENT MORTALITY PREDICTOR IN PATIENTS WITH PANCREAS CANCER. RESULTS OF A PILOT STUDY.**

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**Introduction:** Prognosis of patients with pancreas cancer is very poor.

**Aims:** The aim of the study was to test the significance of laboratory parameters in the prognosis of patients with pancreas cancer.

**Patients and Methods:** The studied group included 57 patients (31 men, 26 women, mean age 65±9 years). Blood was collected at the time of diagnosis of pancreas cancer and basic laboratory parameters, including nutritional and inflammatory markers and tumour markers were measured. Patients were followed up until death (median survival 147 days).

**Results:** Multivariate Cox regression demonstrated ferritin, iron and albumin as independent mortality predictors (RR(95%CI)), per unit: ferritin 1.001(1.000-1.002), p=0.002, albumin: 0.943(0.892-0.996), p=0.035, iron: 0.936(0.890-0.985), p=0.010). Iron correlated significantly with albumin (r=0.397, p=0.002) but neither iron nor albumin correlated with ferritin. Patients who survived 100 days had significantly lower ferritin (median 239 µg/l vs. non-survivors 435 µg/l, p=0.014), significantly higher albumin but the difference in serum iron was not quite significant. ROC analysis for ferritin revealed AUC for 100 days survival 0.710, p=0.007 (and 0.725, p=0.004 for 200 days survival). AUC for albumin for 100 days survival was not significant (p=0.073).

**Conclusion:** This study points out ferritin as an independent mortality predictor in patients with pancreas cancer. High serum levels of ferritin at the time of diagnosis of pancreas cancer indicate bad prognosis of the patient.

Acknowledgement: Supported by research projects MSM0021620807, MZO00000VFNZ2005 and by grant IGA MZ CR NS 9769-4.

**P90**

**A MULTICENTER, PROSPECTIVE, COMPARATIVE, RANDOMIZED OPEN-TRIAL OF ENDOSCOPIC ULTRASOUND CYTOLOGIC BRUSHING VS FINE-NEEDLE ASPIRATION (FNA) FOR THE PATHOLOGICAL DIAGNOSIS OF CYSTIC PANCREATIC LESIONS.**


Gastroenterology Department, Foundation for Research in Digestive Diseases, University Hospital of Santiago de Compostela. Gastroenterology Department. Hospital Puerta del Mar de Cadiz. Gastroenterology Department. Hospital Morales Meseguer de Murcia. Gastroenterology Department. Hospital La Mancha Centro de Alcázar. Gastroenterology Department. Hospital de Navarra. Gastroenterology Department. University Hospital of Cordoba. Pathology Department. University Hospital of Santiago de Compostela.

Diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) for cystic pancreatic lesions (CPL) is hampered by the low cellularity of samples obtained. A new system (EchoBrush; Cook-Medical) has been developed to improve the quality of the samples.

**AIM:** To evaluate diagnostic accuracy of Echobrush versus FNA for cytopathological diagnosis of CPL.

**METHODS:** Prospective, randomized, multicenter, open and comparative trial of Echobrush versus FNA for the cytological diagnosis of CPL (>15 mm in diameter). Patients were randomized to standard EUS-FNA (group I) or Echobrush (group II). Main outcome was the percentage of correct diagnosis by Echobrush versus FNA. Complication rate was also evaluated. Data were compared by chi-square test.

**RESULTS:** 65 patients (mean age 64 years, range 31-84, 33 male) were included (34 in group-I and 31 in group-II). Three of the patients allocated to group II with the lesion in the head of the pancreas had to be changed to group I since Echobrush was technically unfeasible. CPL mean size was 28.2mm (range 16-60mm). Final diagnosis was IPMN (n=32), serous cystoadenoma (n=10), pseudocyst (n=11), mucinous cystoadenocarcinoma (n=5), pancreatic adenocarcinoma (n=5), Panin lesion (n=1), and inconclusive diagnosis (n=1). A correct diagnosis was achieved in 19/37 cases from group I (50.1%) and in 11/27 cases from group II (40.7%) (p=0.28). There were two mild complications in group I and one in group II (mild bleeding).

**CONCLUSIONS:** The use of Echobrush does not improve the diagnostic accuracy of standard EUS-FNA for the differential diagnosis of CPL.
P91

EVALUATION OF THE NUTRITIONAL STATUS AS A DIAGNOSTIC METHOD FOR PANCREATIC EXOCRINE INSUFFICIENCY (PEI) IN CHRONIC PANCREATITIS (CP).

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Diagnosis of PEI in clinical practice is hindered by complexity and unavailability of appropriate function tests.

Aim of our study was to investigate if PEI in CP can be predicted by the evaluation of serum nutritional markers.

Methods: Retrospective analysis of a prospectively collected database of CP patients. Diagnosis of CP was based on EUS and MRI/MRCP. PEI was diagnosed by the 13C-mixed triglyceride breath test. The association between PEI and hemoglobin, mean corpuscular volume, lymphocytes, prothrombin time, total protein, albumin, prealbumin, retinol binding protein (RBP), cholesterol, triglycerides, amylase, folic acid, vitamin-B12, HbATC, transferrin, ferritin, magnesium and zinc was analyzed by multivariate logistic regression analysis. The probability of PEI according to the number of abnormal parameters was calculated.

Results: 114 consecutive CP patients were included (97 males, mean age 48.1 years, 54 with alcoholic CP). 38 patients (33%) had PEI. Magnesium below 2.05mg/dL, hemoglobin, albumin, prealbumin and RBP below lower limit of normal and HbATC above upper limit of normal were significantly associated with PEI. A direct relation was found between the number of abnormal nutritional parameters (0, 1, 2, 3, or >3) and the probability of PEI (0%, 27%, 50%, 67% and 100%, respectively).

Conclusion: The presence of PEI in patients with CP can be predicted by a standard nutritional evaluation with a negative predictive value of 100% and a positive predictive value that increases together with the number of abnormal nutritional parameters. A direct relation was found between the number of abnormal nutritional parameters (0, 1, 2, 3, or >3) and the probability of PEI (0%, 27%, 50%, 67% and 100%, respectively).

P92

PROBIOTIC PROPHYLAXIS IN PATIENTS WITH PREDICTED SEVERE ACUTE PANCREATITIS WITHOUT ORGAN FAILURE

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Background: We previously demonstrated that probiotic prophylaxis, in patients with predicted severe pancreatitis, did not prevent infectious complications but increased the risk of mortality.

Methods: In a retrospective analysis, all patients with acute pancreatitis admitted to a medium care facility of a teaching hospital in Prague from January 2003 to December 2010 were included. All patients with predicted severe disease without initial organ failure routinely received probiotic prophylaxis. Total parenteral nutrition (TPN) was routinely started and shifted towards total enteral nutrition. Infectious complications, mortality and the incidence of bowel ischemia were recorded.

Results: 99 consecutive patients, mean age 56 years, were included. Infectious complications occurred in 42 patients (42%), consisting of bacteremia (n=40), pneumonia (n=11) and infected necrosis (n=11). Bowel ischemia was detected in two patients (2%) and overall mortality was 8%.

Conclusion: In this retrospective cohort no apparent positive or negative impact of probiotic prophylaxis was demonstrated when administered to patients with predicted severe acute pancreatitis without initial organ failure.

P93

REPEATING TRANSABDOMINAL ULTRASOUND IS A SIMPLE AND ACCURATE STRATEGY TO DIAGNOSE A BILIARY ETIOLOGY IN ACUTE PANCREATITIS PATIENTS


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Background: Gallstones/microlithiasis are the most frequent cause of acute pancreatitis (AP), and can be detected by trans-abdominal Ultrasonography (US). Guidelines suggest to repeat US in patients without identified causes. The accuracy of such repeated US as compared to the first US and to Magnetic Resonance Cholangiopancreatography (MRCP) have not been investigated.

Aim: to evaluate the accuracy of repeated US in detecting biliary AP as compared to the first US, MRCP, ±serum ALT levels>150 UI/L. Material and methods: Unicentre retrospective analysis of consecutive AP patients (2006-2012). Accuracy of tests for biliary AP diagnosis according to the “gold-standard” (final diagnosis based on clinical, biochemical, radiological findings). Comparison between tests by the ROC areas under the curve (AUC).

Results: 155 AP patients: biliary 52%, alcohol 20%, other etiologies 18.3%, idiopathic 9.7 %. 107 (69%) received US at emergency room (US1); 120 (77.5%) repeated US (within 7 days) (US2). MRCP was carried out in 89 patients (57.5%). Accuracy of such repeated US as compared to the first US and to Magnetic Resonance Cholangiopancreatography (MRCP) have not been investigated.

Aim: to evaluate the accuracy of repeated US in detecting biliary AP as compared to the first US, MRCP, ±serum ALT levels>150 UI/L. Material and methods: Unicentre retrospective analysis of consecutive AP patients (2006-2012).

Accuracy of tests for biliary AP diagnosis according to the “gold-standard” (final diagnosis based on clinical, biochemical, radiological findings). Comparison between tests by the ROC areas under the curve (AUC).

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Comparison of the AUC showed a significant difference (0.65% vs 0.70%, p=0.001).

Conclusions: In clinical practice, biliary AP can be diagnosed by repeated US when a first examination is inconclusive. Combination of repeated US and biochemical tests seems a cost-effective approach, while MRCP may be reserved to selected cases, or with likely choledocal obstruction.
P94

SITAGLIPTIN

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Several large clinical studies have confirmed the efficacy and safety of the dipeptidyl peptidase (DPP)-4 inhibitor sitagliptin for the management of type 2 diabetes. Pharmacological inhibition of DPP-4 is an alternate approach to increase circulating concentrations of endogenous active GLP-1 and thus glucose-dependent insulin secretion. Sitagliptin is a new oral glucose-lowering medication that acts via the incretin hormone system. The most common side-effects are headache and pharyngitis. Sitagliptin therapy has been shown to result in increased pancreatic duct replication, acinar to ductal metaplasia and less frequently, acute pancreatitis in a rat model of type 2 diabetes. We report four cases of pancreatitis that developed in patients after between 9 days and 18 months of treatment with sitagliptin and that was attributed to treatment after a thorough search for etiology.

Patients and methods: 2 men and 2 women aged 49 to 67 years (BMI 23 to 33) were admitted for acute pancreatitis 9 days to 18 months after administration of sitagliptin for type 2 diabetes. Balthazar score was 2 points in 3 patients and 3 points in 1 patient. All patients promptly improved after withdrawal of sitagliptin. No reintroduction was done. There was no other risk factor for of pancreatitis (lithiasis, alcohol consumption, metabolic disorder – triglyceridemia or calcemia, or tumour). There was no familial history of pancreatitis but there was no other risk factor for of pancreatitis (lithiasis, alcohol consumption, metabolic disorder – triglyceridemia or calcemia, or tumour).

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Conclusions: Acute pancreatitis in patients receiving sitagliptin seems to be rare but physicians should be aware of this possibility and be cautious about the monitoring of long-term treatment. Underlying genetic alterations (SPINK1, CFTR) may favor pancreatitis.

P95

ASSESSMENT OF THE ACCURACY OF ENDOSCOPIC ULTRASOUND (EUS), EUS CYTOLOGY AND CT COMPARED WITH A GOLD STANDARD IN THE DIAGNOSIS OF PANCREATIC LESIONS.

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Introduction: Histology and malignant cytology are the gold standard for establishing the diagnosis of pancreatic neoplasms. The diagnosis is established using CT and EUS with cytology.

Aim: To assess the accuracy of EUS, CT and EUS cytology in patients with pancreatic lesions undergoing EUS in comparison with the gold standard.

Patients and Methods: Sixty-one consecutive patients undergoing evaluation of pancreatic lesions at a tertiary referral centre were selected over a twelve-month period. Reports were categorized into non-diagnostic, benign, mucinous neoplasms and malignant.

Results: 61 patients were included in the study. 47/61 (77%) had complete data sets for the three modalities. The gold standard was present in 26/59 (44%) patients. 17 patients had malignant lesions, 3 patients had neoplastic mucinous cysts, and benign lesions in 3 patients. Cytology was found to have a sensitivity of 91% and a specificity of 100% with a negative predictive value (NPV) of 50% for non-malignant lesions. The positive predictive value (PPV) for malignant lesions was 100%. EUS was found to be 82.6% sensitive and 50% specific with a NPV of 33% for benign lesions and PPV of 100% for malignant lesions. CT was found to have a specificity of 76% and a specificity of 66% with a PPV of 89% and a NPV of 40%.

Conclusion: Despite the relatively small number of patients in this series, the accuracy of EUS, CT and cytology is consistently high for malignant lesions. However, this is reduced in the event of benign lesions.

P96

SELENIUM DEFICIENCY AND PAIN IN CHRONIC PANCREATITIS

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Introduction: Patients with chronic pancreatitis (CP) are at high risk of antioxidant deficiencies. Pain is a frequent symptom in CP patients and difficult to treat.

Purpose: to determine the feasibility of sodium selenite (SS) in the treatment of patients with CP.

Patients & Methods: 40 patients with CP and 20 healthy subjects (HS) were included into the study. The dynamics of pain on 3-point Likert scale were analyzed in the beginning and every 5th day for 30 days. The content of selenium plasma was studied at the beginning and at the 30th day of study. Patients were divided into two groups. The first group received standard therapy (ST): prifiniy bromide, pantoprazole, pancreatin. The second group was receiving ST and SS 300 µg/ day for 5 days, then 200µg / day for 30 days.

Results: The average selenium plasma of patients with CP was 64,99 ± 3,2 µg/l, which was below the average in the control group 83,3 ± 3,26 µg/l (p <0.001). On the 5th,
INTRODUCTION: Pancreatic cystic lesions evaluation by endoscopic ultrasonography (EUS) (echogenic debris, presence of septae, endocystic projections, central scar, central calcifications and/or calcifications in the tumor wall) and fine needle aspiration (FNA) are methods used for detection of early signs of malignancy.

OBJECTIVES EUS and EUS-FNA diagnostic assessment of high risk pancreatic cystic lesions diagnosed by routine radiological screening methods. METHODS Retrospective single centre study including 203 patients (mean age 68.5 years) with high risk cystic lesions of the pancreas diagnosed by CT, MR, US or EUS. Cysts with suspicious for high malignant potential underwent FNA-cytology. CEA 200-500ng/mL was evaluated as intermediate, more than 500ng/mL was significant for mucinous cystic neoplasms. Patients with solid mass lesions were excluded.

RESULTS: Mean cysts size was 26.4±10.8(6-90)mm. Cystic lesions less than 20mm (n=82), lesions bigger than 20mm (n=121). IPMN type lesions were n=3 (1.5%). EUS-FNA study of the cyst content (n=182); malignant cells (n=28,), inflammatory content (n=73), non-inflammatory content (n=121). IPMN type lesions were n=3 (1.5%). EUS-FNA study of the cyst content (n=182); malignant cells (n=28,), inflammatory content (n=73), non-inflammatory content (n=121). IPMN type lesions were n=3 (1.5%). CEA elevation was obtained in 2% of cases. Comparison to EUS-FNA due to limited technical access. Cytology (n=81). CEA elevation was obtained in 2% of cases. Comparing to EUS-FNA due to limited technical access. Cytology (n=81). CEA elevation was obtained in 2% of cases.

CONCLUSIONS: Diagnostic sensitivity of EUS alone is lower comparing to EUS-FNA due to limited technical access. Cytology alone has poor results (definite diagnosis was made in 15.4% cases). Combined CEA and cytology studies enhanced diagnostic sensitivity comparing each method separately. Majority of included patients with cystic lesions had benign structure. Cystic lesions more than 20mm in size had higher malignancy rate.

Introduction: Pancreatic hypertension and neuroimmune inflammation are the main reasons of severe abdominal pain in cases of chronic pancreatitis (ChP). But routine surgical procedures (Frey, Partington) are successfully not always.

Aims: Basing of new reason of severe chronic abdominal syndrome in patients with ChP and proposal of new surgical approach for it correction.

Patients and methods: During 1990-2011 years we operated on 454 patients with ChP. From 2009 year we performed 12 antegrade double balloon enteroscopy (DBE) examinations of the pancreatiejenoanastomoses «side-to-side» and detected in their lumen in 5 cases residual pancreaticolithes. During last two years in randomized trial we performed 50 Bern procedures added Izbicki resection (in 25 cases) and opened common bile duct (22). 74% of our operations were repeated. For pancreatic head and tail resection we used electrocoagulation (27 cases) and national three-wave infrared impulsive laser (23). We showed during laser resection and lithotripsy, by morphology and postoperative DBE that so called «calcines» really are the peripheral pancreaticolithes which obstructed the tributary ducts. They are the reason of peripheral pancreatic hypertrehension and chronic abdominal pain. Therefore we propose during primary surgery of ChP the laser longitudinal «cylindric» virsungectomy (4 cases).

Results: After laser resections we received: full haemostosis without additional vessels ligation and pancreatiejenoanastomosis leakage, low level of complications (8.7% vs 33.3% after electroresections) and adequate postoperative functional results.

Conclusion: Besides magistral pancreatic hypertension due to the virsungolithes and strictures exist peripheral too because of tributaryductolithes. For their extraction primary cylindric virsungectomy or Izbicki resection in repeated cases are indicated.

P99

INFLUENCE OF PREOPERATIVE BILIARY DRAINAGE ON SURGICAL OUTCOME AFTER PANCREATICODUODENECTOMY

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Introduction: Controversy exists regarding the impact of preoperative biliary drainage on morbidity and mortality rates after pancreaticoduodenectomy.

Aims/Objectives: Aim of the present study was to determine whether preoperative biliary drainage is associated with increased morbidity and mortality rates after pancreaticoduodenectomy.

Patients and Methods: Between February 2005 and December 2010, 131 consecutive cases underwent pancreaticoduodenectomy and were included in a prospective observational study. 29% of patients (38/131) had no jaundice, while 71% (93/131) had jaundice at the diagnosis. Among these jaundiced patients 57% (53/93) underwent preoperative biliary drainage, while 43% (40/93) were not drained.

Results: Perioperative mortality rate was 3% (4/131), while 54% of patients (71/131) experienced complications after surgery. Pre-operative bilirubin serum levels higher that 4.5 mg/dl discriminated patients with complications from those without post-operative complications (sensitivity: 82%, specificity: 52%). The multivariate logistic regression analysis demonstrated preoperative biliary drainage as unique predictor of post-operative complications (OR=8.24, CI95% 3.16-22.54, p<0.01). The frequencies of would infection (p=0.001),
post-pancreatectomy haemorrhage (p<0.05) and delayed gastric emptying (p<0.05) were higher in patients with jaundice drained than in those without jaundice and with jaundice not drained. However, when patients with jaundice drained were compared to those without drainage, associations with would infection and delayed gastric emptying persisted and increased frequencies of pancreatic fistula (p<0.05) and hyperglycemia (p<0.05) were also observed.

Conclusions: With the exception of the classical indications such as cholangitis or scheduled surgical delay for more than 2 weeks, preoperative biliary drainage should be carefully evaluated in patients with potentially resectable pancreatic and peripancreatic lesions

P101
THE FIRST HEREDITARY PANCREATITIS FAMILY IN HUNGARY
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INTRODUCTION: Determination of the etiology of recurrent acute pancreatitis is often difficult.

CASE DESCRIPTION: A fourteen-year-old girl had had acute pancreatitis on ten occasions, the first episode occurring at the age of four years, with subsequent recurrences at six to nine-month intervals apart from a four-year-long silent period at the age of six years. The pancreatitis was edematous in all cases, but on two occasions intensive care was needed. A viral infection was suspected in the etiology, but the laboratory and morphological work-up did not identify any etiological factor (e.g. bile stone, dietary abuse, anatomical malformations, hyperlipidemia, cystic fibrosis or autoimmune pancreatitis) either then or later. After the third recurrence, the abdominal MRI indicated chronic pancreatitis, while ERCP following the fifth attack demonstrated changes in the caliber of the main pancreatic duct. Genetic examination revealed heterozygous mutation R122H in the cationic trypsinogen gene (PRSS1 gene) either then or later. After the third recurrence, the abdominal MRI indicated chronic pancreatitis, while ERCP following the fifth attack demonstrated changes in the caliber of the main pancreatic duct. Genetic examination revealed heterozygous mutation R122H in the cationic trypsinogen gene (PRSS1 gene) either then or later. After the third recurrence, the abdominal MRI indicated chronic pancreatitis, while ERCP following the fifth attack demonstrated changes in the caliber of the main pancreatic duct. Genetic examination revealed heterozygous mutation R122H in the cationic trypsinogen gene (PRSS1 gene) either then or later.

DISCUSSION: Hereditary pancreatitis is an autosomal dominant condition where recurrent attacks of acute pancreatitis lead to chronic pancreatitis. In most of the cases, the causative factor is a point mutation in the cationic trypsinogen gene, which results in the enhanced activation of trypsin. Acute and particularly recurrent pancreatitis at a young age should suggest the possible role of genetic factors, even if the family history is not typical.

P102
GEPATOPANCREATIC DYSFUNCTION IN PATIENTS WITH METABOLIC SYNDROME
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Objective: To study the impact of the state of the liver and pancreas on the course of metabolic syndrome (MS) and hormone-metabolic status of patients.

Methods: In 32 patients (men 45-59 years) with grade 1 obesity (BMI 32.2 ± 2.1 kg/m²) with MS by criteria IDF (2007), grade 1-2 hypertension and the control group (n = 10).

Methods: In 32 patients (men 45-59 years) with grade 1 obesity (BMI 32.2 ± 2.1 kg/m²) with MS by criteria IDF (2007), grade 1-2 hypertension and the control group (n = 10). Investigation: echosonography, coprogram, elastase-1 in feces, CRP, fibrinogen, cholesterol, HDL, LDL, VLDL, triglycerides, FFA, malondialdehyde (MDA), indicators of hormonal balance (insulin, HOMA-IR, cortisol, growth hormone, TSH, prolactin), cytokines (IL-6, TNF-α).

Results: The presence of markers of insulin resistance (IR) were accompanied by a significant increase in HOMA-IR, sonographic signs of nonalcoholic hepatic steatosis. Sonography was determined by increasing the size and echogenicity of the pancreas. Changes coprogram detected in 52.6%. Elastase-1 in feces was significantly reduced relative to control (180.7 ± 16.2 mg / g, p <0.05). Such changes have described as a phenomenon hepatopancreatic dysfunction (GPD). GPD was accompanied by a lack of antiatherogenic and the accumulation of atherogenic fractions. IR was shown against a background of pronounced hormonal imbalance: with a hypercortisolemia, with an increase in TSH, with hyperprolactinemia and growth hormone levels decline. Hyperglycemia is accompanied by increased levels of MDA. GPD was accompanied by increased levels of proinflammatory cytokines in the serum, CRP and fibrinogen.

Conclusions: Hepatic steatosis and steatosis pancreas accompany MS with grade 1 obesity. GPD is accompanied by the presence of atherogenic hyperglycemia, increased levels of proinflammatory cytokines, activation of lipid peroxidation to the damage of hormone-metabolic status.

P103
LAPAROSCOPIC DISTAL PANCREATIC RESECTION: IS THERE A LEARNING CURVE?
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Introduction: Laparoscopic distal pancreatic resections (LDPR) are more and more performed. The impact of the learning curve is not well known. Our aim was to study the results of LDPR during 2 consecutive periods.

Methods: From a prospective unicentric maintained database, 55 patients who underwent LDPR between January 2008 and December 2011 were included and divided in 2 periods, including period 1 (January 2008-decembre 2009; n=20) and period 2 (January 2010-decembre 2011; n=35). Age, sex, body mass index (BMI), indication, operative (duration, blood loss, conversion, hand-assisted, necessity of sacrifice of the spleen or its vessels) and postoperative data (mortality, pancreatic fistula [PF], re intervention, mean hospital stay) were studied. No difference between periods 1 vs 2 regarding age (51 vs 56; p=0.12), sex (F/M = 14/6 vs 17/18. p=0.12), BMI (24.8 vs 26.3 kg/m²; p=0.48).

Results: Comparison of Periods 1 vs 2 showed less resections for adenocarcinoma (5% vs 20%; p=0.129), more blood loss (256 ml vs 215 ml; p=0.63), longer duration (254 mn vs 172 mn, p<0.001), more conversion (15% vs 8.6%; p=0.46), less hand-assisted (0% vs 17.1%; p=0.021%) and re interventions (10% vs 0%; p=0.05). In the subgroup of patients scheduled for pancreatectomy without splenectomy (n=33), we note higher rate of splenectomy (21.4% vs 0%. p=0.025) but no significant difference regarding the sacrifice of splenic vessels (28.5% vs 43.3%, p=0.53). No difference was regarding mortality (0%), PF rate (70% vs 62.9%; p=0.87) and the hospital stay (24 [8-70] vs 18 [10-34], p=0.11).

Conclusions: There is probably a learning curve allowing more rapid and safer resection with little impact on the postoperative course. The lower conversion and unnecessary splenectomies rate can be explained by the learning curve, the hand assisted procedure and the sacrifice of the splenic vessels.
**P104**

**METASTATIC PATTERN DIFFERENTLY AFFECTS PROGRESSION-FREE SURVIVAL IN Pancreatic Neuroendocrine Tumors**

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**Introduction:** Pancreatic neuroendocrine tumors (PNETs) are advanced in 60% of cases since diagnosis. Little is known about prognosis of these patients according to different site and number of metastases.

**Objectives:** Our aim was to investigate progression-free survival (PFS) and risk factors for progression in advanced PNETs according to metastatic pattern.

**Patients and Methods:** Sporadic PNETs, metastatic at diagnosis, seen between 1995 and 2009 were divided in 3 groups according to different metastatic pattern: 1) only unilobar liver metastases; 2) only bilobar liver metastases; 3) extra-abdominal metastases. PFS and risk analysis were assessed by Kaplan-Meier and Cox-proportional hazards regression model.

**Results:** 135 consecutive patients were included: 8.9% were classified in group 1, 84.4% n group 2 and 6.7% in group 3. Median Ki67 was 7% (range 1%-95%). Median PFS was 13 months. Different PFS was observed for: G grading (P<0.001; 5-yr PFS G1/G2/G3: 18.9%/18.4%/not reached) and metastatic pattern (P= 0.05; 5-yr survival group 1/2/3: 25.4%/18.4%/11.1%). Significant risk factors were: Ki67 (for each increasing unit: HR 1.03; P<0.001), metastatic pattern (HR 1.80; P= 0.02), G Grading (HR: 2.22; P<0.001). At multivariate analysis, prognostic factors for progression were both Ki67 (HR 1.03, P<0.001) and metastatic pattern (HR 1.79; P= 0.02).

**Conclusion:** In patients affected by metastatic PNETs, Ki67 and metastatic pattern are two independent risk factors for disease progression.

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**P105**

**BRANCH DUCT INTRADUCTAL PAPILLARY-MUCINOUS NEOPLASIA: THIN RED LINE WALKING BETWEEN SURGERY AND SURVEILLANCE**

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**Introduction:** Performing pancreatic resection on surveillance in patients affected by branch duct intraductal papillary mucinous neoplasms (BD-IPMN) is mainly based on radiological features.

**Aim:** To identify whether different subgroups of BD-IPMN display a characteristic clinical behavior and to investigate clinical and radiologic predictors of dysplasia/invasiveness.

**Patients and Methods:** 52 specimens of resected BD-IPMN were reviewed by a pathologist. A correlation between histologic subtypes (gastric, intestinal, pancreatobiliary and oncocytic) and degree of dysplasia (mild, moderate, severe dysplasia and invasive carcinoma) was made. Histologic subtypes were dichotomized into gastric and non-gastric, and the degrees of dysplasia into adenosomas and borderline-to-invasive IPMN. Symptoms, tumor markers and magnetic resonance cholangiopancreatography (MRCP) features were correlated with pathological findings.

**Results:** A non-gastric subtype was associated with borderline-to-invasive BD-IPMN (p<0.01). Adenomas arose only from the gastric subtype, in borderline-to-invasive BD-IPMN arisen from a gastric epithelium a correlation with tumor diameter (>3cm) was found. A dilated main pancreatic duct, the presence of mural nodules and thickness of the cystic wall on MRPC were associated with borderline-to-invasive BD-IPMN (p<0.01). The dilation of the main pancreatic duct (MPD) is highly correlated to the risk of degeneration at the multivariate analysis (p< 0.05).

**Conclusion:** BD-IPMNs encompass a group of neoplasms with different biological behaviors. Gastric type IPMNs show a more indolent behavior and the risk of malignancy increases with the diameter. We confirm the role played by the radiological features as predictors of malignancy. The dilation of the MPD is highly related to the risk of degeneration.

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**P106**

**HIGH INCIDENCE OF Pancreatic CANCER IN PATIENTS WITH AUTOIMMUNE PANCREATITIS UNDERGOING SURGERY**

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**Introduction:** Autoimmune pancreatitis (AIP) is a rare disease that may present with signs and symptoms mimicking pancreatic cancer. AIP is characterized by a dramatic response to corticosteroid therapy. Thus, patients diagnosed with AIP can avoid surgery and undergo immunosuppressive treatment. Only a few cases of pancreatic cancer in AIP patients have so far been reported worldwide.

**Methods:** We performed a retrospective analysis of data of all patients who underwent pancreatic resection in our department for suspected cancer/focal pancreatic enlargement.

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**44th European Pancreatic Club (EPC) Meeting**

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Results: Two hundred and twenty pancreatic resections were performed in 153 males and 67 females (mean age 59 years, range 36-72 years). Indication for surgery was tumor suspicion based on clinical symptoms, imaging methods and laboratory findings. In 14 patients (6.4%, 9 males, 5 females), autoimmune pancreatitis was diagnosed based on histology of the resected specimen. In 5 patients, abundant IgG4 cells were present. In 3 AIP patients (21.4%, all males, one IgG4 positive), pancreatic adenocarcinoma was also present in the resected tissue. No differences were observed in the preoperative characteristics of patients with and without cancer (CT, EUS, ERCP, bile duct involvement, laboratory findings including CA 19-9). In none of the patients the diagnosis of AIP was made prior to surgery; however the diagnostic algorithm was not fully completed.

Conclusions: AIP patients may develop pancreatic cancer. Thus, the preoperative diagnosis of autoimmune pancreatitis in patients with focal pancreatic enlargement may not always rule out the simultaneous presence of cancer.

P107
RELAPSE OF AUTOIMMUNE PANCREATITIS FOLLOWING SURGERY: A CASE REPORT

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Introduction: Autoimmune pancreatitis (AIP) may have various presentations including pancreatic enlargement, recurrent pancreatitis or chronic abdominal pain. Because it is difficult to distinguish between AIP and cancer, patients often undergo surgery where the definitive diagnosis is made. It is unknown whether patients who enter complete clinical remission following partial pancreatic resection should be treated with corticosteroids.

Case report: A 45-year-old woman presented with mild chronic abdominal pain. She had an 18 mm focal mass in the pancreatic tail on CT with a corresponding pancreatic duct stricture on ERCP. Laboratory findings were not suggestive of AIP. She underwent a pancreatic tail resection with splenectomy. On histology, periductal lymphoplasmacytic infiltrate with fibrosis and phlebitis diagnostic of AIP type 2 were present. IgG4 serology and staining were negative. Because surgery resulted in patient’s clinical remission (symptomatic and radiologic remission), no further treatment was initiated. As a complication of surgery, the patient developed a pancreatic cutaneous fistula which further developed into a colocolutaneous fistula that was treated by a temporary diverting ileostomy. Eighteen months after the initial surgery, she experienced a relapse in the remaining pancreas. She presented with an attack of severe acute pancreatitis, pancreatic head enlargement and bile duct stenosis which all resolved on supportive and corticosteroid treatment.

Conclusions: The presented case describes a severe relapse of AIP following distal pancreatectomy. It remains speculative whether the latter presentation may have been prevented by earlier immunosuppressive treatment during the asymptomatic course of the disease.

P108
IMPLEMENTATION OF NO-TOUCH PANCREATICODEOUDENECTOMY (PD). SINGLE CENTER 3-YEAR EXPERIENCE.

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Introduction: The long-term results of pancreatic tumors resections are disappointing. In order to increase postoperative survival after resections by surgical control of liver metastasis and peritoneal dissemination no-touch techniques of PD were proposed.

Methods: We investigated the results of no-touch PD for malignant periamillary tumors in 31 patients, treated in our clinic in the period of November 2008-2011 years. In 14 patients tumors of papilla of Vater (PV) were diagnosed, in 12 - tumors of the pancreas, 1 - neuroendocrine tumor, in 3 patients- tumors of bile ducts (BD), 1 – gastrointestinal stromal tumor (GIST) of the duodenum. In 19 patients pylorus-preserving PD were done, in 12- standard PD. In 3 patients additional resections of the affected portal or superior mesenteric vein were done.

Results: Duration of the operation was 440,4 + 77,4 minutes (from 340 to 745). Mean blood loss was 575,0 + 320,1 ml (from minimal to 1800). Morbidity was 22,6% (7 patients). Mortality was zero.

Median survival in the group of BD cancer patients was 21,5 month. 1- and 2-year survival in pancreatic cancer patients was 63,5%, maximal follow-up- 26 months. 1- and 2-year survival for PV cancer patients was 100%, 3-year survival- 85,7%, disease free 3-year survival- 57,1%. Patient with GIST is alive 34 months after procedure with metastatic disease from second postoperative year. Patient with neuroendocrine tumor is alive without metastatic disease 26 months after operation. Further investigations should be done to evaluate potential benefit of the procedure.

P109
WHO-2010 AND WHO-2000 CLASSIFICATIONS FOR PANCREATIC ENDOCRINE TUMORS. IS IT TIME TO CHANGE?

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Background: In 2010 WHO released a new classification system for pancreatic endocrine tumours (PETs).

Aim: To compare WHO-2010 with WHO-2000 classification in patients affected by PETs, underwent surgery.

Patients and Methods: From January 1980 to December 2011, 89 consecutives patients who underwent surgical operation for PETs were prospectively collected. Data regarding sex, age, presence of symptoms, hormonal status, presence of MEN1, surgical procedure, R status, TNM stage, WHO-2000 and WHO-2010 classifications were related to disease specific survival(OSS). Multivariate analysis, was carried out to evaluate the independent factors related to disease specific survival. A sensitivity analysis was
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performed to include patients in which WHO-2010 was impossible to be calculated.

**Results:** Mean age of patients was 54.7 ± 14.2 years. There were 46 (51.7%) female and 43 (48.3%) male. Symptoms were present in 68 (76.4%) patients. Fifty-two (58.4%) patients had non-functioning PETS. Left pancreatectomy was performed in 48 (53.9%) cases, atypical resection in 22 (24.7%), pancreaticoduodenectomy in 12 (13.5%), total pancreatectomy in 2 (2.2%) and palliative surgery in 5 (5.6%). R0/1 resection was carried out in 79 (88.7%) cases. According TNM stage there were: I, 27 (30.3%); II 29 (32.6%); III, 22 (24.7%); IV, 11 (12.4%). According WHO-2000, 46 (51.7%) patients had a well differentiated tumours (WDT), 32 (36%) well differentiated carcinoma (WDCa), 11 (12.4%) poorly differentiated carcinoma (PDCa). The WHO-2010 was available only in 49 (55.1%) patients: 20 (22.5%) neuroendocrine tumors (NET) grade 1 (G1), 25 (28.1%) NET, grade 2 (G2), 4 (4.5%) neuroendocrine carcinomas (NEC), grade 3 (G3). At multivariate analysis WHO-2000 and R2 status were the independent factors related to DSS (RR=6.7, P<0.001 and RR 2.0, P=0.018 respectively). WHO-2000 stratifies DSS better than WHO-2010: RR 0.12 (C.I 95% 0.01-0.99; P=0.049) and RR 0.16 (C.I 95% 0.16-0.05; P=0.002) comparing WDT vs WDCa and WDCa vs PDCa, respectively. The sensitivity analysis confirmed in two model the superiority of WHO-2000 while in others two we did not find any difference.

**Conclusion:** In our experience, WHO-2000 represents a valid and good prognostic factor to predict DSS in patients with PETS. To establish if WHO-2010 is better than WHO-2000 are necessary further multicentric studies.

**P110 USEFUL OF CHOI’S CRITERIA AFTER NEOADJUVANT CHEMORADIOOTHERAPY IN PATIENTS WITH RESECTABLE Pancreatic CANCER.**

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**Background:** Assessement of response after neoadjuvant therapy for solid tumours is usually based on RECIST criteria. In 2007 Choi et al. (1) proposed a new classification system for restaging tumors after neoadjuvant therapy.

**Aim:** To evaluate the accuracy of the two classifications system in predicting pathological response to neoadjuvant therapies in patients with resectable pancreatic cancer.

**Patients and Methods:** Patients affected by resectable pancreatic cancer who underwent neoadjuvant therapy (gemcitabine plus radiotherapy), within a randomized study comparing chemoradiotherapy plus surgery vs surgery alone, were collected. Radiological response after neoadjuvant therapy was assessed applying RECIST and Choi’s criteria. The accuracy of each classifications system was evaluated comparing radiological with pathological data according AJCC. A statistical analysis was made with Kendall’s concordance test.

**Results:** From 2008 to 2011, 13 patients were enrolled in neoadjuvant arm: restaging was performed in 12 patients, because one died during neoadjuvant therapy. Using RECIST criteria,10 (83.2 %) patients had stable disease and 2 (16.8 %) had a progression of the disease with liver metastases. Choi’s criteria assessed: 5 (41.6 %) partial responses, 5 (41.6%) stable diseases and 2 (16.8%) progressive disease. Ten patients were considered resectable but 2 (25%) underwent palliative surgery for locally advanced neoplasm, intraoperatively found.

For 8 patients undergone resection the pathologic examination showed 2 cases (25 %) of minimal response and 6 (75 %) moderate response. All patients who did not resected were considered as poor response (n=4).

Comparing concordance between each classification with intraoperative and pathological findings, we found a significative concordance for Choi’s criteria (p=0.022) while RECIST criteria did not show any correlation (p=0.061).

**Conclusion:** In our experience, Choi’s criteria seems to predict pathological response after neoadjuvant therapy in patients with resectable pancreatic cancer better than RECIST. Due to the small number of patients, larger prospective studies are needed.

**P111 BISAP SCORE AND PROCALCITONIN VERSUS APACHE II SCORE AND C-REACTIVE PROTEIN IN EARLY ASSESSMENT OF THE SEVERITY AND OUTCOME OF ACUTE PancreatITIS**

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**Aims/Objectives:** Early assessment of the severity and continuous patients monitoring are key factors for the adequate treatment of acute pancreatitis (AP). The objective was to determine the value of BISAP score and procalcitonin (PCT) as prognostic markers in early stages of AP with comparison to “Acute physiology and chronic health evaluation” (APACHE II) score and C-reactive protein (CRP).

**Patients and Methods:** Prospective study included 51 patients (29 with severe AP). In the first 24 h of admission the APACHE II and BISAP score, CRP and PCT serum concentrations were determined. The values of PCT serum concentrations and BISAP score were compared with values of CRP serum concentrations and APACHE II score, in relation to disease severity and outcome.

**Results:** Values of PCT, CRP, BISAP score and APACHE II score were significantly elevated in patients with severe AP. In predicting the severity of AP at 24 h of admission, sensitivity and specificity of BISAP score were (74%; 59%), APACHE II score (89%; 69%), CRP (75%; 86%) and PCT (86%; 63%). The strength to predict severe AP with accuracy, APACHE II score was significantly stronger than BISAP score (Z=2.738, p=0.006). PCT was significantly elevated in patients with fatal outcome (p<0,001).

**Conclusion:** In early prediction of AP severity, PCT has better predictive value than CRP, and similar to APACHE II score. PCT is better predictor of fatal outcome than CRP, BISAP score and APACHE II score. APACHE II score is a better predictor of disease severity than BISAP score, but similar to BISAP score in prediction of fatal outcome.

**Key words:** acute pancreatitis; procalcitonin; scoring system; severity; outcome

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**P112**

**A SPECIFIC DIAGNOSTIC WORK-OUT HAS A HIGH DIAGNOSTIC RATE IN PATIENTS WITH CHRONIC ASYMPTOMATIC PANCREATIC HYPERENZYMENIA**


**Background and Aim:** Chronic asymptomatic pancreatic hyperenzymenemia (CAPH) is defined as an abnormal fluctuating increase in serum pancreatic enzymes without symptoms or defined pancreatic disease. In such cases the pancreatic parenchyma and ductal system need to be carefully. CAPH has also been reported in celiac disease (CD) patients, but the rate of CD in CAPH is unclear.

We therefore aimed at analyzing the rate of pancreatic disorders and CD in subjects with CAPH.

**Methods:** All subjects with CAPH defined as asymptomatic increase in pancreatic enzymes for at least 12 months and a negative US seen at our Centre (2008-2011) were offered a specific diagnostic work-out including sCPRM and CD screening.

**Results:** 24 subjects (16 male; median age 52) with a median 35.5 months-follow-up enrolled. 8 patients (33.3%) presented with isolated hyperamylasemia, 2 (8.3%) isolated hyperlipasemia, 14 (58.3%) both. 19 patients underwent sCPRM (2 refused the examination, 3 excluded due to prosthesis/claustrophobia). Significant findings diagnosed in 52% including BD-IPMN in 2 (10%), pancreas divisum in 5 (26%), 1 chronic pancreatitis (5.2%), and 2 specific abnormalities of the ductal system (10.5%). CD was diagnosed in 1/25 (4%) patients, who also had CP. Diagnostic rate was not related with fold of enzyme elevation, nor with the increase of either of the 2 pancreatic enzymes.

**Conclusions:** Pancreatic ductal system abnormalities are common in CAPH patients, including IPMN, CP and pancreas divisum. The rate of CD seems higher than expected. S-MRPC and screening for CD should be proposed to patients with CAPH.

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**P113**

**MINOR PAPILLA SPHINCTEROTOMY IS AN EFFECTIVE THERAPY IN RECURRENT PANCREATITIS DUE TO SANTORINICELE: EXPERIENCE OF A SINGLE CENTRE.**

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**Background:** Santorinicele is a focal cystic dilatation of the terminal portion of the dorsal pancreatic duct at the minor papilla in patients with pancreas divisum that results from a combination of a weakness of the duodenal wall and a minor papilla obstruction that prevents the outflow of pancreatic juice causing recurrent pancreatitis. Pancreatic sphincterotomy could relieve obstruction, facilitating the outflow of the pancreatic juice throw the papilla reducing pancreatitis recurrences.

**Aim:** evaluate the clinical outcome of patients affected by Santorinicele after endoscopic treatment for reduction of acute pancreatitis frequency.

**Patients and Methods:** From December 2008 to June 2011 12 patients (4 male and 8 females, mean age of 57.83 ± 13.69 years) with symptomatic Santorinicele (recurrent pancreatitis), were diagnosed by MRCP with secretin stimulation. 10 patients underwent to pancreatic sphyncterotomy of minor papilla.: 9 de novo sphincterotomy and 1 re-sphincterotomy were performed. In 2 patients cannulation of the minor papilla was unsuccessfully due to not recognition of the minor papilla. Time interval between the onset of symptoms and endoscopic treatment was 6.3 ± 7.39 years. Injection of secretin during endoscopic examination facilitate recognition of minor papilla. Minor papilla sphincterotomy was performed using a standard minor papilla sphincterotome; prophylactic pancreatic stent was not routinely inserted (6 patients: 7Fr 5 cm stent; 1 patient: nasopancreatic drainage).

**Results:** mean follow-up after endoscopic treatment was 11.5 ± 8.8 months. Mortality of procedure was 0% and morbidity 16.6% (1 case of mild acute pancreatitis and one case of retroperitoneal perforation). There were no episodes of recurrent pancreatitis. Three patients undergone MRCP follow-up with secretin stimulation with a complete normalization of morphological and functional test.

**Conclusion:** minor papilla sphincterotomy is a successful therapy in patients with recurrent pancreatitis due to Santorinicele

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**P114**

**PRELIMINARY RESULTS OF PANCREATIC SPHINCTEROTOMY AS TREATMENT OF SYMPTOMATIC IPMN**

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**Background:** recurrent pancreatitis can be presenting symptoms of intraductal papillary mucinous neoplasm (IPMN) caused by a transient papillary obstruction by mucus. In main duct IPMN (MD-IPMN) surgical treatment is indicated for the high risk of neoplastic evolution; in side branch-IPMN (SB-IPMN) surgery is suggested only in symptomatic patients. In patients with MD-IPMN unfit for surgery or in symptomatic SB-IPMN without radiological evidence of malignancy (tumor diameter < 30mm, mural nodules, dilated main pancreatic duct or positive cytology) pancreatic sphincterotomy (PS) can be considered as an alternative treatment to reduce attacks of acute pancreatitis by facilitating drainage of mucus through the papilla.

**Aim:** reduce the frequency of acute pancreatitis attacks performing PS in patients affected by symptomatic SB-IPMN without radiological evidence of malignancy or in patients with MD-IPMN unfit for surgery.

**Patients and Methods:** from October 2010 to June 2011, 6 patients (3 male, mean age 53 ± 14,23years) with IPMN (2 with mixed form: MD + SB-IPMN and 4 with SB-IPMN) diagnosed by MRCP with secretin stimulaton underwent PS. Pancreas divisum was diagnosed in 1 patient. In 5 patients IPMN was localized in the head of the pancreas whereas 1 patient was affected by mixed-IPMN haed and body. Mean diameter of cystic lesions was 18,8 ± 10,64 mm. All patients were symptomatic for acute pancreatitis: 5 cases mild acute pancreatitis and 1 case severe acute pancreatitis.

**Results:** in 5 out of six patients pancreaticography showed cystic lesions communicating with main pancreatic duct and confirmed pancreas divisum in 1; in one case with mixed type-IPMN visualization of cystic lesion localized in the body was not obtained. Six PS were performed (5 major papilla and 1 minor papilla). Mucus go out after sphincterotomy in only 2 cases (mixed-IPMN). Mortality of procedure was 0% and morbidity was 16% (one patient presented self-limiting bleeding post-ERCP, 5 days after sphincterotomy).
**P115**

**RANSON SCORE AND PANCREATITIS ASSOCIATED PROTEIN IN ACUTE BILIARY PANCREATITIS. PRELIMINARY STUDY**

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**Introduction:** Acute pancreatitis (AP) is a severe inflammatory process with autodigestion of the pancreas. The main etiology is biliary, named Acute Biliary Pancreatitis (ABP). During this process, inflammatory markers such as C-reactive protein (hsCRP) and pancreatitis associated protein (PAP) are released. PAP is not detected in the healthy pancreas and is over-expressed during AP. Ranson score has clinical use for evaluation of severity.

**Aim:** was determine the association between these markers and their clinical implication

**Materials-Methods:** We studied 28 patients classified in:

- **Controls:** patients with non-pancreatic digestive disease (n=11, age:59±13 years, ratio:3 males/8 females); and
- **ABP:** patients with AP (n=17, age:69±17 years, ratio:7 males/10 females). For each one of them, biochemical parameters of pancreatitis evaluation were determined (amylase, lipase, glycemia and insulinemia) as well as biochemical parameters of an inflammatory process (hsCRP and PAP). In ABP group, according to sex, biochemical parameters of hepatobiliary component and Ranson score were also determined.

**Results:** Correlation studies between different biochemical parameters indicated a direct association between AP and its biliary etiology. No correlation was observed with inflammatory parameters, except an association between PAP and Ranson Score (P < 0.0001). We observed that 53% of ABP patients presented mild AP (Ranson ≤ 2) and 47% presented severe AP (Ranson > 3). Male patients presented Ranson Score values of 1 and 2 y female patients, of 2 and 4. 80% of the female patients presented severe AP with PAP significantly increased, indicating a much more severe AP.

**Conclusion:** In this preliminary study demonstrated the existence of a direct association between Ranson Score, PAP serum concentration and AP severity.

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**P116**

**AN AUDIT OF TIME TO DEFINITIVE MANAGEMENT IN GALLSTONE PANCREATITIS**

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**Introduction:** The British Society of Gastroenterology (BSG) recommends that cases of acute pancreatitis secondary to gallstones should undergo definitive management of the gallstones during the acute inpatient episode or within two weeks of discharge.

**Aims/objectives:** This aims of this audit were to assess the time taken from presentation to cholecystectomy in patients presenting with gallstone pancreatitis at a District General Hospital, and to identify any morbidity and mortality that resulted from a delay in treatment beyond two weeks.

**Patients and Methods:** All cases of gallstone pancreatitis from October 2010-December 2011 were included. The length of time from admission to cholecystectomy in each case was noted. Readmissions and morbidity as a result of delay were recorded.

**Results:** There were 24 patients (15 women (63%); age 50 (22-89)) with confirmed gallstone pancreatitis. Two (8%) underwent definitive management within two weeks or during acute admission (one ERCP and sphincterotomy, one cholecystectomy). 14 (58%) were listed for surgery. Mean time from admission to surgery was 132 days (10-396). 8 are awaiting or died whilst awaiting surgery (1 unrelated to gallstones). Those patients awaiting surgery have already had a mean wait of 127 days (39-199). There were 8 related readmissions amongst 7 patients (29%); 5 with acute pancreatitis.

**Conclusion:** This audit demonstrates a marked discrepancy between evidence based guidelines and current practice within an UK institution. If this is representative of practice throughout the UK, then it should act as a motivational trigger for developing a robust and effective solution.
the patients with severe acute pancreatitis as compared with the healthy controls (38% vs 20%, and 41% vs 18% respectively). The GG protective genotype of C-44G SNP was much less frequent (1%) among the patients than among the controls (9%). A higher frequency of a lower (-4) copy number of the DEF84 gene was observed in the patients with severe acute pancreatitis than in the healthy controls (62% vs 24% respectively).

Conclusions: The genetic variations in the genes encoding the human β-defensin 1 and that of human β-defensin 2 may be associated with the risk of severe acute pancreatitis.

P118
MINIMALLY INVASIVE TREATMENT OF POSTNECROTIC PANCREATIC CYSTS UNDER ULTRASOUND GUIDANCE
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Percutaneous puncture draining of 156 postnecrotic cysts of the pancreas were performed. The intervention was performed under continuous ultrasound guidance via a safe acoustic window; during the installation of drainage, assessment of the cyst’s standing, adequacy of drainage and the absence of leakage into the peritoneal cavity the energetic Doppler mode was used. In 5 cases, the absence of safe acoustic window draining was performed through the stomach. The optimum implementation of the intervention was considered on 3-4 clinical stage of maturation of the cyst, with the need to implement interventions at earlier stages were used a drainage-systems with larger diameter. The adequacy of the drainage standing was assessed by CT fistulography. Microbiological research of cysts content were performed. Considered mandatory drug therapy to prevent recurrence and complications after the intervention, including adequate analgesia, correction of pancreatic insufficiency, proton pump inhibitors, and early nutrition.

Duration of drainage standing ranged from 4 to 25 days. In all cases the clinical effect was achieved in the form of improved physical condition of the patient, reducing the size of the cystic cavity until its complete reduction. The complications observed: pain, which required relief, in 5 patients, perforitosis in 1 case. In such a way percutaneous drainage is the method of choice in the treatment of postnecrotic pancreatic cysts. The optimum is a continuous ultrasound guidance using the Doppler mode; CT has advantages in the assessment of drainage standing. This approach avoids the open and endoscopic surgery and improve outcomes in patients with pancreatic cysts.

P118A
ENHANCED RECOVERY AFTER SURGERY IN PANCREATIC SURGERY: PRELIMINARY DATA ON SAFETY AND ADHERENCE FOR NEW PATHWAYS.
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INTRODUCTION: In recent years different surgical specialties benefited from the application of Enhanced recovery after surgery (ERAS) programmes, improving postoperative rehabilitation and reducing morbidity, its role for pancreatic surgery is still controversial and data on its application are few.

AIMS: To test safety and feasibility of an ERAS pathway for patients undergoing pancreatectoduodenectomy (PD) and left pancreatectomy (LP).

METHODS: From October 2010 to December 2011, 113 consecutive patients undergoing PD (n=66) and LP (n=47, laparoscopic 57%) were treated with a multimodal, inter-disciplinary, perioperative ERAS pathway. Items implemented were: preadmission counselling, no preoperative bowel preparation, and intraoperative iv fluid restriction (5 ml/kg/hr), PONV and hypothermia prophylaxis, no NG tube, early mobilization, solid food diet on POD1, early stop of iv infusions.

RESULTS: Adherence on its pathway. Preadmission counselling 72%. Epidural analgesia 95% for PD and 85% for LP. PD patients mobilized on POD1 51% (median 80 minutes), on POD2 95%. Median day for solid diet intake was POD3[1] with iv infusions stopped on POD4[2]; only 6% of pts needed repositioning of a NGT.
LP patients mobilized on POD1 72% (median 75 minutes), on POD2 94%. Median day of solid diet intake was POD2[1] and iv infusions stopped on POD3[1]. Surgical outcome: major complications % in PD and 6% in LP, and mortality 4% and 0%, DGE occurred in 10% of PD patients. Readmission rate was 8%(PD) and 14%(LP). Postoperative LOS was 10[3] days for PD and 7[2] days for LP.

CONCLUSION: ERAS protocols proved to be safe with no increase in morbidity and readmission rate. Adherence to preoperative and intraoperative was high. Compliance with postoperative items had suboptimal results. Data on length of stay are encouraging.

P118B
A NEW MINIMALLY INVASIVE TECHNIQUE FOR BENIGN NEOPLASM OF THE PANCREATIC BODY: LAPAROSCOPIC SPLEEN-PRESERVING DISTAL PANCREATECTOMY WITH AUTOLOGOUS ISLET TRANSPLANTATION (AIT).
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Introduction: Benign pancreatic tumours can require resection for the risk of malignant transformation. When the neoplasm is located in the neck region, an extended left pancreatectomy is indicated, but such operation is associated with the risk of diabetes. Autotransplantation of islets obtained by processing the parenchyma distal to the neoplasm, can prevent this event. The association of AIT, laparoscopy and spleen preservation can minimize all the possible consequences of surgery.

Methods: Three non-diabetic, female patients (age 37-44) were candidate to surgery because of pancreatic cystic lesions between May and September 2011. The lesions were located at the body/neck of the pancreas and measured 3, 4 and 10 cm, respectively. Patients underwent laparoscopic left pancreatectomy with preservation of the spleen and splenic vessels; AIT was performed in postoperative day 1 through islets infusion into the portal vein.

Results: Mean operation time was 266 minutes. Surgical complications occurred in one patient (grade-A pancreatic fistula). Postoperative stay was 6, 6, and 7 days. Histopathology revealed 2 mucinous cystic neoplasm and 1 serous cystoadenoma. Pancreas weight was 33, 22, 30g and 105.200, 94.790, 94.790 Islet Equivalents were isolated respectively. Patients underwent laparoscopic left pancreatectomy with preservation of the spleen and splenic vessels; AIT was performed in postoperative day 1 through islets infusion into the portal vein.

Conclusions: In case of benign neoplasm of the pancreatic body-neck, the combination of laparoscopy, spleen-preservation and AIT can minimize the surgical damages.
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**BASIC SCIENCE - BLOCK I**
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**P119**

**PHARMACOLOGICAL STIMULATION OF THE VAGAL SYSTEM ATTENUATES MORPHOLOGICAL DAMAGE IN EXPERIMENTAL NECROTIZING Pancreatitis**

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**Introduction:** The endogenous immune response is influenced by vagotomy. Stimulation or destruction of the vagus nerve leads to direct release of anti- or pro-inflammatory mediators. These mediators play a key role in the progression of mild edematous to severe necrotizing pancreatitis with systemic complications as pulmonary damage, SIRS and sepsis. The presented study analyzes the influence of pharmacologic stimulation of the vagal nerve system on the severity of experimental necrotizing pancreatitis in rats.

**Methods:** A severe acute necrotizing pancreatitis was induced in rats by using the GDOC-model. Therapy groups received either nicotine, physostigmin or neostigmin for stimulation of the vagal nerve system. The agents were applied either directly after induction of acute pancreatitis (prophylactic) or 3 hours in a delayed therapy group (therapeutic). The results were compared to animals that had pancreatitis alone or healthy controls. The evaluation was performed 12 hours after induction of acute necrotizing pancreatitis.

**Results:** Histological evaluation of the pancreas in the pancreatitis only group confirmed a severe necrotizing pancreatitis compared to healthy controls regarding edema, inflammation and necrosis. Pharmacologic stimulation of the vagal nerve with nicotine, physostigmin or neostigmin revealed an attenuated morphologic damage with regard to inflammation (p<0.005, respectively) and necrosis (p<0.05, respectively). The attenuated injury was independent of the application time (prophylactic or therapeutic).

**Conclusion:** Pharmacologic stimulation of the vagal nerve attenuates pancreatic morphological injury in acute necrotizing pancreatitis in rats and should be further evaluated as a treatment approach.

**P121**

**CELL CYCLE INHIBITOR p21/Waf1 CONTROLS ACINAR TO-DUCT METAPLASIA IN CERULEIN-INDUCED Pancreatitis**

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**Introduction:** In patients and in animal models of pancreatitis a transdifferentiation converting pancreatic acinar cells to duct-like cells (acinar-to-duct metaplasia (ADM)) has been observed together with acinar cell proliferation. Mouse models suggest that ADM is a precursor lesion of pancreatic adenocarcinoma. p21/Waf1 is a major regulator of cell cycle and activation of this protein leads to the cell cycle arrest.

**Aims/Objectives:** In this study we aim to investigate the contribution of p21/Waf1 to ADM and acinar cell proliferation during pancreatitis.

**Methods:** Chronic pancreatitis was induced in WT and p21/-/- mice by multiple injections of cerulein over a period of 14 days. The expression of proliferation markers, cell cycle regulators, growth factors and the severity of tissue inflammation wsd analyzed by immunohistochemistry and qRT-PCR.

**Results:** p21/Waf1 expression was upregulated after induction of chronic pancreatitis in WT mice. After cerulein treatment p21/-/- mice showed considerable areas of ADM along with downregulation of amylase and p48. A high number of infiltrating leukocytes together with extended fibrosis was observed in metaplastic areas. In p21/-/- mice gene expression of the four main cyclins (D,E,A,B) was elevated with the highest increase in cyclin B. However, the increase in the number of proliferating acinar cells was modest in p21/-/- compared to WT mice. Moreover, the absence of p21/Waf1 was accompanied by upregulation of other cell cycle inhibitors, especially p16.

**P120**

**CUX1 STIMULATES Pancreatic Cancer PROGRESSION BY MODULATING THE NFκB-DEPENDENT CYTOKINE EXPRESSION IN TUMOR-ASSOCIATED Macrophages**

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**Introduction:** Pancreatic ductal adenocarcinoma (PDAC) is characterized by extensive infiltration of inflammatory stroma cells including tumor-associated macrophages (TAM). Previously, we could demonstrate high expression levels of the transcription factor CUX1 in both pancreatic tumor cells and tumor-associated macrophages. In addition, we identified CUX1 as an important mediator of tumor progression and invasiveness in pancreatic cancer cells.

**Objectives:** In vivo and in vitro characterization of the effects of CUX1 in tumor-associated macrophages.

**Methods:** CUX1 expression in TAM was analyzed by immunohistochemistry in PDAC tissues. The role of CUX1 in macrophages was evaluated using siRNA and overexpression techniques, and its effect on transcription of secreted cytokines was profiled using a multiplex quantitative RT-PCR approach. CUX1 target genes were validated with RT-PCR, ELISA and reporter assays. The regulation of these genes by CUX1 was examined performing DNA-pulldown experiments. The functional impact of CUX1 and its targets was analyzed using migration and angiogenesis assays.

**Results:** Immunohistochemical co-staining revealed strong expression levels of CUX1 in TAMs of pancreatic cancer tissues. Profiling experiments showed that CUX1 downregulates several cytokines which have been associated with M1 differentiation and tumor suppression. The downregulation of CCL10 and CCL5 was verified on RNA and protein level, and the transcriptional regulation of CCL10 by CUX1 could be verified on promoter level. DNA-pulldown experiments showed that CUX1 directly binds to the promoters of CCL5 and CCL10 and is able to inhibit the binding of NFκB. Functionally, we could show that suppressed CCL10 led to a enhanced tumor neoangiogenesis.

**Conclusion:** CUX1 promotes the tumor progression of pancreatic cancer by modulating the cytokine profile in tumor-associated macrophages via inhibition of NFκB activity.
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SEROTONIN REGULATES AMYLASE SECRETION AND CYTOSKELETON DYNAMICS DURING MURINE PANCREATITIS

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Objective: Serotonin (5-hydroxytryptamine, 5-HT) is a potent bioactive molecule involved in a variety of physiological processes. In this study, we analyzed whether 5-HT regulates zymogen secretion in pancreatic acinar cells and cytoskeleton re-organization during the development of pancreatic inflammation, a potentially lethal disease whose pathophysiology is not completely understood.

Methods: 5-HT regulation of zymogen secretion was analyzed in pancreatic acini isolated from wild-type or tryptophan hydroxylase-1 knock-out (TPH1−/−) mice, which lack peripheral 5-HT, and in amylase-secreting pancreatic cell lines. Zymogen granule distribution and actin cytoskeleton were analyzed by confocal and electron microscopy. Pancreatitis was induced by cerulein stimulation and biochemical and immunohistochemical methods were used to evaluate disease progression.

Results: Absence and reduced intracellular levels of 5-HT inhibited the secretion of zymogen granules both ex vivo and in vitro and altered the dynamics of zymogen granules re-localization following induction of pancreatitis. Furthermore, we observed both in vivo and in vitro that reduced 5-HT availability modulates the re-arrangement of actin cytoskeleton, a critical process for acinar secretion, and the activation of intracellular trypsinogen. In addition, absence of 5-HT resulted in attenuated pro-inflammatory response after induction of pancreatitis.

Conclusions: Our results underline the involvement of 5-HT in the secretory processes of pancreatic acinar cells and in the regulation of pro-inflammatory mediators in the development of inflammation, thus directly linking 5-HT to the pathophysiology of cerulein-induced pancreatitis. These findings provide novel insights not only into the normal physiology of pancreatic acinar cells, but also into the pathophysiology of pancreatitis, with potential therapeutic implications.

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OBESE RATS EXHIBIT HIGH LEVELS OF ISOPROSTANES IN ACUTE PANCREATITIS

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Introduction: Obesity is a prognostic factor for severity in the evolution of acute pancreatitis in humans1. Necrotizing acute pancreatitis is associated with increased mortality in obese animals2.

P122

IN INVOLVEMENT OF THE RNA-BINDING PROTEINS Sam68 AND SRSF1 IN THE ACQUISITION OF THE RESISTANCE TO GEMCITABINE IN Pancreatic adeNOCARCinoma CELLS

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Introduction: The limited effect of conventional chemotherapy in pancreatic adenocarcinoma (PDAC) urges for novel therapies, targeting more directly the molecular aberrations of this disease. The molecular characterization of the drug resistant phenotype of PDAC cells remain unexplored, even though some evidence suggests a correlation with the expression of mesenchymal markers (1).

The epithelial-to-mesenchymal transition (EMT) is promoted by finely-tuned changes in gene expression, at both transcriptional and splicing levels (2). In addition to the well described role of transcription factors in EMT, recent observations have shown the requirement for select splicing factors in this transition (3,4).

Aim/Objectives: Characterization of the molecular events that lead to chemotherapeutic resistance in PDAC cells.

Methods: Drug resistant PDAC subpopulation was selected after chronic exposure to gemcitabine. Western blot analyses for the expression of cancer related proteins; RNA-interference of selected genes to investigate their function. Trypan blue staining to analyze cell survival.

Results: Chronic exposure of PDAC cells to gemcitabine selected a subpopulation of cells displaying a mesenchymal phenotype, which remains less sensitive to drug-induced cell death. These cells express higher levels of Sam68 and SRSF1 splicing factors. Depletion by RNA-interference of Sam68 and SRSF1 expression cause a partial recovery of drug sensitivity.

Conclusions: Our results show that chronic exposure of PDAC cells to gemcitabine leads to selection of a drug-resistant subpopulation overexpressing Sam68 and SRSF1. Importantly, the depletion of these proteins leads to a partial recovery of the sensitivity to gemcitabine, suggesting that they may represent suitable molecular-targets to overcome drug resistance in PDAC.


Poster Sessions

44th European Pancreatic Club (EPC) Meeting
Aims: To study the role of oxidative stress and abdominal fat in the increased severity of taurocholate-induced acute pancreatitis in obese Zucker rats.

Methods: Necrotizing pancreatitis induced by retrograde perfusion of taurocholate was performed in lean and obese Zucker rats. Levels of reduced glutathione, oxidized glutathione, L-cysteine, and S-adenosyl methionine were measured in pancreas by mass spectrometry. Serine/threonine protein phosphatase and tyrosine phosphatase activities were determined in pancreas. Maldondialdehyde, isoprostanes, triglycerides, and free fatty acids (FFA) levels were measured in plasma and ascites.

Results: Under basal conditions obese rats exhibited lower glutathione levels in pancreas as well as higher isoprostane, triglyceride, and FFA levels in plasma than lean rats. Necrotizing pancreatitis in obese rats was associated with more intense glutathione depletion and oxidation and decreased protein phosphatase activities in pancreas. Acute pancreatitis triggered an increase in isoprostane levels in plasma and ascites, especially in obese rats. Free fatty acid levels were extremely high in pancreatitis-associated ascitic fluid from obese rats in parallel with an increase in binding of lipase to white adipose tissue and especially to areas of necrosis.

Conclusion: Our results show that taurocholate-induced acute pancreatitis in obese rats is associated with increased local and systemic oxidative stress, particularly high levels of isoprostanes in plasma and ascites, and extremely high levels of FFA in ascites.

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Introduction: Pancreatic cancer (PC) is the fourth cause of cancer-related death in Czech Republic. Pancreatic cancer is among cancers related to obesity and insulin resistance. Insulin resistance is connected with the change in composition of plasma fatty acids. FA composition in plasma phospholipids (PL) and cholesteryl esters (CE) reflects both dietary intake of FA, as well as endogenous FA metabolism, which can be influenced by tumour growth.

Aim: We decided to analyze profile of FA in plasma lipid classes in patients with PC with relation to degree of malnutrition and tumor staging.

Patients and Methods: Study included 86 patients (47M/39F) with PC and 66 controls (34M/32F). FA patterns were analyzed in plasma lipid classes by gas-chromatography. The data were processed with statistical software STATISTICA® for Windows.

Results: We observed increased proportion of total monounsaturated FA (MUFA) in PC group, increased activities of Δ9-desaturase and Δ5-desaturase. Proportion of dihomo-γ-linolenic acid (DHGLA) correlated positively with visceral protein levels and negatively with CRP level. Correlations of MUFA with these variables were opposite. Proportions of α-linolenic (ALA), DHGLA, eicosapentaenoic acid (EPA) and total polyunsaturated FAPUFA n-3 displayed negative trend with tumor staging. Contents of MUFA showed positive trend with stage of malnutrition according to nutritional risk index.

Conclusion: Plasma lipid FA pattern in PC patients resulted from decreased dietary fat intake, increased de novo synthesis of FA with transformation into MUFA. Changes in FA profile implicated some pathophysiological mechanisms responsible for disturbed FA metabolism in PC and importance of appropriate nutritional support.

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P126

NFATC1 AND p53 IN FAILSAFE AND PROGRESSION OF Pancreatic CANCER

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Introduction: The mutational activation of KrasG12D is an early event in premalignant pancreatic ductal lesions and deletion of either Ink4a/Arf or p53 enable their malignant progression. However, the key signaling pathways that function downstream of KrasG12D remains elusive. Activation of the nuclear factor of activated T cells (NFAT)-signaling pathway has been found in a number of human cancers, where it controls key cell fate decisions.

Aim: To explore the interactions and consequences of oncogenic NFATC1 activation and KrasG12D mutations in PDAC development.

Methods: We generated mouse strains with combined pancreas-specific expression of constitutive active NFATC1 (c.a.NFATC1) and KrasG12D using Cre-Lox technology. Pathophysiological examination was done by Immunohistochemistry, RT-PCR and western blot.ChIP-seq and microarray analysis were performed in isolated mice tumour cells to identify NFATC1 target genes. Protein-protein interactions, promoter regulation, and histone modifications were analyzed by IP and sequential ChIP assays (both In vitro & in vivo).

Results: We present first evidence that NFATC1 accelerates KrasG12D driven PDAC development. Initially, NFATC1 induces strong tumour failsafe mechanisms via direct p19ARF promoter regulation, leading to p53 stabilization and apoptosis. During carcinogenesis, however, disruption of the p19ARF-p53 tumour suppressor pathway favors development of invasive and widely metastatic carcinoma, nicely recapitulating the human disease.

Conclusion: This study identifies a novel NFATC1-p53 signaling axis as a key mediator in pancreatic carcinogenesis, thus providing an attractive target for future therapeutic development.
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FATTY ACID CHLOROHYDRINS GENERATED DURING ACUTE PANCREATITIS INCREASES THE INFLAMMATORY RESPONSE

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Background: Acute pancreatitis is an inflammatory process of the pancreas gland that in the severe forms triggers the inflammation in remote organs. An additional characteristic of pancreatitis is the inflammation and necrosis of peripancreatic adipose tissue. Here we have evaluated in a model of acute pancreatitis the generation of fatty acids chlorohydrins and its effects on the inflammatory response.

Methods: Pancreatitis was induced in male rats by intraductal administration of 3.5% sodium taurocholate. We obtained samples of adipose tissue and ascitic fluid and the levels of free fatty acids as well as fatty acid chlorohydrins were evaluated by GC-MS. In additional experiments we administered fatty acid chlorohydrins, generated by chlorination of adipose tissue lipid extracts, on the peritoneum of animals after the induction of a mild pancreatitis (1% sodium taurocholate). Three hours later we obtained peritoneal macrophages and samples of plasma, pancreas, lung and adipose tissue to evaluate the inflammatory process.

Results: During pancreatitis, necrotic areas of adipose tissue generate and release free fatty acids as well as its chlorohydrins of oleic and linoleic acids. Administration of chlorinated lipids in the peritoneal cavity results in the activation of peritoneal macrophages and in an increase of systemic inflammatory response.

Conclusion: We conclude that during severe acute pancreatitis, the necrotic areas of the peripancreatic adipose tissue generate chlorinated fatty acids. These halogenated lipids contribute to the exacerbation of the systemic inflammatory response.

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INTRADUCTAL DELIVERY OF CYTOTOXIC ADENOVIRUSES TO THE PANCREAS INDUCES TUMOR REGRESSION IN MOUSE MODELS OF PANCREATIC CANCER

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Gene-based anti-cancer therapies delivered by adeno viral vectors or oncolytic adenoviruses are commonly applied in vivo through intratumoral injections or by systemic delivery. However, intratumoral and systemic administration result in poor distribution of the virus into the tumor. In the current work we have explored the feasibility of targeting pancreatic tumors through a loco-regional route. We have taken advantage of the ductal network in the pancreas to retrogradelly inject adenoviruses through the common bile duct of wild type (wt), Ela-myc transgenic mice, and mice bearing orthotopic xenografts in the pancreas. We studied tumor targeting and the anti-cancer effects of cytotoxic adenoviruses and conducted comparative studies between intraductal or intravenous (i.v) administration. Ductal delivery of a reporter adenovirus in wt and Ela-myc mice revealed a peak of luciferase activity at 4 days post-injection that localized in the pancreas with almost no detection in the liver. Expression in the pancreas of wt or Ela-myc mice was respectively 40 and 5 times higher than that obtained after viral i.v injection. The in vivo application of AdµPTAT8TK through the common bile duct followed by GCV treatment significantly delayed tumor growth in Ela1-myc mice. Importantly, the intraductal injection of TK-armed oncolytic adenoviruses in mice bearing pancreatic xenografts improved mean survival from 34 to 92 days. Of notice, with the two treatments the antitumoral effects were stronger by ductal viral application than through i.v delivery. In summary our data shows that adenoviruses retrogradelly injected into the common bile duct can be a feasible approach for pancreatic cancer treatment.

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A FRAME-SHIFT MUTATION IN THE CARBOXYL-ESTER LIPASE GENE ALTERS THE INTRACELLULAR LOCALIZATION OF THE CEL PROTEIN.

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

Objectives: We aimed to study the subcellular distribution of CEL.

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

Results: We found that a significant fraction of the CEL-MUT protein accumulated in large cytoplasmic vacuoles, while CEL-WT was predominantly detected in the ER and Golgi compartments. Both CEL variants were localized to the pericentrosomal domain of the pre-Golgi intermediate compartment, suggesting the involvement of non-conventional pathway(s) in CEL trafficking. Inhibition of the proteasomal and lysosomal degradation pathways followed by confocal
microscopy showed that CEL-MUT partly colocalized with Lamp-1-containing organelles. Electron microscopy demonstrated the presence of large CEL-MUT aggregates in the lumen of single-membrane vacuoles. In addition, protein aggregates were found to line the cell membranes. Furthermore, experiments in cells devoid of CEL expression indicated that CEL protein presented extracellularly could be internalized via endocytosis and degraded via the lysosomes.

**Conclusions:**
- CEL-MUT is prone to form intracellular and extracellular aggregates.
- Both CEL-MUT and CEL-WT can be internalized by endocytosis and transported to the lysosomes for degradation.
- Inhibition of the lysosomal proteases results in a prominent accumulation of CEL-MUT compared to CEL-WT.

**P133**

**GENE-WIDE ASSOCIATION STUDY ON THE TERT LOcus AND PDAC SUSCEPTIBILITY - RESULTS FROM THE PANDoRA CONSORTIUM**

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Introduction: Single nucleotide polymorphisms (SNPs) in the telomerase reverse transcriptase (TERT) locus have been reported to be associated with pancreatic cancer risk in the PanScan project, a genome-wide association study (GWAS). The TERT gene encodes the catalytic subunit of telomerase which is essential for maintaining telomere ends. When over-expressed in normal cells, TERT can lead to prolonged cell lifespan and transformation. While telomerase activity cannot be detected in most normal tissues, it is seen in approximately 90% of human cancers.

**Aims:** We attempted to replicate and expand the association with the locus in a series of PDAC and healthy controls of European ancestry within the newly formed Pancreatic Disease ReseArch (PANDoRA) consortium.

**Patients and Methods:** We genotyped thirteen SNPs in 1034 PDAC cases and 2443 controls from the PANDoRA consortium. We tested each SNP for association with PDAC risk and also assessed whether the risk SNPs have an impact on survival of the patients.

**Results:** We were able to replicate the association reported in the GWAS with rs401681 (OR=1.53; CI 95%:1.22-1.92; Pvalue=0.0002) and we found a novel association between rs2736098 and decreased PDAC risk (OR=0.75; CI 95%:0.63-0.88; Pvalue=0.001). We observed also that another polymorphism (rs4246742) was statistically significantly associated with worse survival (HR=1.75, 95%CI=1.15-2.67; Pvalue=0.009).

**Conclusion:** We report here two novel findings in pancreatic cancer genetics: one association with risk (rs2736098) and one with survival of the patients (rs4246742). These results further our understanding in the genetic etiology of pancreatic cancer and suggest a new marker for disease prognosis.

**P134**

**GENETIC SUSCEPTIBILITY TO PANCREATIC CANCER AND ITS FUNCTIONAL CHARACTERIZATION: THE PANCREATIC DISEASE RESEARCH (PANDoRA) CONSORTIUM**

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Introduction: Pancreatic cancer is the fourth leading cause of cancer deaths in the European Union and in the USA. In spite of this little is known about the genetic susceptibility to this deadly disease.

Aims: We have established the PANcreatic Disease ReseArch (PANDoRA) consortium with the driving idea of joining the efforts of different research groups and creating a large bio- and databank aimed at uncovering: 1) new genetic risk factors for pancreatic cancer; 2) genetic factors that influence the outcome of treatment of pancreatic cancer patients; 3) genetic factors that influence the survival of pancreatic cancer patients.

Patients and Methods: The consortium currently includes 13 groups across Europe. So far 1436 cases of exocrine pancreatic cancer and 2581 healthy controls from the same regions of the cases have been collected. For all cases and controls a DNA sample is available, as well as a minimal set of covariates.

Results: We have replicated the hits from the three published genome-wide association studies on pancreatic cancer, performed in the Caucasian (PanScan), Japanese and Chinese populations. We have also explored the genetic variability of the ABO, TERT and CDKN2A/p16 loci with encouraging results. For all the loci we have also investigated whether genetic polymorphisms influence the survival of the patients.

Conclusion: This consortial effort is particularly important for pancreatic cancer because it is a disease which is poorly understood from the point of view of etiopathogenesis and risk factors. The recruitment of additional collaborators and partner institutions is continuously ongoing.

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ADVANCES IN THE TREATMENT OF RESECTABLE PANCREATIC CANCER. LESSONS LEARNED FROM TWO DECADE.

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INTRODUCTION: A trend toward improved overall survival was reported in pancreatic cancer (PDC). It is unclear whether progress in the field of pancreatic cancer over the past two decades has translated into a measurable improvement in survival in patients who present with resectable disease.

AIMS: The intent of this investigational design was to focus specifically on changes in oncologic outcome after pancreatic resection for PDC between decades. The end point of the study was to evaluate long-term survival.

PATIENTS & METHODS: From 1990 to 2009, 544 patients with histologically proven PDC were resected at the Department of Surgery of the University of Verona. Patients were categorized according to the decade in which they underwent resection (the 90s or 2000s).

RESULTS: 544 pancreatic resections were performed for PDC. The 1- and 3 year survival rate were 64% and 17% in the first period and 84% and 42% in the second, respectively (P<0.0001). The median disease specific Survival significantly

Poster Sessions
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LIPID PEROXIDATION AND ANTIOXIDATIVE PROTECTION IN PATIENTS WITH AN EXACERBATION OF CHRONIC PANCREATITIS.


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AIM: To assess the levels of lipid peroxidation (LPO) products malondialdehyde (MDA) and glutathione system in patients with the exacerbation of chronic pancreatitis (CP).

Materials and Methods: 60 patients with exacerbation of CP and 20 controls were investigated. The level of reduced glutathione (GSH) and activity of enzymes glutathione reductase (GR), glutathione transferase (GT) were determined in plasma and erythrocytes. While the MDA was studied in plasma.

Results: The MDA levels in plasma were higher for 164% in CP patients (p<0.001) as against the values of the controls. The MDA level correlated positively with intensity of a pain (p<0.02). Increased GSH concentration by 110% (p<0.001) and activity of GT by 20% (p<0.001) were revealed in plasma. In the erythrocytes a reduction in GR activity by 23% (p<0.01) and GSH concentration by 22% (p<0.002) were determined. The inverse correlation between GT in plasma and GSH in the erythrocytes (p<0.02) and a positive correlation of GT in the erythrocytes and GSH in the erythrocytes (p<0.01) were revealed.

Conclusions: In the exacerbation of CP the increased concentration of GSH and the activity of GT in plasma, that is probably due to vascular permeability changes or a damage to pancreatic tissue cells were detected. The increase of plasma MDA level in the exacerbation of CP indicates to activation of lipid peroxidation. The decrease of erythrocytes GR activity and GSH concentration the weakening of the antiradical protection suggest.

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PANCREATIC TEXTURE STUDY (PaTeSt). PRELIMINARY RESULTS OF INTRAOPERATIVE ELASTIC MODULE MEASUREMENT.


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Background: Pancreatic texture has been identified as one of the most important risk factors for postoperative pancreatic fistula after partial pancreatectomy. Texture definition (classically soft/hard) is however subjective and based on intraoperative gland palpation.

Objective: to develop a reproducible method for the assessment of pancreatic texture by using elastic module measurement.

Methods: Study population consisted of 140 patients who underwent pancreatic resections at our institution from November 2010 to November 2011. Before pancreatic transection, a calibrated coiled valve was employed to test pancreatic resistance to compression. Texture was expressed by using pancreatic elastic module (Newton/mm²). Measurements were then correlated with a pathologic score (0-100) based on percentage of fibrosis, pancreatic acini and fat infiltration of the resection margin. Furthermore, the pancreas was palpated by an experienced surgeon (blinded to the elastic module measurement) who subjectively assessed texture on a 1-to-10 scale.

Results: There was a significant correlation between pancreatic elastic module and pathologic score (p=0.005). In order to define “soft” and “hard” texture, an arbitrary cut off was set at the 75th percentile for pathological score (Total amount of fibrosis >45%). Mean values of elastic modules for soft/hard pancreas did differ significantly (p<0.001), and - surprisingly – surgeon’s manual evaluation correlated with both elastic module and pathological assessment.

Conclusions: Pancreatic texture can be assessed using elastic module. This is a reproducible method which may represent a common framework for future multicentric studies. The next step of this analysis will be the correlation between pancreatic texture assessed by elastic module and the development of postoperative pancreatic fistula.

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DECISION SUPPORT SYSTEM FOR DIAGNOSIS OF INFECTED PANCREATIC NECROSIS

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Introduction: Infected pancreatic necrosis (IPN) is associated with high morbidity and mortality and is mandatory for surgical or minimally invasive intervention. Objectives: The aim of this study was to construct and validate the decision support system (DSS) to diagnose IPN.

Methods: To create DSS applied clinical, laboratory and instrumental data survey 146 patients before three days to infection identification. IPN confirmed by the results of microscopic/microbiological studies (FNAB, surgery). 1 group - training of artificial neural network (ANN) (73 examples);
2 group - testing of ANN (73 examples); 3 group - determining of the validity of the developed DSS (128 patients). We comparatively studied M-APACHE, Infection Probability Score (IPS), SIRS 3-4, and DSS for the diagnosis of IPN.

Results: The optimal configuration of DSS was determined a four-layer ANN. The total error of the developed network is 0.81%; the exact classification of the cases - 99%; the AUC - 0.987. In the diagnosis of IPN is a satisfactory diagnostic value M-APACHE (AUC=0.683 ± 0.042), p<0.05; IPS (AUC=0.740±0.040) and SIRS 3-4 (AUC=0.706±0.041) demonstrated better quality of diagnosis, p<0.05. The best quality of the diagnostic model showed DSS (AUC=0.854±0.032), p<0.001. DSS in the studied sample of patients demonstrated a sensitivity of 81.8%, specificity - 89.0%. There were significant differences in diagnostic performance comparable scales: DSS - IPS, p=0.03; DSS - SIRS 3-4, p=0.005; DSS - M-APACHE, p=0.0009.

Conclusion: DSS was able to help in diagnosis of IPN with considerable accuracy and outperformed other scoring systems.

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**COMPLEMENT FACTOR C5 CONTRIBUTES TO FIBROSIS FORMATION DURING CHRONIC PANCREATITIS IN MICE**

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Aim of the study: Chronic pancreatitis is a progressive inflammatory disorder in which pancreatic exocrine tissue undergoes necrosis and is replaced by fibrous tissue. We investigated the role of Complement factor C5/C5a, a strong chemo-attractant for neutrophils and macrophages, in experimental chronic pancreatitis.

Material and Methods: Chronic pancreatitis was induced by pancreatic duct ligation in mice and a single i.p. injection of caerulein (10μg/kgBW) 2 days after surgery using C5-/- and C5+/+ mice (B10.D2-H2dH2-T18Chc0 / o2Sn (C5)) or by 7 repetitive injections of caerulein twice weekly over 10 weeks. Acute pancreatitis was induced by 7 repetitive injections of caerulein. Pancreatic tissue was examined at day 3, 7 and 21 after duct ligation. Pancreatic fibrosis was evaluated by histological scoring of Goldner-stained tissue and light microscopy. Local and systemic damage markers of pancreatitis were monitored.

Results: All animals developed acute pancreatitis with increased levels of serum amylase and lipase 3d after pancreatic duct ligation and progressive pancreatic necrosis until day 7. Progressive fibrosis developed by 21d. In C5-deleted animals the severity of acute pancreatitis was not different from controls but in chronic pancreatitis we found a significant reduction in fibrosis and a decreased number of infiltrating M2 macrophages.

Conclusion: Complement factor C5a contributes to the progression of fibrosis in chronic pancreatitis but not to the severity of acute pancreatitis. Whether C5a directly stimulates fibroblasts and stellate cells or whether its effect is mediated by infiltrating inflammatory cells needs to be investigated.

**P141**

**PMN-ELASTASE CONTRIBUTES TO THE SEVERITY OF EXPERIMENTAL ACUTE PANCREATITIS VIA DIRECT EFFECTS ON ACINAR CELLS**


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Introduction: In various types of inflammation neutrophil transmigration into parenchymal tissue is an essential step. We have previously shown that neutrophils use elastase (PMN-elastase) to dissociate cell-cell-contacts which then permits tissue transmigration during experimental pancreatitis. Here we studied whether genetic deletion of PMN-elastase affects the severity of acute pancreatitis and whether it regulates earlier disease events such as premature protease activation.

Methods: Acute pancreatitis was induced in PMN-elastase knock-out mice and wildtype controls by serial caerulein injections. Severity of pancreatitis was assessed by measuring serum lipase and myeloperoxidase (MPO) levels as well as histology. In a second approach we isolated pancreatic acini, stimulated them with supramaximal concentrations of cholecystokinin (CCK) and co-incubated them with splenocytes from either PMN-elastase knock-out or wildtype animals. In a third approach we compared the direct effects of PMN-elastase and pancreatic elastase on early intracellular trypsinogen activation in isolated acini.

Results: Absence of PMN-elastase led to a milder course of pancreatitis. Interestingly, neutrophils from PMN knock-out mice had significantly higher endogenous MPO activities. Addition of PMN-depleted splenocytes to CCK-stimulated acini induced less intracellular trypsinogen activation than splenocytes from wildtype animals. Along the same line, purified PMN-elastase induced intracellular trypsin activation in isolated acini whereas pancreatic elastase did not.

Conclusion: The presence or absence of PMN-elastase affects the disease severity in acute experimental pancreatitis. PMN-elastase is not only involved in the transmigration of leukocytes into the pancreatic tissue during pancreatitis but also has a direct effect on intra-acinar cell trypsinogen activation.

**P142**

**CTSL MUTATIONS DO NOT MODULATE DISEASE PENETRANCE OF PANCREATITIS IN SPINK1 N34S CARRIERS.**

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Introduction: Mutations of the pancreatic-secretory-trypsin-inhibitor SPINK1 are common in patients with idiopathic chronic pancreatitis. However, even in the general population the most frequent N34S-variant was found in 1-2%.
Experimental evidence suggests that Cathepsin L can not only affect the activity of trypsin but also the integrity of SPINK1 protein. Here we investigated whether CTSL mutations determine the risk of a N34S carrier to develop pancreatitis.

**Patients and Methods:** Among 4300 randomly recruited individuals of the population-based SHIP-Study we identified 68 N34S carriers without history of pancreatitis. In these and 77 patients with idiopathic chronic pancreatitis carrying N34S we sequenced the entire coding region of the ctsl-1 gene including the promoter region.

**Results:** We identified a total of 22 mostly rare (found only once or twice) sequence variations (6x promoter, 6x exon 10x intronic ). Of the 6 exon mutations 2 were located in the 5’UTR (equally distributed in both groups or found only once in ICP patients). The known variant p.N2T was found twice in both groups and a frame shift mutation c.89delA was detected once in the ICP cohort. A silent mutation p.G284G was found once in both groups and the silent mutation p.Q134Q was no more frequent in ICP patients than in controls. Identified promoter variations were either rare or not significantly associated with pancreatitis.

**Conclusion:** In N34S-carriers we could not demonstrate a correlation between CTSL mutations and pancreatitis. CTSL mutations appear not to be involved in modulating the disease penetrance of individuals carrying the N34S SPINK1 mutation.

**P144**

**HEREDITARY PANCREATITIS CAUSED BY A THREE AMINO-ACID INSERTION WITHIN THE ACTIVATION PEPTIDE OF HUMAN CATIONIC TRYPsinogen (PRSS1)**

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**Introduction:** Hereditary pancreatitis is caused by missense mutations in human cationic trypsinogen. A subset of mutations alters the activation peptide and increases autoactivation of trypsinogen to trypsin. In a hereditary pancreatitis family from Denmark we identified an intragenic duplication of 9 nucleotides in exon-2 of the PRSS1 gene which at the protein level results in a 3 amino-acid insertion within the activation peptide (p.K23_I24insDK).

**Aims:** The aim of the present study was to characterize the effect of this unique genetic defect on the function of human cationic trypsinogen.

**Materials and methods:** Wild-type and mutant cationic trypsinogens were produced recombinantly and purified to homogeneity. Trypsinogen activation was followed by enzymatic assays and SDS-PAGE. Trypsinogen secretion was measured from transfected HEK 293T cells.

**Results:** Recombinant cationic trypsinogen carrying the p.K23_I24insDK mutation exhibited >10-fold increased autoactivation. Activation by human cathepsin B was also accelerated by 10-fold. Activation by human enteropeptidase was unaffected. Secretion of the p.K23_I24insDK mutant from transfected cells was diminished, consistent with intracellular autoactivation.

**Conclusions:** This is the first report of an intragenic duplication within the PRSS1 gene causing hereditary pancreatitis. The robust autoactivation of the novel mutant is consistent with the similar phenotypic behavior of previously described activation peptide mutants such as p.D22G and p.K23R. The accelerated activation by cathepsin B is a unique biochemical property not found in any other pancreatitis-associated trypsinogen mutants, therefore, it is unlikely to be of pathogenic significance. Finally, the observations confirm and extend the notion that increased autoactivation is a diseaserelevant biochemical alteration in cationic trypsinogen mutants.
COMBINATION CYTOKINE, CHEMOKINE AND GROWTH FACTOR BIOMARKERS FOR DIAGNOSIS OF PANCREATIC CANCER

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Introduction: Pancreatic cancer (PDAC) diagnosis is problematic; its presentation is similar to benign disease such as obstructive jaundice and chronic pancreatitis where bilirubin levels are also increased. The clinically used PDAC biomarker, CA19-9, shows raised levels with biliary obstruction, decreasing its specificity for detecting PDAC versus benign biliary obstructive diseases. Biomarkers capable of distinguishing PDAC from benign biliary obstructive diseases are needed.

Aims/Objectives: To identify a panel of serum cytokines, chemokines and growth factors (CCGFs) capable of detecting PDAC from benign biliary diseases, with greater sensitivity and specificity than CA19-9 alone.

Patients/Methods: Luminex analysis of 27 CCGFs was performed on serum from patients with PDAC (n=122), chronic pancreatitis (n=45) and benign biliary obstruction (n=26). Following normalisation and log transformation, feature finding and stepwise logistic regression was undertaken to identify the optimum combination of analytes. Results were validated in two additional independent data sets.

Results: Receiver Operating Characteristic (ROC) curve analysis revealed a panel of 4 CCGFs plus CA19-9 (sensitivity=70%, specificity=89%) that was significantly better than CA19-9 alone (sensitivity=77%, specificity=63%) at distinguishing PDAC from chronic pancreatitis and benign biliary disease (AUCs 0.83 versus 0.73 respectively, p value 0.0027). Two independent sample sets confirmed this with AUCs of 0.90 versus 0.63, and 0.86 versus 0.78 respectively.

Conclusion: Combinations of biomarkers can distinguish PDAC from benign pancreatic disease with better specificity than CA19-9 alone. Further work is required to refine the diagnostic equation in a larger prospective data set.

GEMCITABINE- UKRAIN COMBINATION AFFECTS MMP9 EXPRESSION IN PRIMARY PANCREATIC ADENOCARCINOMA CELL CULTURES (PPCCs)

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Introduction: Pancreatic ductal adenocarcinoma (PDAC) is among the most lethal tumors mostly because of its invasive behavior and resistance to most chemotherapy regimens. Our previous results suggested that NSC-631570 (Ukrain) modulates extracellular matrix remodeling of PDAC cell lines [Funel et al., Pancreatology 2010]. Therefore, the present study investigated the modulation of key determinants of invasive behavior such as MMP9 protein by Gem-Uk, using appropriate preclinical models.

Methods: Two PPCCs were seeded in multi-well chamber slides (8000 each/well) and exposed to Gem[10 nM], Uk[1 µm] and their combination. After 48-h treatment the cells were stained with the polyclonal antibody (CST-Euroclone) for MMP9. Untreated cells were used to evaluate the basal level of MMP9, and not-stained cells as negative control. Protein expression levels were evaluated with novel software for image analysis, checking both nuclei and cytoplasm staining intensity. Differences in expression values were compared by t-test/ANOVA analyses.

Results: We observed a significant reduction of MMP9 expression in both PPCCs treated with Gem-Uk combination with respect to their controls and to cells treated with Gem or Uk alone (p<0.01). Moreover, drug combination reduced significantly the number cells, and modified the structure of most nuclei with respect to untreated cells.

Discussion: New approaches to reduce the metastatic behavior of PDAC are warranted, and Gem-Uk showed promising results in our preclinical studies. The new computerized approach to evaluate MMP9 staining at ICC is an ease-of-use and fast method that should be further developed both in preclinical models and for IHC analyses of PDAC tissues.

A RELATIONSHIP BETWEEN DIFFERENT FORMS OF NON-BILIARE ACUTE PANCREATITIS AND ABO BLOOD GROUPS.

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Aim: Our short epidemiological study aimed to determine whether ABO blood could increase or decrease the risk for severe form of acute pancreatitis.

Patients and Methods: It was one-hospital, two years study (from 1/01/2010 to 31/12/2011). 108 patients with severe form and 363 patients with mild form of non-biliare AP were included. These selected cohorts were compared with control group: 4660 voluntary blood donors.

Results: In the control group, the frequency of blood groups was the following: 0 – 0.3365, A – 0.359, B – 0.2195, AB – 0.085. In group with severe form of AP we have a similar distribution. In group with mild form A-blood group was nonsignificantly more cases (41.87% vs 35.90%) and at the same time 0-blood have nonsignificantly less cases (30.85% vs 33.65%)

Conclusions: The results of this study do not support an association between risk of acute pancreatitis and the ABO blood groups in population. But as a discussion we suggest that the effect of A blood type and 0 blood type can modified the risk of severity of non-biliare acute pancreatitis.
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MICROVASCULAR DENSITY (MVD) AND PROLIFERATIVE INDEX (PI) IN PANCREATIC NEUROENDOCRINE TUMORS (PNET) TISSUES: ANALYSES BY COMPUTERIZED ANALYSIS (CA)

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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). Aim of our study was to correlate MDCT post-con- trastographic patterns of PNET with their MVD, PI and biological behaviour in ADN, BRD and WDC tissues by computerized analysis (CA).

Materials and Methods: We compared 22 patients, who underwent quadriphasic MDCT study in early arterial (15’), pancreatic (30’), venous (70’), delayed (180’ ) phases. Three different post-con- trastographic patterns were identified: pattern A (early arterial/ pancreatic enhancement and rapid wash-out, 5 cases); pattern B1 (early wash-in and no wash-out, 9 cases) and pattern B2 (enhancement only in venous or delayed phase, 8 cases). 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) in surgical specimens. We evaluated the PI by Ki-67 staining for grading in 7/21 tumors (expressed by number of positive nuclei/total nuclei).

Results: Pathological analysis demonstrated 5 ADN, 5 BRD and 12 WDC. All ADN were associated with pattern A, showing high MVD (463 vessels/mm2); 3/4 lesions showing pattern B1 were BRD, with middle level of MVD (373 vessels/mm2) while 3/4 lesions with pattern B2 were WDC, demonstrating low level of MVD (vessels/mm2, p < 0.0001). We found not statistically differences between the grading evaluation by pathologist compared with those obtained from CA (p>0.05).

Discussion: In our opinion the MDCT post-contrastographic pattern and the MVD of PNET can suggest their biological behavior. The CA system can help the pathologist to have a rapid evaluation of Ki-67 for grading in PNET.

P149

THE FUNCTIONAL POLYMORPHISM -262 C>T IN THE CATALASE GENE (CAT) BUT NOT THE POLYMORPHISM V16A IN THE MANGANO-SUPEROXIDE DISMUTASE GENE (SOD2) IS ASSOCIATED WITH CHRONIC PANCREATITIS.

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BACKGROUND: Oxidative stress may contribute to pancreatic inflammation. The enzymes catalase and manganese-superoxide dismutase counteract free radical activity within the cytosol and the mitochondria. Moreover, catalase activity contributes to transformation of ethanol to acetaldehyde, a toxic intermediate product of ethanol metabolism. Common functional polymorphisms have been described at position -262 in the CAT promoter region (rs1001179) and codon 16 of SOD2 (rs4880). The aim of this study was to investigate the role of these polymorphisms in a cohort of patients with predominantly alcoholic pancreatitis.

PATIENTS AND METHODS: 297 patients with chronic pancreatitis (208 male, 89 female, median age 50 (18-89) years; 184 alcoholic, 113 nonalcoholic disease) were genotyped for the SNP’s rs1001179 and rs4880 by means of allelic discrimination. Results were compared with data from 357 healthy controls. Association analysis was performed using contingency table analysis and the chi-square test for allele and genotype frequencies of the individual polymorphisms. Fisher’s exact test was used when appropriate. A p value < 0.05 was considered significant.

RESULTS: A significant difference was found in the frequency of the -262 C>T polymorphism between CP patients and controls. The relative frequency of the T allele was 25.6% in CP patients vs. 20.0% in controls (p < 0.02). No significant association was found for the V16A SOD2 polymorphism.

CONCLUSIONS: We observed an association between the CAT -262 C>T polymorphism and chronic pancreatitis. Decreased antioxidant capacity in conjunction with altered ethanol metabolism may represent an additional genetic risk factor for the development of chronic pancreatitis.

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PRECLINICAL EMERGENCE OF NOVEL LACTATE DEHYDROGENASE INHIBITORS AS POTENT ANTITUMOR AGENTS IN HYPOXIC MODELS OF PANCREATIC CANCER: MOLECULAR MECHANISMS UNDERLYING THEIR SYNERGISTIC INTERACTION WITH GEMCITABINE.

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Introduction: Hypoxia plays a key role in pancreatic cancer metastasis and chemoresistance. Since LDH-A constitutes a major checkpoint to ensure sufficient energy supply in hypoxic environments, we investigated the pharmacological activity of a series of novel LDH-A inhibitors (Granchi et al, Eur J Med Chem 2011).

Methods: In vitro studies were performed in 7 pancreatic cancer cell lines and 7 primary cultures, characterized by differential expression of LDH-A. Cytotoxicity was evaluated...
with sulforhodamine-B assay, whereas LDH-A modulation was investigated by RT-PCR, Western-blot and activity assays, using also specific siRNA. Cell cycle perturbation and apoptosis were studied with flow-cytometry, while pharmacological interaction with gemcitabine was investigated with the combination index (CI) method. Furthermore, we examined if LDH-A inhibition modulated invasiveness, expression of cancer stem cell (CSC) markers and EMT phenotype, in adherent-cells and spheroids. All these experiments were performed in both normoxic and hypoxic conditions (1% O2).

**Results:** LDH-A correlated with HIF-1alpha expression and significantly increased under hypoxic conditions. The novel LDH-A inhibitors proved to be particularly effective under hypoxic conditions, with IC50s ranging from 0.1 to 0.8 μM. These compounds induced apoptosis, affected invasiveness and spheroid growth, reducing CSC markers and EMT. Their synergistic interaction with gemcitabine (CI values<0.8) might be attributed to modulation of gemcitabine metabolism, with increased synthesis of phosphorylated-metabolites as detected by LC-MS/MS.

**Conclusions:** 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 tumors.

**P151**

**COUP-TFII DOWNREGULATION INHIBITS Pancreatic CANCER GROWTH**

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**Background and aim:** Alterations in molecular pathways regulating cell survival, proliferation, metabolism, and migration have been identified in pancreatic cancer. However, no substantial improvements in the clinical prognosis have been made and pancreatic cancer continues to be a leading cause of cancer death in the Western World. The orphan nuclear receptor COUP-TFII is a regulator of a wide range of biological processes. Interestingly, COUP-TFII exerts a pro-oncogenic role modulating tumor vascularization, and the proliferative and metastatization behavior of cancer cells. Although there are not direct evidences linking COUP-TFII to pancreatic cancer, indirect evidences suggest that the receptor could be involved in this disease. In fact, COUP-TFII is a downstream effector of hedgehog, Wnt/β-catenin, and RAS-MAPKs pathways that are constitutively activated in pancreatic cancer. Furthermore, activation of PPARγ suppresses pancreatic cancer growth and COUP-TFII down-regulates PPARγ. The aim of this study is to evaluate the expression of COUP-TFII in human pancreatic tumors and to examine its role in the regulation of tumor growth in nude mice.

**Methods:** COUP-TFII expression in pancreatic tumor samples was evaluated by immunohistochemistry. Pancreatic cancer cell lines expressing inducible shRNA against COUP-TFII were produced and injected in nude mice.

**Results:** COUP-TFII is expressed in primary samples and correlates with overall survival. Silencing of COUP-TFII reduces the proliferative modulated invasiveness, anchorage independent growth and it strongly inhibits tubule formation, whereas in nude mice the silencing reduces tumor growth by 50%.

**Conclusions:** COUP-TFII influences the behavior of pancreatic adenocarcinoma, thus representing a new target for pancreatic cancer therapy.

**P152**

**NEAR TOTAL DISTAL PANCREATECTOMY**


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**Introduction:** Brittle diabetes typically plagues the quality of life of patients after total pancreatectomy. Sparing even a small amount of endocrine tissue avoids extreme glycemic fluctuations.

**Aim:** We herein report on the outcome of a selected group of patients undergoing ninety percent distal pancreatectomy (90%DP).

**Methods:** 90%DP is defined as the resection of at least 90% of the pancreas. The pancreatic margin lies well on the right side of the superior mesenteric/portal vein, at the level of the gastroduodenal artery. 90%DP may be indicated for tumors of the neck of the pancreas/proximal body, to avoid total pancreatectomy.

From April 2000 to July 2011, 90%DP was performed in 25 patients: 7 males and 18 females, with a mean age of 68 yrs. 22 patients underwent conventional open resection while 3 had a laparoscopic operation (robot-assisted in 2 of them). Segmental resection of peripancreatic vessels was associated in 4 patients (1 celiac trunk-hepatic artery, and 3 superior mesenteric/portal vein).

**Results:** 16 patients were diagnosed with ductal adenocarcinoma, 3 with well-differentiated endocrine tumor, 3 with a serous cystadenoma, 1 with a mucinous cystoadenocarcinoma, 1 with carcinoma on IPMN, and 1 patient with chronic pancreatitis. Mean operative-time was 330 minutes. There was no post-operative mortality with a morbidity of 40%. Pancreatic fistula was recorded in 8 patients. 13 patients developed insulin dependent diabetes and 15 developed exocrine insufficiency.

**Conclusions:** 90%DP may be considered in patients with centrally located pancreatic lesions. In selected patients 90%DP may be performed laparoscopically, especially if robotic assistance is available.

**P153**

**SEGMENTAL RESECTION AND RECONSTRUCTION OF MAIN PERIPANCREATIC VESSELS DURING LAPAROSCOPIC ROBOT ASSISTED Pancreatectomy**


**Department of General and Transplant Surgery University of Pisa, Pisa, Italy**

**Introduction:** Segmental resection (SR) and reconstruction of main peripancreatic vessels are performed at our Institution from 1987.

**Aims:** To describe the first world experience with SR and reconstruction of main peripancreatic vessels during laparoscopic robot-assisted pancreatectomy (LRAP).

**Methods:** Between October 2008 and February 2012, SR of main peripancreatic vessels was performed in 5 patients out of 105 undergoing LRAP. In 4 patients SR was required to achieve R0 resection. Three of these patients had portal-mesenteric vein resection and reconstruction during pancreaticoduodenectomy (PD), and one celiac trunk resection without reconstruction during distal pancreatectomy (DP).

In the fourth patient the splenic vein, accidentally injured, was ligated and reconstructed using the splenic artery. The celiac trunk was interrupted and reconstructed using the splenic artery. A Kistler's clamp was used for the portal venous reconstruction after suture ligation in two patients.

A morbidity of 40% was recorded. Pancreatic fistula was recorded in 8 patients. In 7 cases the pancreatic fistula closed during the stay on the ICU. In 1 patient the fistula was managed by endoscopic stenting. The postoperative course was uneventful in 24 patients. Pancreatic fistula closed after a mean time of 15 days.

**Conclusions:** This single-center experience confirms the feasibility of SR and reconstruction of main peripancreatic vessels during LRAP.

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was resected and reconstructed during DP. Vein reconstruction was always carried out using autologous jump grafts.

**Results:** No patient was converted. Final pathology disclosed ductal adenocarcinoma in 2 patients; adenosquamous carcinoma in 1 patient, endocrine neoplasia in 1 patient and mild dysplasia on BD IPMN in 1 patient. All were R0 resection. Mean operative time was 740 minutes in PD and 472 in DP. The post-operative course was uneventful in all but one patient, requiring repeat surgery because of intra-abdominal bleeding. Thirty-day mortality was nil, there was no pancreatic fistula. The overall mean hospital-stay was 19 days.

**Conclusions:** SR of main peripancreatic vessels can be performed during LRAP in selected patients, in high volume centers of pancreatic surgery having also extensive experience with open surgery. The enhanced dexterity of the da Vinci gives the opportunity to manage these cases without accepting oncologic compromise or technical shortcut.

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**P154**

**MIA PaCa-2 PANCREAS CANCER CELL LINE - PHENOTYPIC AND GENOTYPIC CHARACTERIZATION**

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**Introduction:** Pancreas cancer, a tumour resistant to surgery, chemotherapy and radiotherapy, is the fourth leading cause of cancer worldwide. MIA PaCa-2 is a human pancreatic duct adenocarcinoma cell line, a cancer that represents about 90% of all pancreatic tumours. Somatostatin 2 (SSTR2) and neurotensin 1 (NT1) receptors are molecular targets for the therapy of pancreatic cancer.

**Aims/Objectives:** The phenotyping of the cell line is essential for the characterization of the tumour. For phenotyping we looked for epithelial (CK-19), mesenchymal (MNF-116), endocrine (chromogranin A, CD56, synaptophysin), SSTR2 and NT1 markers. For genotyping we studied (k-ras, p53, microsatellite instability) aiming to understand the carcinogenic mechanisms.

**Materials and methods:** For the phenotypic studies (PS), immunohistochemical staining (IHCS) with antibodies against CK-19, MNF-116, vimentin, chromogranin A, CD56 and synaptophysin were used. SSTR2 and NT1 receptors were detected by Western Blotting (WB). Genotypic studies (GS) were carried out by PCR and sequencing (k-ras codons 12, 13 and 61; p16 exons 1, 2 and 3; p53 exons 4, 5, 6, 7 and 8) and by PCR and capillary electrophoresis (BAT25, BAT 26, NR21, NR22, NR24 microsatellite instability).

**Results:** PS was positive for CK-19, MNF-116, vimentin and chromogranin A. WB was positive for SSTR2 and NT1 receptors. GS revealed a double deletion in exons 2 and 3 of p16 and a mutation G>T (GGT>TGT) in codon 12 of k-ras.

**Conclusions:** MIA PaCa-2 cells are epithelial-mesenchymal transition cells of pancreas adenocarcinoma with neuroendocrine-like differentiation, SSTR2 and NT1 receptors, a k-ras mutation and a double deletion in p16. This research was supported by the Portuguese Society of Gastroenterology
P156

LAPAROSCOPIC ROBOT-ASSISTED PANCREATIC RESECTIONS FOR PANCREATIC AND PERIAMPULLARY CANCER

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Introduction: Minimally invasive surgery, when dealing with pancreatic and peripancreatic cancer, cannot accept oncologic compromise since local radicality is key for all tumor types.

Aim: We herein report on 44 patients undergoing robotic pancreatic resection because of pancreatic or peripancreatic cancer.

Methods: Between October 2008 to February 2012 44 patients diagnosed with malignant tumors were selected for laparoscopic robot-assisted pancreatectomy. There were 24 males and 20 females, with a mean age of 59.5 yrs (range 24-78 yrs). 24 patients underwent pancreaticoduodenectomy (PD), 13 distal pancreatectomy (DP), 5 total pancreatectomy (TP) and 2 central pancreatectomy (CP).

Results: Final pathology disclosed neuroendocrine carcinoma (NEC) in 7 patients (16%), cancer arising on IPMN in 8 patients (18%), ductal adenocarcinoma (DA) in 14 patients (32%), cholangiocarcinoma (CHC) in 5 patients (11%), carcinoma of the papilla of Vater in 5 patients (11%), solid-pseudopapillary tumor in 2 patients (6%), carcinoma of the duodenum in 1 patient (2%), mucinous cystadenoma in 1 patient (2%) and adenosquamous carcinoma in 1 patient (2%). Resection margins were always negative. A mean number of 29.8 lymph nodes (range 0-74) was retrieved en-bloc with the specimen. After a mean follow-up period of 14.5 months (range 1-40) all but 2 patients are disease-free (94.2%).

Conclusions: Laparoscopic robot-assisted pancreatic resection seems to offer the potential for radical tumor clearance in selected patients without locally advanced pancreatic and peripancreatic cancer. Further experience and longer follow-up are both needed before any final conclusion can be drawn.

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TARGETING PANCREATIC CANCER CELLS IN VITRO WITH SUPER-PARAMAGNETIC IRON OXIDE NANOPARTICLES

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Introduction: Pancreatic cancer patients continue to have a poor prognosis. Custom nanoparticle (NP) systems may improve outcomes by facilitating tumour targeting and cellular uptake mechanisms.

Aims/Objectives: We have manufactured nanoparticles with a super-paramagnetic iron oxide core and coated with a functionalised stealth polymer capable of stably presenting two binding domains. The first holds an identifying fluorophore; the second a specific ligand enabling targeting of tumour cells. Experiments were performed on pancreatic cancer cell lines, testing the ability of such nanoparticles to specifically target cells and undergo facilitated preferential uptake by them.

Methods: Nanoparticles were constructed with either a conjugated anti-CA19.9 monoclonal antibody (NP-CA19.9-Rh), an isotype control antibody (NP-ISO-Rh) or no antibody (NP-Rh). All three NPs contained a rhodamine (Rh) fluorophore. The affinity for BxPC-3 (CA19.9 expressing) and MiaPaCa-2 (CA19.9 non-expressing) cells was assessed using immunofluorescent microscopy. Intracellular iron concentrations following incubation with NPs for twelve hours were measured using a ferrozine assay.

Results: In BxPC-3 cells, NP-CA19.9-Rh uptake was achieved at 1 hour compared to both NP-ISO-Rh and NP-Rh, which showed uptake between 9 and 18 hours. In MiaPaCa-2 cells no difference in the speed of particle uptake was observed. Iron concentrations were higher after 12 hours in cells incubated with NP-CA19.9-Rh, compared to both control groups.

Conclusion: The novel specific custom-NPs described here can effectively target pancreatic cancer cell lines and exhibit facilitated uptake into those cells. This is the first step towards achieving cancer specific particle uptake, which has a myriad of diagnostic and therapeutic applications.

P158

NUCLEAR NFATC1 INTEGRATES STAT3 SIGNALING TO PROMOTE KRAS-DRIVEN PANCREATIC CARCINOGENESIS

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

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

Methods: Transgenic mice conditionally expressing mutated KrasG12D and/or nuclear NFATc1 (NKC mice) and NFATc1 knockout mice were engineered and analyzed in terms of inflammation-induced carcinogenesis. Immunohistochemistry, Western blot and qPCR analyses, ChIP-Seq and genome-wide expression profiling were performed to investigate the mechanisms of NFATc1-Kras cooperation in tissues and tumor cells isolated from NKC tumors.

Results: Concomitant activation of NFATc1 and Kras as a result of inflammation or in NKC mice dramatically accelerates carcinogenesis and reduced survival. Mechanistically, nuclear NFATc1 activated expression of oncogenic STAT3 transcription factors. High correlative expression levels of NFATc1 and p-STAT3 could be confirmed by immunohistological and immunofluorescence staining of human and murine cancer tissues. Activated STAT3 in turn physically interacted with NFATc1 to regulate its binding to chromatin enhancer sites and subsequently stimulated NFATc1-dependent gene transcription of newly-identified target genes during pancreatic carcinogenesis. Pharmacologic and genetic depletion of the NFATc1/STAT3-axis significantly arrested carcinogenesis in mouse models and confirmed the requirement of NFATc1 in Kras-driven pancreatic carcinogenesis.
**P159**

**COPY NUMBER VARIANTS OF THE CARBOXYL ESTER LIPASE GENE IN PANCREATIC DISEASE**


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**Introduction:** We have previously described a syndrome of exocrine and endocrine pancreatic dysfunction caused by a single-base mutation in the highly polymorphic carboxyl ester lipase (CEL) gene. Copy number variations (CNV) of the CEL gene have also been reported.

**Objectives:** We aimed to characterize the structure of CEL CNV alleles and to examine if such alleles predispose to chronic pancreatitis.

**Patients and methods:** PCR-based methods were developed for genotyping of CEL CNV alleles. We examined materials of German subjects with idiopathic chronic pancreatitis (n=91) and alcoholic chronic pancreatitis (n=214). German (n=256) and Norwegian (n=190) blood donors were used as controls.

**Results:** We identified and fine-mapped three recombined CEL CNV alleles, two with gene duplication and one with a deletion. These alleles have all probably arisen from recombination events within the CEL locus. One duplication allele was not detected among the idiopathic chronic pancreatitis patients. The other duplication allele was present at similar frequencies (2.2%-4.7%) in the investigated cohorts. The frequency of the CEL deletion allele was 10.9% among the cases with idiopathic chronic pancreatitis, 1.4%, in alcoholic chronic pancreatitis, and 0.8% and 0.5% in German and Norwegian blood donors, respectively. We expressed the corresponding, truncated protein in HEK293 cells and performed functional studies that indicated disturbed protein secretion.

**Conclusion:** We have determined the structure of three recombined CEL alleles and showed that one of them encodes a shorter CEL protein. This allele may be a risk factor in idiopathic chronic pancreatitis, but it is probably not involved in the development of alcoholic chronic pancreatitis.

**P160**

**TISSUE TOLERABLE PLASMA (TTP) INDUCES APOPTOSIS IN THE HUMAN PANCREATIC CANCER CELL LINE COLO-357 IN VITRO AND IN VIVO.**


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**Introduction:** The development of non-thermal atmospheric plasmas displaying spectra of temperature within or just above physiological ranges, i.e. tissue tolerable plasmas (TTP), has made the use of plasmas possible for biological or medical applications.

**Aims/Objectives:** The aim of the study was to evaluate the effect of TTP on pancreatic cancer cells.

**Patients and Methods:** We have investigated the effects TTP on the pancreatic cancer cell line Colo-357 in vitro as well as in the tumour chorioallantoic membrane (TUM-CAM) assay in vivo.

**Results:** Applying TTP in vitro we found a mild elevation of the original surface temperature (i.e. 23.7°C) of 2.02°C +/−0.56°C after 5 seconds TTP, of 2.57°C +/−0.23°C after 10 seconds TTP and 2.93°C +/−0.40°C after 20 seconds of TTP treatment. Plasma application leads to a significant decrease of cell viability of Colo-357 pancreatic cancer cells in vitro (Annexin-V-FITC/DAPI assay), p=0.0003. The Propidium iodide cell cycle analyses demonstrated that this is due to induction of apoptosis with 10 seconds of Plasma treatment showing the strongest effect (p<0.05). The effects of plasma treatment increase over time levelling off after 72 hour. Longer treatment (20 seconds) had no additional effects in vitro. In the TUM-CAM in vivo model combining the results of HE staining, Ki67 immunohistochemistry and TUNEL-Assay the depth of effective tissue penetration (DETiP) of up to 60 µm was found.

**Conclusion:** TTP could prove a valuable tool in the search of adjuvant treatment options to decrease minimal residual disease of surgery of pancreatic cancer in the future.
males and 65 females, with mean age of 58 yrs. 39 patients underwent pancreaticoduodenectomy (PD), 49 distal pancreatectomy (DP), 9 total pancreatectomy, 5 tumor enucleation, 3 central pancreatectomy. Since our activity spans over a 3-year period, data were analyzed to verify the learning curve.

Results: No conversion were performed. Mean operative time (OT) was 437.8 minutes. In the first year OT was 512 min for PD and 420 for DP. The mean number of lymph nodes (LN) examined was 16.8. Pancreatic fistula (PF) occurred in 41% of patients. In the second year OT was 596 min for PD and 402 for DP. The LN examined was 16.7. PF occurred in 36.3% of patients. In the third year OT was 443 min for PD and 394 for DP. The LN examined was 28.7. PF occurred in 37% of patients. 61 patients were diagnosed with benign or low-grade tumors, 44 with cancer. Surgical margins were always negative. Post-operative mortality was nil, morbidity 52%. Mean hospital-stay was 16 days.

Conclusions: Despite the existence of a learning curve, experienced pancreatic surgeons are not expected to pay to robotics the same price that they would have been asked for by laparoscopy.

P162

RESECTION OF AN ISOLATED ARTERIAL SEGMENT DURING PANCREATECTOMY

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Aims: Isolated involvement of an arterial segment in pancreatic and peripancreatic tumors occurs infrequently, and does not necessarily mean tumor unresectability being possibly caused by tumor location rather than by excessive growth. We report on the outcome of a selected group of patients undergoing pancreatectomy plus resection of an isolated arterial segment at a single Institution.

Methods: Resection of an isolated arterial segment was performed during 26 pancreatectomies. There were 12 males and 14 females, with a mean age of 63.6 yrs. Two patients underwent total pancreatectomy, 5 pancreaticoduodenectomy, 19 distal splenopancreatectomy. Resected arterial segments were celiac trunk (14), hepatic artery (8), celiac trunk and hepatic artery (4). Reconstruction was required in 6 patients.

Results: Final pathology disclosed ductal adenocarcinoma (DA) in 18 patients, other pancreatic/peripancreatic tumors in 5, metastatic tumor in 3. Post-operative morbidity and mortality were 55.5% and 3.8%, respectively. After a mean follow-up period of 111 months, actual survival rate was 64% at 1-year and 20% at 3-years. Equivalent figures for DA were 30% and 15%, respectively. These data favorably compare with an historical cohort of patients with locally advanced DA undergoing palliation without resection.

Conclusions: In DA resection remains key for cure and possibly provides the best palliative treatment. Our experience shows that selected patients with isolated involvement of celiac trunk and/or hepatic artery may undergo pancreatectomy with results similar to patients without vascular involvement and superior to those offered by palliation or medical therapy alone.

P163

THE IMPACT OF TRAIL, ITS RECEPTORS AND BINDING PROTEINS ON PANCREATIC CANCER CELLS

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Introduction: TRAIL is a member of the TNF-family inducing apoptosis in many tumour cells whereas untransformed cells are usually not affected. However, many tumour cells have developed mechanisms enabling them to escape TRAIL-mediated apoptosis.

Aims/Objectives: To asses the role of TRAIL, its receptors DR4, DR5, DcR1 and DcR2, their binding partners OPG and RANKL and inflammatory and stress stimuli in pancreatic cancer.

Methods: Four different pancreatic cancer cell lines, MiaPaCa2, Panc1, BXPC3 und Colo357, were analyzed to investigate the above aims in vitro.

Results: TRAIL could increase apoptosis in MiaPaCa2 (27%) and Colo357 (35%); BXPC3 (14%) was only moderately inducible, Panc1 (<6%) was TRAIL-resistant. The gain of TRAIL-resistance correlated with a decrease of functional TRAIL receptors DR4 and/or DR5 (p<0.01=Panc1, p<0.001=BXPC3) and an increase of non-functional decoy receptors DcR1/2 (p<0.01=BxPc3) whereas the stress-inducing catecholamine analogue isoproterenol did not have any significant impact on the actions of TRAIL.

Conclusions: Future TRAIL therapeutic strategies have to aim at restoring TRAIL sensitivity by increasing functional TRAIL-receptors, by blocking decoy receptors and other TRAIL-binding proteins as well as by reducing the inflammatory micro milieu in pancreatic cancer.

P164

ATP-BINDING CASSETTE TRANSPORTER INHIBITION BY TYROSINE KINASE INHIBITOR NILOTINIB

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Introduction and Aim: Tyrosine kinase inhibitor Nilotinib (Tasigna®) has been shown to interact with the ABCG2 drug transporter and prevent Hoechst dye exclusion in side-population (SP) cells. Additionally, it inhibits kinases involved in proliferation. Thus, we investigate the effect of Nilotinib on cell proliferation, SP dye efflux and ABC-transporter expression in gemcitabine-sensitive and -resistant pancreatic cancer cells in vitro.

44th European Pancreatic Club (EPC) Meeting
P165
SECRETIN-STIMULATED DUODENAL MARKERS ASSOCIATED WITH INCREASED RISK FOR PANCREATIC DUCTAL ADENOCARCINOMA


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Only a small minority of patients manifests surgically treatable disease at the diagnosis of pancreatic cancer. The deficiency of clinically useful biomarkers in pancreatic cancer led us to study CEL-MODY, a monogenic form of diabetes associated with pancreatic cancer. We studied samples from both CEL mutation carrying and non-carrying subjects with pancreatic ductal adenocarcinoma, and we propose some candidate markers potentially involved in the early stages of pancreatic cancer.

P166
DO MICROVESICLES REPRESENT POTENTIAL NOVEL DIAGNOSTIC MARKERS IN PANCREATIC CANCER?

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Introduction: Microvesicles (MVs), one of the major types of extracellular vesicles, represent a novel form of cell-to-cell communication involved in several physiological and pathological functions, including tumorigenesis and metastatic activity.

Objectives: Our main goal was to set up a method for isolation and detection of MVs, and to establish a protocol for examination of the intravesicular protein content.

Materials and methods: All experiments were performed using monolayer cell cultures of pancreatic ductal adenocarcinoma (PDAC) cell lines (PANC-1 and MiaPaCa-2). Cell lines were grown in serum-free medium for the period of time of MV production. MVs were isolated from the cell culture supernatants using a new isolation procedure. Later, MVs were subjected to analyses carried out by fluorescence-activated cell sorting (FACS), electron microscopy (EM) and dynamic light scattering (DLS).

Results: Viability and apoptosis/necrosis of the cells were analyzed by FACS. The membraneous character of MVs was checked by staining with the lipophilic membrane marker (PKH) and annexin V binding. After the isolation procedure, visual confirmation of the presence of MVs was provided by EM. The size distribution and heterogeneity of MVs was examined by DLS, while intravesicular protein content was analyzed by immunofluorescence staining.

Conclusion: Our method seems suitable to isolate and detect MVs in cell culture supernatants of PDAC cells. In further experiments we plan to use xenograft settings for in vivo results. Our hope is that this approach may lead to important findings related to tumor behavior, and MVs could be used in routine clinical work as potential diagnostic markers.
undertaken to unravel signaling mechanisms involved in S100A8/S100A9-mediated effects on pancreatic cancer cells. **Results:** Recombinant S100A8 and S100A9 proteins stimulated secretion of specific cytokines (e.g. IL-8, FGF and TNF-alpha), whereas, PDGF secretion was stimulated by S100A8 only. S100A8/A9 activated phospho-p38 and phospho-p44/42 MAPK and enhanced NF-kB activity through RAGE. S100A8 and S100A9 also induced Smad4 signaling as evidenced by phosphorylation of Smad2/3 and activation of the Smad4 luciferase. Baseline cytokine profiles for pancreatic stellate cells have been obtained, and the effects of S100A8 and S100A9 are currently under assessment.

**Conclusion:** S100A8 and S100A9 promote specific cytokine secretion from pancreatic cancer cells. Interestingly, a number of these cytokines, in turn, induce the secretion of S100A8 and S100A9 from monocytes, creating a paracrine loop. These events may create a favorable environment for tumour development and metastases.

**P168**

**ACUTE Pancreatitis as the first manifestation of duodenal MALT Lymphoma**

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Acute pancreatitis as the first presentation of duodenal MALT lymphoma is extremely rare. We report a case of 67-years old woman, who was diagnosed with acute pancreatitis caused by duodenal lymphoma infiltration.

The patient showed clinical evidence of abdominal pain with bile duct obstruction. Laboratory and ultrasonographic findings were typical for acute biliary pancreatitis. Endoscopic retrograde cholangiopancreatography (ERCP) was completed and it showed duodenal exofytic exulcerative infiltration in the Vater’s region. Neither drainage nor cholangiography was feasible. This finding ant the results of other investigations raised the suspicion of malignant pancreatic tumor or ampulloma of Vater’s papilla. The first histology, which was obtained during ERCP, was negative. Therefore upper endoscopy was performed and more biopsies were gained. The second histology confirmed marginal zone B-cell lymphoma (MALT lymphoma).

The patient was treated for acute biliary pancreatitis. Clinical symptomatology and laboratory findings were normalized after 11 days. She was dimissed and entrusted to the care of hematoooncologic clinic. Patient achieved complete remission after receiving courses of chemotherapy R-CHOP 6+8 (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), thus 8 months after diagnosis.

In summary, MALT duodenal lymphoma, despite its rarity, should be considered in the differential diagnosis of causes of acute pancreatitis.

**P169**

**Defensin Alpha 1 Plays a Crucial Role in the Carcinogenesis of Ductal Adenocarcinoma of the Pancreas**


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**Background:** Antimicrobial peptides, so-called defensins, contribute to innate immunity and epithelial cell-regeneration, and may also play a specific role in the carcinogenesis of various inflammation-triggered malignant tumors. The aim of the present study was to analyze the role of defensins in the carcinogenesis of ductal adenocarcinoma of the pancreas (PDAC) and its suspected association with chronic pancreatitis (CP).

**Methods:** Defensins were detected in human tissue specimens of healthy pancreas, CP, and PDAC by immunohistochemical staining. Expression levels of the immunohistochemically identified defensins alpha 1 (DEFA1) and beta 1 (DEFB1) were quantified by mass spectrometry. Furthermore, in vitro analysis of expression profiles of DEFA1 were studied in the pancreatic cancer cell lines CAPAN-1, T3M4, and PANC-1. The effects of proinflammatory cytokines on tumor cell-specific expression levels of DEFA1 were investigated.

**Results:** Immunohistochemistry showed the accumulation of defensins alpha 1, 2, 3 and 5 in malignant pancreatic ductal epithelia, whereas DEFB1 was particularly found in healthy ductal epithelia. Slightly increased expression levels of DEFA1 were measured in CP compared to healthy pancreas (p<0.3) by mass spectrometry. Levels were significantly increased in PDAC (p<0.001). Furthermore, specific expression of DEFA1 by pancreatic cancer cell lines was verified in vitro. After incubation of cancer cells with TNF-alpha, IL-18, and IFN-gamma, a significant decrease of DEFA1 expression in cell lysate was seen (p<0.001), combined with a significantly elevated amount of the protein in the cell culture supernatant (p<0.01).

**Conclusion:** Defensins seem to play a crucial role in the carcinogenesis of PDAC, possibly triggered by an inflammatory stimulus as seen in CP. Since DEFA1 is highly expressed in human ductal adenocarcinomas and in pancreatic cancer cell lines, specific interventions on the intra- or intercellular level may offer promising new diagnostic and therapeutic options in pancreatic cancer.

**P170**

**Extra-Pancreatic Secretory Function in Ethanol-Feeding Rats.**


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**Introduction:** The usefulness of the typical direct methods involving duodenal intubation, such as the secretin and secretin–cholecystokinin tests, in the diagnosis of exocrine pancreatic dysfunction is widely accepted. However, these diagnostic tests tend to be avoided because of their technical
complexity and the burden on patients. Recently, a simple breath test was developed for assessment of exocrine pancreatic function employing 13C-dipeptide [i.e., benzoyl-L-tyrosyl-[1-13C]alanine (Bz-Tyr-Ala)]. Although alcohol abuse causes pancreatic damage in humans, this has been unclear in rats.

**Aims:** The aim of the study is to evaluate the effect of ethanol exposure beginning at an early age on extra-pancreatic secretory function in rats.

**Materials and Methods:** Twelve female rats of the F344 strain aged 12 months were used. Seven rats were fed on a commercial mash food with 16% ethanol solution (Japanese Sake) as drinking-fluid since at 29 days of age (ethanol group). They drank a 16% ethanol solution with net ethanol 9.7g/kg body weight on average. The remaining five rats were fed on a nutrient-matched isocaloric diet with water as drinking-fluid (control group). After 24-hr fasting, rats are orally administrated 1cc of water containing sodium 13C-dipeptide (5 mg/kg) and housed in an animal chamber. The expired air in the chamber is collected in a breath-sampling bag using a tube and aspiration pump. The 13CO2 concentration is measured using an infrared spectrometer at 10-min interval for 120 min and expressed as delta per mil.

**Results:** The breath 13CO2 level increased and peaked at 20 min in both two groups. In general, 13CO2 excretion peaked rapidly and also decreased sooner in ethanol rats than in control rats. The mean value of the maximal 13CO2 excretion is 34.7 per mil in ethanol rats, greater than in control rats (31.4 per mil), but the difference did not reach the statistically significance (Figure).

**Conclusions:** Chronic ethanol feeding beginning at an early age does not affect extra-pancreatic secretory function in rats.

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**P171**

**USING 13C-DIPEPTIDE BREATH TEST IN PRIMARY CARE.**


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**Introduction:** Recently, a simple breath test was developed for assessment of exocrine pancreatic function employing 13C-dipeptide [i.e., benzoyl-L-tyrosyl-[1-13C]alanine (Bz-Tyr-Ala)]. In our hospital, 13C-dipeptide breath test has been used for diagnosis of exocrine pancreatic secretory insufficiency in various situations.

**Aims:** The aim of this study is to evaluate the efficacy of 13C-dipeptide breath test in primary care.

**Materials and Methods:** We experienced 6 cases underwent 13C-dipeptide breath test for 2 years. Underlying diseases are chronic pancreatitis with pancreas tumor, hyperthyroidism, alcoholic liver disease with diabetes mellitus, Sjogren syndrome with a past history of AIP, malnutrition after total gastrectomy due to cardiac cancer, and malnutrition due to unknown reason. Patients are orally administrated 100cc of water containing sodium 13C-dipeptide (5 mg/kg) and breath samples were collected at 10-min interval for 120 min. The 13CO2 concentration is measured using an infrared spectrometer and expressed as delta per mil.

**Results:** 13CO2 excretion at 30 minutes after administration ranges from 2.2‰ to 40.3 ‰. Two patients had severe pancreatic exocrine insufficiency. Pancreatic enzyme replacement therapy was done in patients with mild to severe pancreatic exocrine insufficiency. This therapy was markedly effective for patients with severe pancreatic exocrine insufficiency, whereas the treatment had little effect on patients with mild to moderate pancreatic exocrine dysfunction.

**Conclusions:** 13C-dipeptide breath test has a great advantage when pancreatic exocrine function is evaluated in a clinical practice. It is because none of intubation, test meal, collection of stool, urine, and blood, or stimulation with secretin is needed for procedure of 13C-dipeptide breath test. I expect that this test may predict an efficacy of pancreatic enzyme replacement therapy.
P172

METHYL GUANINE DNA METHYL TRANSFERASE (MGMT) EXPRESSION PREDICTS RESPONSE TO TEMOZOLOMIDE (TMZ) IN PATIENTS WITH DIGESTIVE NEUROENDOCRINE TUMORS (NETS)

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TMZ is an orally given drug used in patients (pts) with malignant NETs, with very encouraging results in pancreatic NETs in a recent retrospective study (Strosberg et al, 2011). MGMT is a DNA repair enzyme which induces cancer cell resistance to alkalyting agents such as TMZ. A higher treatment efficacy seems to be correlated to MGMT tumor deficiency (Kulke et al, 2010).

Aim: To assess MGMT expression in digestive NETs and to correlate with the efficacy of TMZ-based chemotherapies.

Patients and Methods: All consecutive pts with histologically proven, well differentiated, progressive, non resectable NETs treated with TMZ (alone or in combination with capécitabine (Cap) were included. Treatment efficacy was defined according to RECIST criteria. Pts with progression or only stable disease were considered as “non-responders”.

Nuclear expression of MGMT was assessed by immunohistochemistry on primary tumors (10 pts) or metastases (12 pts) and graded according the product of the intensity of staining (0 to 3) and the rate of positive cells (%), leading to a score comprised between 0 and 300. A score ≥ 80 was defined as “high” staining.

Results: 22 pts (16 men, median age 59 years (36-81)) with pancreatic (14 pts), small bowel (5 pts) or other (3 pts) NETs, grade 1 (5 pts) or 2 (17 pts) (WHO 2010 classification) were included. They received TMZ alone (19 pts) or combined with Cap (3 pts) as first line (3 pts) or 2+ line (19 pts). After a median of 6 cycles (3-16), objective response, stable disease and progression rates were seen in 32 % (7 pts, all with pancreatic NETs), 41% (9 pts, 5 with pancreatic NETs) and 27% (6 pts, 4 with small bowel NETs), respectively. Median (range) MGMT score was 10 (0-300). A “High” MGMT score was seen in 36% of pts (small bowel 4/5, pancreas 3/14 pts) ; it was correlated with primary tumor location (more frequent in small bowel NETs, p=0.02) and predictive of the absence of response (p=0.02). A “Low “MGMT score tended to be associated with objective response (p=0.06) whereas none of the pts with “high” score had tumor response. Response rate in pts with “low” MGMT score was 50%.

Conclusion: MGMT deficiency is more frequent in pancreatic than in small bowel NETs. Patients with pancreatic NET and low MGMT score are good candidates for TMZ, whereas those with high score should be treated with another drug in first intention. In patients with small bowel NET who have most often a high MGMT score, tumor stabilization using TMZ seems to be rare.

P173

IMPACT OF BMI ON SHORT AND LONG TERM OUTCOME AFTER ONCOLOGICAL PANCREATICODUODENECTOMY

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Background: Increased BMI is generally considered a risk factor for postoperative complications after pancreaticoduodenectomy (PD). In contrast, data are scarce regarding BMI as long term prognostic factor.

Aim: To evaluate the impact of BMI on short and long term results after PD.

Methods: Patients undergone PD 2004-2010 was retrieved from our prospective database. Demographics, peri-operative data, morbidity, mortality, pancreatic fistula rate (PF), length of stay (LOS), and survival were analyzed. The cohort was divided by BMI into overweight/obese (O: BMI ≥ 25 Kg/m²) and controls (C: BMI < 25 Kg/m²).

Results: A total of 367 PDs were included (O=141/C=226). No significant differences were found between O and C regarding demographics, peri-operative data, morbidity (O 47 vs. C 54 %) or mortality (O 3.4 vs. C 3.5 %). O had a significantly higher rate of PF (O 20 vs. C 9.5 %; p=0.006) and longer LOS (O 18 vs. C 15 days; p=0.05) compared to C. An increasing risk for PF was observed with increasing BMI: Underweight 0 %, normal-weight 10 %, overweight 16 %, and obese 32 % PF rate respectively. A similar 1-, 3- and 5-year survival rate was observed for O and C both in pancreatic ductal adenocarcinoma, and in other periampullary cancers.

Conclusion: Overweight/obesity increases the risk for PF and thus LOS, but do not otherwise alter short term outcome or survival rate after oncological PD for pancreatic or periampullary cancer.

P174

ANALYSIS OF XRCC2 AND XRCC3 GENES POLYMORPHISMS IN PANCREATIC CANCER

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Introduction: The double-strand break DNA repair pathway, including XRCC2 and XRCC3 genes, is implicated in maintaining genomic stability and therefore could affect pancreatic cancer risk.

Aims: The purpose of this study was to evaluate the clinical significance of the XRCC2 and XRCC3 genes polymorphisms in patients with pancreatic cancer.

Patients and Methods: The study included 203 patients: 101 with pancreatic cancer (PC) and 102 healthy controls. The Arg188His XRCC2 and the Thr241Met XRCC3 genes polymorphisms have been studied in DNA isolated from blood samples. The associations of the analysed genotypes and clinical data at diagnosis have been evaluated.
**Poster Sessions**

**P175**

**ROLE OF GENETIC FACTORS IN THE FORMATION CHRONIC PANCREATITIS IN MOSCOW.**

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**Aim:** Identify the prevalence of mutation in genes CFTR, SPINK1 N34S or PRSS1 in patients with chronic pancreatitis.

**Patients and Method:** 92 patients with chronic pancreatitis were examined. All patients had a severe course of disease: acute pancreatitis in anamnesis, calcifications and cysts in pancreas, endured pancreatoduodenal resection, and other diseases of pancreas: cancer and cystadenoma. Were presented 28 patients with idiopathic, 48 alcoholic, 8 biliary, 8 other (cancer and cystadenoma). Patients was conducted to identify mutations in genes CFTR, SPINK1 N34S or PRSS1 by polymerase chain reaction.

**Results:** No patient with mutation in CFTR gene was detected in this group. Mutation in SPINK1 N34S gene was detected in 7 patients (7,6%). Idiopathic pancreatitis 3 (10,7%), alcoholic 3 (6,25%), biliary 0, other (cancer and cystadenoma) 1 (12,5%). Mutation in PRSS1 gene was detected in 23 patients (25%). Idiopathic pancreatitis 6 (21,4%), alcoholic 12 (25%), biliary 1 (12,5%), other (cancer and cystadenoma) 4 (50%). While the two mutations (SPINK1 N34S and PRSS1) in 3 patients: 1 alcoholic and 2 idiopathic.

**Conclusion:** Mutation in CFTR gene is not typical for patients with chronic pancreatitis in Moscow. In patients with chronic pancreatitis in Moscow frequently detected mutation in gene PRSS1, these patients have a high risk of cancer and cystadenoma.

**P176**

**MODERN PRINCIPLES OF DIAGNOSIS AND SURGICAL TREATMENT OF COMPLICATED PANCREATIC PSEUDOCYSTS.**

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**Introduction:** Complicated pancreatic pseudocysts is a dangerous disease, mortality for certain complications is up to 50%.

**Methods:** We have analyzed the results of 237 patients treatment with complicated pancreatic pseudocysts, treated in our clinic in the period of 2000-2011 years. There were 78 (33%) female patients and - 159 (67%) male patients, with an age, ranging from 21 to 70 years. Among the complication infected pseudocysts occurred in 89 patients, bleeding - 39, rupture of pseudocysts - 9, pancreaticopleural fistula - 4, compression of adjacent organs - 3.

**Results:** We used step-by-step procedures with individualized treatment tactics, using minimally invasive techniques on the first stage for treatment of the complication. Minimally invasive techniques we used: in patients with bleeding-endovascular occlusion in 19 patients; with infected pseudocysts - percutaneous ultrasound-guided interventions and laparoscopic drainage in 60; with rupture of pseudocysts - percutaneous ultrasound-guided interventions and laparoscopic drainage in 4 patients; with pancreatic-pleural fistula we used drainage of pleural cavity and then - percutaneous ultrasound-guided interventions in all cases. With compression of adjacent organs we used only one step procedures: percutaneous ultrasound-guided interventions - 5, laparoscopic cystojejunostomy - 6, endoscopic cystogastrostomy - 8, cystoduodenostomy - 6; open surgical intervention we used in 65. Mortality was 1,3%.

**Conclusion:** In the treatment of pseudocysts we prefer minimally invasive techniques, open surgical procedures are performed in the cases when it is impossible to use minimally invasive surgery.

**P177**

**PANCREATIC CYSTIC TUMOURS: A SINGLE CENTRE RETROSPECTIVE STUDY**

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**Introduction:** In the last decade an increasing incidence of pancreatic cystic lesions has been observed.

**Aim:** To describe a characteristics of patients with cystic tumours and to evaluate the role of endosonography (EUS) in the diagnostics and management of pancreatic cystic lesions.

**Methods:** During years 2008-2011 a total of 182 patients (median of age 63 years, range 29-86) with EUS finding of pancreatic cystic lesion were examined in our department. History data and EUS description were retrospectively analyzed. Final diagnosis was based on histological/cytological verification or on further clinical course.

**Results:** Out of 182 patients with cyst on EUS, 42 (23.1%) had cystic tumour. 40 (22%) chronic pancreatitis, 35 (19.2%) simple cyst, 28 (15.4%) adenocarcinoma and 21 (11.5%) postpancreatic cyst. Cystic tumours were predominantly (71%) localized in the head or body of the pancreas. A median size of the lesions was 30 mm (range 7-150). Surprisingly, 33.3% of cystic tumours were found incidentally. The most frequent were serous cystadenomas (23.8%) and intraductal papillary mucinous neoplasms (19%). A total of 25 patients were treated without a need of surgery, 17 patients underwent pancreatic resection. Sensitivity, specificity, positive and negative predictive value of EUS (eg morphology, cytology, fluid analyses) for distinguishing benign and malign lesion was 100%, 60%, 84.6% and 100% respectively.

**Conclusions:** A large proportion of pancreatic cystic tumours is found incidentally. EUS predicts malignant cyst with high sensitivity but low specificity.
P178

**PANCREATICOGASTROSTOMY - A SAFE RECONSTRUCTION TECHNIQUE AFTER PANCREATIC HEAD RESECTION**

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The pancreatoenteric anastomosis after pancreaticoduodenectomy (PD) is considered as the Achilles heel of the Whipple procedure. Anastomotic failure contributes to major complications as peritonitis, abscess formation and hemorrhage. In this retrospective study we compared the outcome after PD using pancreaticogastrostomy (PG) versus pancreaticojejunostomy (PJ) for drainage of the pancreatic remnant.

From 2009 until now we performed a series of 40 elective PD (26 male, 14 female patients; age 29-86) for periampullar and pancreatic adenocarcinoma (n=28) and for chronic pancreatitis (n=12). All PD were performed as pylorus-preserving PD according to Longmire-Traverso.

End-to-side PJ was used in the first 30 patients with placement of a plastic stent in the pancreatic duct and transmural Maxon 3-0 interrupted sutures. Three leakages of the PJ occurred (7.5%) requiring relaparotomy with repair of a pseudoaneurysm (n=1) and need of pancreatectomy (n=1).

End-to-side PG was performed in the last 10 consecutive cases with stenting of the pancreatic duct and insertion of the pancreatic remnant in the posterior stomach wall via an anterior gastrotomy. The pancreatic stump was secured by running 2-0 polyglactin suture between pancreatic capsule and stomach wall. No leakages, no delayed gastric-emptying or gastric hemorrhage occurred after PG (0%). In both groups no mortality and no insufficiencies of end-to-side choledochojejunostomies or gastrojejunostomies occurred (0%).

In our single-center experience, PG was superior to PJ in terms of complication rate and technical feasibility so that we abandoned PJ for reconstruction after pancreatic head resection. We recommend PG as the method of choice for pancreatic drainage if soft remnant pancreatic tissue is present as in periampullar carcinoma.

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**ADENOSQUAMOUS PANCREATIC CANCER: REPORT OF FOUR CASES**

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**Introduction:** Pancreatic adenosquamous carcinoma (PASC) represents 0.4-4% of the exocrine pancreatic neoplasms and has a more aggressive behaviour than ductal adenocarcinoma, but its natural history is unknown.

**Aims/Objectives:** To evaluate clinical presentation, preoperative investigations, surgical approach, histological features and follow up (FU) in PASC.

**Patients and Methods:** We reviewed clinical data of patients who underwent pancreatic resection for PASC in the last decade in our Department.

**Results:** From January 2002 to December 2011 we performed 211 pancreatic resections for malignant cancer of exocrine pancreas and 4 of them were PASC (1.8%). All patients (4 M, averaging 63.7 yrs) had a tumor located in the pancreatic head. Symptoms of presentation: upper abdominal pain (50%), hyperglycaemia (50%) and jaundice (25%). CA19-9 was high in 2/4 patients without jaundice. All patients underwent pancreaticoduodenectomy (mean tumor size 3.4 cm) and in 3/4 cases a vascular resection was performed. In 2/4 cases a preoperative pancreatic biopsy was positive for pancreatic adenocarcinoma. FU to December 2011 (mean FU 21.3 months).

Two patients had an intrabdominal bleeding in the perioperative period: one died after an early reoperation and the other died of tumor progression (after 14 months). Another patient died with hepatic relapse (FU 8 months) and the last one developed an urothelial cancer but is still alive (FU 42 months).

**Conclusion:** Surgical treatment is the only reasonable therapeutic approach for PASC, but early relapse is frequent. The role of non-operative therapies for PASC is less clear. If preoperatively known, PASC could be candidate to neoadjuvant therapy.

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**THE ASSOCIATION BETWEEN PANCREATIC NEUROENDOCRINE TUMORS AND STROMAL TUMORS OF GI TRACT: REPORT OF FIVE CASES**

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**Introduction:** Neuroendocrine pancreatic tumors (NPT) are occasionally associated with mesenchimal tumors in the gastrointestinal tract (GIST) and GIST, 1 malignant metastatic gastrinoma with a jejunal and 2 functioning NPT with a gastric GIST and 2 duodenal GISTs respectively, 1 non functioning metastatic NPT with a cecal GIST, 1 malignant metastatic gastrinoma with a jejunal and 2 duodenal GISTs. In all cases the mesenchimal lesions were low-risk neoplasms. Mean follow up was 48.7 months. Two patients are still alive without disease 26 and 57 months after surgery.

**Aims/Objectives:** To evaluate surgical approach, histological features and follow up in NPT associated with other rare stromal tumors of gastro-intestinal tract (GIST).

**Patients and Methods:** We report five cases of NPT associated with GIST observed in our Department from 2003 to 2011.

**Results:** All five patients (3M/2F, averaging 67 years) had preoperative diagnosis of NPT. They all underwent surgical resection: 1 middle pancreatectomy, 2 left pancreatectomy and 2 pancreaticoduodenectomy. The following associations were observed: 1 benign insulinoma with a jejunal GIST, 2 non functioning NPT with a gastric GIST and 2 duodenal GISTs respectively, 1 non functioning metastatic NPT with a cecal GIST, 1 malignant metastatic gastrinoma with a jejunal and 2 duodenal GISTs. In all cases the mesenchimal lesions were low-risk neoplasms. Mean follow up was 48.7 months. Two patients are still alive without disease 26 and 57 months after surgery.

**Conclusion:** All mesenchimal tumors of the GI tract were incidental findings, small size and low-risk neoplasms. In no case they recurred after excision or influenced the prognosis of the NPT.
**DISTAL PANCREATECTOMY FOR NEUROENDOCRINE PANCREATIC TUMORS**


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**Introduction**: Left pancreatectomy for neuroendocrine tumors localized in the body-tail of the pancreas (NPT) can be performed either with splenectomy (DP) or with a spleen-preserving procedure (SPLP).

**Aims/Objectives**: To evaluate histological features, staging, type of surgery, early and late complications, follow-up (FU) and disease free survival (DFS).

**Patients and Methods**: We reviewed clinical data of patients who underwent laparotomic left pancreatectomy for NPT from January 1981 to December 2010 in our Department.

**Results**: We enrolled 59 patients (29F/30M – averaging 53.8 yrs). We performed 29 DP (49.2%), 28 SPLP (47.4%), 23 cases with splenic vessels preservation) and 2 left pancreatectomy in previous splenectomy (3.4%). Mortality was 3.9% and morbidity was 42.4%, equally distributed in DP and SPLP groups. We had 10 pancreatic fistulas (16.9%, 6 in DP and 4 in SPLP group), 8 abdominal fluid collections, 5 pseudocysts (8.5%, 4 in DP group) and 2 splenic infarctions in SPLP with splenic vessels ligation (2/5 of Warshaw operation). Mean FU was 111.2 months (range 10 – 338), and mean DFS was 120.7 months. Twelve patients with metastatic disease had a mean time to progression of 30.75 months.

**Conclusion**: The complication rate for laparotomic left pancreatectomy in NPT is still high and is comparable between the two surgical procedures.

**PREOPERATIVE PREDICTIVE FACTORS INFLUENCING SURVIVAL AFTER PANCREATECODUODENECTOMY FOR Pancreatic CANCER**

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**Background**: The median survival in resected pancreatic ductal adenocarcinoma (PDAC) is about two years. However, a considerable percentage of patients die within the first year after resection.

**Aim**: The aim of this study was to evaluate pre-operative factors predicting a short survival after pancreaticoduodenectomy (PD) for PDAC.

**Methods**: One hundred consecutive patients undergone PD for PDAC without in-hospital mortality Oct 2006 – July 2010 were retrieved from our prospective database. The cohort was divided by survival into short term (<12 months: group A) and long term (> 12 month: group B) survivors and evaluated regarding pre-operative factors including age, weight loss, BMI, tumor size and proximity (no contact-contact) to the portal/mesenteric vein (PV/SMV).

**Results**: No significant differences were found between group A (n=27) and group B (n=73) regarding mean age (68 ± 2 vs. 66 ± 1 years: p=0.3), weight loss (87 vs. 85%; p=1.0), BMI (24 ± 0.6 vs. 24 ± 0.5 Kg/m2: p=0.7) or adjuvant treatment. Group A had bigger tumors (35 ± 2mm vs 29 ± 1mm; p=0.01) but no significant difference in proximity of the tumor to the PV/SMV (no contact: A 33 vs. B 51 %: p=0.1; contact: A 67 vs. B 49 %: p=0.2) or venous resections. Group A had more frequently pre-operative diabetes (33 % vs. 9.6 %; p=0.01) compared to group B.

**Conclusion**: Tumor size and pre-operative diabetes seems to be important negative prognostic factors for survival after PD for PDAC.

**IDIOPATHIC CHRONIC PANCREATITIS IN INDIA AND IN THE WESTERN WORLD; DIFFERENT PHENOTYPES?**

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**COMPARATIVE ANALYSIS OF THE CLINICAL PROFILES OF 1919 PATIENTS.**

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Background: Chronic pancreatitis (CP) has a heterogeneous aetiology. In the Western world, the predominant cause is alcoholism, while in India tropical chronic pancreatitis (TCP) is thought to be common. TCP has been defined as a form of idiopathic chronic pancreatitis (ICP), with unique epidemiological and clinical features. However, the clinical profile of ICP in India is changing. The aim of our study was to investigate the phenotype of ICP in India compared to the phenotype of ICP in the Western world.

Methods: We included CP patients from 3 registries from India, Germany and the Netherlands. We compared data regarding age, age of onset, cause of CP and the presence of CP complications between the 3 cohorts.

Results: We included 1919 CP patients; (India n=1033; Germany n=528; Netherlands n=358). The majority (68%) of patients were male. Relative to the Western cohorts Indian CP patients were younger, had a younger age of onset and smoked less frequently. The majority of Indian subjects were diagnosed with ICP (65%) (Netherlands 40%, Germany 23%). Endocrine insufficiency and pancreatic calcifications were more frequently seen in Indian ICP patients. Pain was present in the large majority (> 85%) of all CP patients.

Conclusions: The phenotype of Indian ICP patients used to be dominated by TCP, but our analysis demonstrates that most of Indian patients now have a form of CP that can be labeled as ICP.

Indian patients have younger onset of CP with more endocrine insufficiency and pancreatic calcifications, and there is a shift towards the phenotype of ICP in the Western world.

A 30-YEARS CELEBRATION OF “THE DAGRADI-SERIO-ICAONO OPERATION”. SYSTEMATIC REVIEW OF CENTRAL Pancreatectomy AND META-ANALYSIS VERSUS DISTAL Pancreatectomy

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BACKGROUND: Central Pancreatectomy (CP), first performed by Dagradi and Serio in 1982, and described in 1984, is a parenchyma-sparing surgical procedure that allows removing benign and/or low grade malignant lesion from the neck and proximal body of pancreas.

AIMS: The aim of the study was to evaluate, from all published studies, short and long term surgical results of CP and to evaluate results of comparative studies versus distal pancreatectomy (DP).

METHODS: All published studies between 1988 and October 2010 were systematically reviewed. Results of comparative studies, comparing CP versus DP, were pooled by standard meta-analytic techniques using the random effects model.

RESULTS: Ninety-one studies with 1013 cases of CP were recognized and included in the systematic review. Nine-hundred and eighty three open resection were performed, 30 laparoscopic, 11 of whom were robotic assisted. Postoperative morbidity rate was 39.5%; pancreatic fistula rate was 29.32%. Endocrine and exocrine pancreatic insufficiency were reported in 4.55 and 8% of patients, respectively. Overall mortality rate was 0.82%.

Twelve comparative studies, including 359 patients submitted to central CP and 480 to DP, were analyzed for meta-analysis. Surgical operation time, blood loss, length of stay, morbidity and exocrine failure presented a significant heterogeneity across studies; re-operation, endocrine failure and pancreatic fistula did not presented significant heterogeneity. CP had a higher post-operative morbidity, with higher incidence of pancreatic fistula compared to DP. However, the odds ratio for post-operative endocrine insufficiency was 0.27, revealing a statistically significant benefit to CP (p<0.001). The odds ratio for exocrine failure was 0.59, but it was not significant (p=0.084) because of the large heterogeneity among studies.

CONCLUSION: Systematic review and meta-analysis, confirmed CP as a safe surgical procedure with good long term functional reserve although with a low increasing of morbidity (pancreatic fistula) when compared to DP. The “Dagradi-Serio -Iacono Operation” should be considered, with specific indication, not an alternative to DP, but rather a standard surgical procedure.

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PROGNOSTIC FACTORS FOR SURVIVAL AFTER PANCREATICODUODENECTOMY FOR PERIAMPULLARY TUMORS. A SINGLE CENTER EXPERIENCE.


Survival after pancreaticoduodenectomy (PD) for periampullary tumors is limited. The aim of the study was to analyse recent survival data and determine prognostic factors for survival after PD in patients with periampullary tumors.

From January 2004 to March 2011, 112 PDs were performed in our department, 100 of which for periampullary tumors. Ductal adenocarcinoma of the pancreatic head (66 pts) was the commonest tumor followed by ampullary adenocarcinoma (17 pts), neuroendocrine tumors (7 pts) and distal common bile duct (CBD) adenocarcinoma (5 pts). A classical PD was performed in 69 pts and a pylorus preserving PD in 31 pts. Patients with incomplete pathology data or without follow up were excluded from analysis. Finally, 71 patients with periampullary adenocarcinoma were included in the study and were analysed. Survival was calculated by using the Kaplan-Meier method and prognostic indicators were identified by univariate and multivariate analysis.

Perioperative mortality was 4/112 (3.5%). The median number of lymph nodes resected was 11 (2-27). Overall median survival was 13 months and median survival after resection for adenocarcinoma of the pancreas, CBD and ampulla were 12, 8, 20 months respectively (p=0.000).
In univariate analysis, poor tumor differentiation (p=0.012), tumor size > 2 cm (p=0.000), lymph node ratio >0.2 (p=0.021) or >0.3 (0.000), positive margin (p=0.006) significantly decreased survival. There was no difference between classical PD and pylorus preserving PD. In multivariate analysis tumor location, differentiation, size and lymph node ratio >0.3 remained as independent prognostic factors.

In conclusion, survival after resection for periampullary carcinoma remains short. Tumor location, poor differentiation, size >2cm, and lymph node ratio >0.3 independently influence survival.

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PERCUTANEOUS MANAGEMENT OF INFECTED NECROTIZING PANCREATITIS
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Introduction: Infected necrotizing pancreatitis is associated with high level of postoperative complication and death.

Objectives: The purpose of this study was to examine the impact of percutaneous catheter drainage (PSD) under sonography on patients with necrotizing pancreatitis.

Methods: All patients with necrotizing pancreatitis and suspected or confirmed infected necrosis who underwent PSD between 2008 and 2011 were retrospectively evaluated.

Results: A total of 63 PSD procedures were performed in 44 patients. The average multiple organ dysfunction score (MODS) and modified CT severity index (CTSI) were 2(1-6) and 6(4-9), respectively. PSD was used as primary therapy in all patients; PSD alone was used successfully in 21 patients with MODS 1(0-5) and modified CTSI 6(4-9) (5% mortality, one patient died). The remaining 23 patients had PSD followed by surgical intervention with MODS 2(1-6), modified CTSI -7(5-9) (8 patients died). The size of the drains used ranged from 9 to 14 Fr. the median of one catheter was placed (range, 1-5).

Conclusion: PSD should be used as a part of minimally invasive step-up approach of infected necrotic pancreas. 47.7% of patients with suspected infected necrotizing pancreatitis recovered with PSD as the only surgical intervention.

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THE IMPACT OF INSULIN RESISTANCE ON POSTTRAUMATIC PANCREATICITIS DEVELOPMENT
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Introduction: Posttraumatic pancreatitis is the main complication of the blunt pancreatic trauma, which may result in considerable morbidity and mortality. Hyperinsulinemia associated with insulin resistance is common after trauma and can influence the course of posttraumatic disease and outcome activating multiple genes involved in inflammation.

Objectives: The aim of the study was to estimate the effect of insulin resistance on posttraumatic pancreatitis development.

Patients and Methods: This retrospective study included 60 patients treated for pancreatic trauma. Patients were divided into two groups: patients with posttraumatic pancreatitis and without it. The diagnostic, operative information, hospital course and complication rates were abstracted from medical records. Only patients without chronic diseases of pancreas, liver or duodenum, blood diseases and cardiovascular diseases were selected. Blood samples for analysis were collected in patients in 1, 3, 5, 7, 9, 14 and 21 days during the postoperative period. Homeostasis model assessment of insulin resistance (HOMA-IR) was estimated using a single fasting sample of glucose and insulin levels.

Results: We revealed, that IR index in patients with pancreatitis was increased in 3 fold (P<0.02) compared to patients without pancreatitis during the first 5 days of the postoperative period and decreased by 50% (P<0.05) to 21st day. In patients without pancreatitis IR index was not significantly changed during the whole observation period.

Conclusion: Thus, we can conclude that insulin resistance is a risk factor for posttraumatic pancreatitis development.

P189
ENTERAL NUTRITION IN THE TREATMENT OF MODERATE TO SEVERE ACUTE PANCREATITIS
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Introduction: Enteral nutrition is thought to have beneficial effects on clinical outcomes in patients with acute pancreatitis. However, gained evidence is weak, based on a rather small number of patients and showing no statistically significant effect on complications and mortality.

Objectives: To assess the beneficial and harmful effects of enteral nutrition in comparison to intravenous fluid replacement without nutritional support in patients with moderate to severe acute pancreatitis.

Patients and Methods: A 162 consecutive patients with acute pancreatitis and APACHE II score ≥6 were randomized into one of two groups, enteral nutrition group (group I) and group with no nutritional support (group II). Severity of acute pancreatitis was determined by APACHE II and Ranson scoring systems. Patients in group I received daily 105kcal (25kcal)/kg and 1, 5g/kg of proteins in the form of enteral nutrition preparation administered via a nasojejunal tube, while patients in group II received only fluid replacement with crystalloid solutions. The feeding tube was placed within 24 hours of admission. All cases were assessed by CT between days 5 to 10 after admission and graded according to CTSI classification.

Results: Eighty-one patients were randomized in group I and 81 patients in group II. There were no significant differences in age, gender, BMI, etiology and disease severity between groups. There were no significant differences in local (p = 0.102) and systemic (p = 0.066) complications according to the revised Atlanta criteria between the two groups. No significant difference in mortality (p = 0.369) was found either.

Conclusion: We found no significant difference in the outcomes of acute pancreatitis between patients who received enteral nutrition compared to patients with no nutritional support.
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REDO-OPERATIONS IN CHRONIC PANCREATITIS - A SUCCESSFUL OPTION FOR SELECTED PATIENTS.
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Introduction: Surgery in chronic pancreatitis (CP) includes draining and resecting procedures. Besides chronic pain as the main indication, cholestasis and suspicion of malignancy are important indications for operations in CP. In a small number of CP patients a second operation is required due to recurrent CP symptoms. Aim of the study was to determine frequency, indications, surgical procedures and outcome of redo-operations in CP patients

Methods: During an observation period of 8 years, data of all CP patients undergoing surgery were analyzed with regard to recurrent operations. Indications and surgical procedures for the first and second operation were analyzed as well as operative parameters, complications and outcome.

Results: Throughout the observation period 665 operations were performed in CP patients. In 34 patients (5.1%, 22m, 12f; median age 47 years) a second operation was performed. Indications for a redo-operation were recurrent pain (14/34 pat.), symptomatic pseudocysts (6/34 pat.) and obstruction of the pancreatic or bile duct (13/34 pat.) as well as suspected malignancy (1/34 pat.). After preceding duodenum-preserving pancreatic head resection (DPHHR, n=17) 13 patients underwent a Whipple operation, 3 patients received a hepatico-jejunostomy and one underwent a redo-operation of the pancreatic anastomosis. In 5 patients DPHHR or Whipple operations were performed after initial ampullectomies, in all other patients resections were performed after preceding drainage procedures or vice versa (n=12). Median time interval between both operations was 3.1 years. There were no perioperative deaths, overall morbidity was 26.5%. Required opioid pain medication was reduced from 85% before to 16% after the redo-procedure.

Conclusions: Redo-operations in CP patients are rare with an overall frequency of app. 5%. Indications for a second surgical intervention mainly include recurrent episodes of pain and cholestasis. In most of the patients with an initially limited draining or resective procedure, a more extensive resection is required during the second operation. This can be performed with low morbidity and mortality and results in good long-term outcome.

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MAINTENANCE THERAPY WITH ALPHA-INTERFERON (IFN-α) IN LOCALLY ADVANCED PANCREATIC CANCER (LAPC): A PILOT STUDY
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Introduction: Induction chemotherapy (CT) followed by chemoradiation (CRT) is a widely used strategy in the treatment of LAPC. However, prognosis still remains poor with median survival (OS) of 12-14 months. Reports suggest that IFN-α directly inhibits pancreatic tumor growth and exerts antiangiogenic effects and increases antitumoral immune response.

Aim: to explore the role of IFN-α as maintenance therapy in LAPC after induction CT followed by CRT.

Patients and Methods: Adult patients (pts) with pathologic diagnosis of LAPC, performance status (PS) >50%, no radiological PD or CA19.9 raise >20% after 6 months of CT followed by CRT were treated by IFN-α 3 MU subcutaneously three times a week until PD or a maximum of 6 months. Tumor assessment was repeated every 2 months.

Results: Between January 2008 and June 2011, 8 pts were treated. Median age 60 years; median PS 100; median CA19.9 78 (range 52-134); induction CT was four-drug therapy for all pts. Chemoradiation consisted of radiotherapy at median dose of 48 Gy delivered with tomotherapy and concomitant CT with capecitabine. IFN-α was given for a median of 4.5 months (0.3-6). No grade 3-4 toxicity was observed. Median PFS since induction CT start was 15 months. Seven pts (88%) were progression free at 12 months. 2y OS was 37%.

Conclusion: IFN-α as maintenance therapy in LAPC is feasible with a safe toxicity profile and findings on freedom form progression that justify to extend the study to a larger population.

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METASTATIC SITE IN PANCREATIC ADENOCARCINOMA (PA) CORRELATES WITH PROGNOSIS
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Introduction: PA is mostly metastatic at time of diagnosis. Aim: to explore whether metastatic site correlates with prognosis.

Patients and Methods: Patients with pathologic diagnosis of metastatic PA, treated at our Institution with upfront combination chemotherapy between April 1997 and August 2010 were eligible for this analysis. Baseline tumor assessment consisted of contrast enhanced computed tomography scan of the abdomen and the thorax.

Results: 265 patients with metastatic PA, median age 60 years; median PS 90; median CA19.9 1048 were eligible; 19 (7.2%) had prior pancreatic surgery. Metastases were located: in a single organ (N=150; 56.6%); liver (N=227; 85.3%); peritoneum (N=32; 12.1%); lung (N=53; 19.9%). Lung was the only metastatic site in 15 cases (5.6%). Median and 1y overall survival (OS) was 9.0 months and 32.2%. Prior surgery correlated with better OS (11.7 and 51.0% versus 8.9 and 30.8%; p=.006); liver metastases with worse OS (median and 1y OS: 8.8 months and 29.7% versus 11.1 and 47.4%; p=.005); while no difference in OS was observed based on number of metastatic sites (p=.37); peritoneal (p=.50) or lung metastases (p=.10). Patients with lung as isolated metastatic site lived longer (17.3 months and 66.7%) with respect to the whole population (9.0 and 30.1%; p=.01) and to patients with lung metastases associated to other metastatic sites (8.8 and 34.2%; p=.07).

Conclusion: Prior surgery and metastatic site correlate with prognosis and should be performed as a stratification criterion in prospective trials. Patients with lung as isolated metastatic site has a particularly good prognosis.
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IS TOTAL PANCREATECTOMY FOR DUCTAL ADENOCARCINOMA OF THE HEAD OF THE PANCREAS JUSTIFIED BASED ON THE RISK OF TUMOR MULTICENTRICITY?

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Introduction: The risk for multicentricity of ductal adenocarcinoma of the pancreas raises the question if resection of the head of the pancreas is sufficient for the treatment of patients with pancreatic head carcinoma.

Aims/Objectives: To evaluate the incidence of multicentricity of adenocarcinoma of the pancreas in patients who underwent resection of the head of the pancreas with curative intent.

Patients and Methods: A total number of 131 PDs after resection of the head of the pancreas, requiring resection of the pancreas with curative intent were included. The pancreatic remnant was histologically examined in patients with ductal adenocarcinoma to evaluate the proportion of patients with multicentric tumor.

Results: Thirty-three patients had a Bassi C complication after resection of the head of the pancreas, requiring resection of the pancreatic remnant. Eleven of these suffered from ductal adenocarcinoma. Histological examination of the pancreatic remnant revealed multicentric carcinoma in 1 out of these 11 patients (9%). Preoperative computed tomography failed to identify tumor multicentricity in this patient.

Conclusions: The incidence of multicentric carcinoma in our study was high, reaching 9%; however the number of patients included was low. Therefore, total pancreatectomy cannot be reliably appraised based on the evidence from CT and MRI; if CT is considered to show a non-resectable disease, a potentially curative extended pancreatectomy could be performed.

P194

DOES ARTERIAL EBCASEMENT ON CT ALWAYS MEAN ARTERIAL INVASION AT SURGERY IN PANCREATIC CANCER? IF NOT, HOW CAN WE ASSESS RESECTABILITY AND WHAT IS THE STRATEGY?


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Introduction: The salient indication of pancreatic cancer (PC) unresectability is the SMA and CA encasement, signaling arterial wall invasion. Computed tomography (CT) is the gold standard for PC detection and its resectability evaluation.

Method: Preoperative diagnostic radiology data were compared with the findings at 55 standard, 52 extended, 17 total pancreatectoduodenectomies (PDs) and 8 distal resections with CA excision (DPCA) for PC (2006–2011).

Results: CT and MRI showed the SMA and gastroduodenal artery (GDA) (pancreatic body tumor) to be encased in 18 and 2 cases respectively. In all of these cases an operative exploration was performed, basing on equivocal yield of endoUS. No invasion of the arterial wall was revealed in 13 cases out of 20 (65%) in spite of periarterial plexsus being affected. 11 extended PDs and 2 DPCA were carried out. Twelve R1 (arterial margins) and 1R0-resections were accomplished. There was no mortality, 3 patients (23%) developed complications. During follow-up (1,5 year) all the patients are alive and receive chemotherapy with gemcitobine, liver metastases were detected in 2 patients.

Conclusions: 1. Peripancreatic arterial encasement seen on CT and MRI does not necessarily signify arterial wall invasion, which mean that PC can still be radically removed; 2. Such cases render the accuracy of CT in predicting PC resectability rather conjectural; 3. Without recourse to an extended pancreatectomy with skelitalizing the SMA and CA, PC resectability cannot be reliably appraised based on the evidence from CT and MRI; 4. Whenever PC is considered unresectable endoUS or intraarterial US should be used.

195

STUDY OF SERUM PANCREOCLAURYL TEST IN PATIENTS WITH EXOCRINE PANCREATIC INSUFFICIENCY

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Introduction: The diagnosis is based on a clinical study, imaging and laboratory. Serum pancreolauryl test (PLs) indirectly measures the activity of a specific pancreatic cholesterol esterase. The aim purpose of appealing to this noninvasive test is to put evidence an unsuspected exocrine pancreatic insufficiency (EPI) or, if already diagnosed to establish its improvement or otherwise its deterioration as a result of the therapeutic approach.

Aim: Determine PLs values in EPI and control patients, and establish differences between them.

Materials-Methods: We studied 35 adult patients, classified by clinical features and imaging techniques in two groups: Control (n=14, age:50±14, without gastrointestinal disorders) and EPI (n=21, age:51±12, with: primary biliary cirrhosis-n=1, fatty pancreas-n=1, chronic pancreatitis-n=5, pancreatic head resection-n=1, and gastrointestinal disturbances-n=13)

PLs: Together with a breakfast rich in fat, Fluorescein Dilaurate was administered. By venous puncture, serum samples were extracted at different times: Basal and post breakfast at 60,120,150,180,210 and 240 minutes. At all times the free fluorescein was read spectrophotometrically at 492nm. The maximum of absorption was considered for the calculation. The cutoff value used was 4.5 mg/L.

Results: In patients with EPI the PLs was lower than the control (7.5±2.0 vs 2.8±1.3 respectively; P<0.0001)
Conclusion: The PLs is an economic, noninvasive and feasible test to perform in the biochemical laboratory. This study allows us to find patients who consult for diverse gastrointestinal problems, subclinical exocrine pancreatic insufficiency, which is solved by administering supplements enzymatic or therapeutic approach.

**P196**

**MEASUREMENT OF INSULIN RESISTANCE BY HOMA-IR INDEX IN PATIENTS WITH ACUTE PANCREATITIS.**

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**Background:** Insulin resistance (IR) contributes to type 2 diabetes mellitus, non-alcoholic steatohepatitis, metabolic syndrome, arteriosclerosis, obesity, and polycystic ovary syndrome. It has been suggested that acute pancreatitis level may lead to IR, which may represent a new potential therapeutic target.

**Material and Methods:** The study group comprised 35 patients with alcoholic AP (median age 49±26.7 years; 26 men and 7 women). In all cases AP was classified as B according to Balthazar’s CT score and as mild according to Ranson’s criteria. The serum level of insulin and glucose were measured on the first day of hospitalization. Insulin resistance was measured with HOMA-IR index. Median patients’ BMI was 24±5. Patients with diabetes mellitus, impaired glucose tolerance (IGT), or renal malfunction were excluded.

**Results:** The median plasma glucose level was 122±53 mg/dl. The median insulin level was 8.36±5.2 μIU/L. In almost all patients with AP: 32 (92%) - the HOMA-IR index was increased: median 1.50±0.5, range: 1.0 to 3.0. No correlation has been found between HOMA-IR and BMI, HOMA-IR and age or HOMA-IR and sex.

**Conclusion:** Most patients with acute pancreatitis develop insulin resistance, which may be the potential target for new therapeutic regimens, aiming at the prevention of pancreatic endocrine insufficiency.

**P197**

**EXOCRINE AND ENDOCRINE PANCREATIC INSUFFICIENCY AFTER ACUTE NECROTIZING PANCREATITIS**

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**Introduction:** Acute necrotizing pancreatitis is a disease that can lead to the development of exocrine and endocrine pancreatic insufficiency in recovery period.

**Aim of the study:** To examine the incidence of exocrine and endocrine pancreatic insufficiency after acute necrotizing pancreatitis.

**Patients and Methods:** 85 patients with acute necrotizing pancreatitis were involved in the study. Exocrine function was evaluated by determination of fecal elastase-1, endocrine function - by determining of glycated hemoglobin and glucose tolerance test. The survey was conducted every six months.

**Results:** exocrine insufficiency developed in 36 (42.35%) patients; moderate - in 20, severe - in 16 patients. The exocrine insufficiency developed during the first year of the follow up and then remained constant. Endocrine insufficiency occurred in 23 (27.05%) patients: 3 patients during the first year, 8 - in the second year and 12 during the third year after acute necrotizing pancreatitis. Of these, impaired glucose tolerance was found in 35.4% of patients, with pancreateogenic diabetes in 64.6% of patients. Disorders of glucose metabolism have evolved only in patients with exocrine insufficiency, the coefficient of association exocrine and endocrine insufficiency was 0.79 + / - 0.085. Spearman coefficient correlations between the exocrine and endocrine insufficiency was r = -0.673, p = 0.0001.

**Conclusion:** Acute necrotizing pancreatitis in the study group led to the formation of exocrine insufficiency in 42.35% of the patients and endocrine pancreatic insufficiency in 27.05% of the patients; impaired glucose metabolism developed only in patients with formed exocrine pancreatic insufficiency.

**P198**

**RESULTS OF STANDARD AND EXTENDED PANCREATICODUODENECTOMIES FOR PANCREATIC DUCTAL ADENOCARCINOMA**

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**Background:** Extended pancreaticoduodenectomy (PD) for pancreatic adenocarcinoma has been assessed by some retrospective and 4 randomized controlled trials. However, the protocols used and the results found were different.

**Aim:** Assessment of the results of standard (SPD) and extended (EPD) pancreaticoduodenectomies (PDs).

**Methods:** A prospective trial of 30 standard (SPD) and 30 extended (EPD) consecutive PDs for PDA performed from 2004 to 2008. Results. The mean number of excised lymph nodes was significantly higher for EPD (28 vs. 14) (p<0.01). Comparison of mortality (6.6% vs 6.6%), the mean operating time (5.05h for SPD vs. 6.4h for EPD), general morbidity (59% vs. 52%), reoperation (8.3% vs. 13.3%), pancreatic fistula (18.3% vs. 3.3% for EPD), bile leakage rates(11.6% vs. 4%) and blood loss (7.1dl vs. 8.3 dl) have shown a significant difference only in operating time, 30% of EPDs were followed by diarrhea and lymphorrhoea. The three- and 5-year overall survival rate (OSR) after SPD was 0, and 25% and 17% -for EPD with median survival (MS) of 11 and 12 months. For stage 2b MS was 9 months after SPD and 16.5 for EPD. Local recurrence rate was 59% after SPD and 15% after EPD (p=0.006). Tumor stage 9 (30%) patients after EPD was changed from II to IV.

**Conclusion:** EPDs are technically and time-demanding procedures, but they are as safe as standard ones. EPD increases OS and significantly decreases the local recurrence rate. Longer OSR for stage 2b after EPD can be explained by the efficacy of EPD and by inadequate staging after SPD. There were 20 radical and 10 extended radical operations among EPD, one vessel resection in SPD (1.6%) and 9 (30%) in the EPD group.

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**P199**

**SOLID PSEUDOPAPILLARY NEOPLASM OF THE PANCREAS: A DESCRIPTIVE NAME FOR AN OLD STILL ENIGMATIC ENTITY.**

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**Background:** Solid pseudopapillary neoplasm (SPN) of pancreas is infrequently-encountered tumor typically affecting young women without significant symptoms. Its behavior is relatively indolent and largely benign.

**Material and methods:** We report a case series of four patients with SPN of pancreas. Clinicopathological and immunohistochemical parameters as well as therapy and follow-up were investigated retrospectively.

**Results:** All four patients were female whose ages ranged between 15 and 42 years. Two patients presented with abdominal pain, one with abdominal mass and one with acute abdominal signs following blunt trauma. Tumor’s size ranged between 1 and 16 cm. Two of them were diagnosed preoperatively through percutaneous-needle-biopsy and two underwent surgery because of high clinical and radiological suspicion of SPN. By immunohistochemistry, all cases were stained strongly for vimentin, progesterone-receptor and beta-catenin and variably with pankeratin and neuroendocrine markers. Proliferation index (Ki-67) was less than 2%. After median follow-up of 25 months, all patients were alive with no evidence of disease.

**Conclusion:** SPN of pancreas should be considered in differential diagnosis of any solid or partly cystic pancreatic or upper abdominal mass, particularly in young females. It has low malignant potential and treatment of choice consists of surgical resection. Adequate surgical intervention is associated with excellent prognosis.

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**P200**

**SHORT AND LONG-TERM MORTALITY AFTER PANCREATIC RESECTIONS IS DECREASED IN HIGH-VOLUME CENTERS**

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**Background:** Performing pancreatic surgery in high-volume centers has lead to decreased perioperative morbidity and mortality. However, there is sparse data on whether hospital volume affects the long-term outcome.

**Aim:** To evaluate the effect of hospital volume on perioperative and long-term mortality after pancreatic resections in Sweden.

**Methods:** Using the Swedish Patient Register, data on all patients who underwent pancreatic resection between 1987 and 2008 was collected. By linkage to the Swedish Cancer Register, information on underlying malignancy was retrieved. Information on the date of death was retrieved by linkage to the Swedish Cause of Death Register. Multivariate Cox regression analyses were performed to study the effect of hospital volume on short- and long-term mortality after pancreatic resection.

**Results:** Overall, 6,101 patients undergone pancreatic resection were identified during the period. Hospitals were defined according to Birkmeyer criteria into low volume (LV: 1-2 resection/year) and high volume (HV: > 16 resections/year) hospitals. Adjusted for age, sex, Charlson index, type of procedure, tumor location, and time period the overall (HR 0.76; CI 0.67-0.85), 90-day (HR 0.87; CI 0.73-0.99), and 5 year (HR 0.82; CI 0.71-0.95) mortality was decreased in HV compared to LV hospitals (p<0.01). Considering only resections due to malignant disease 90-day (HR 0.65; CI 0.45-0.93) and 5-year (HR 0.61; CI 0.39-0.93) mortality was further decreased in HV compared to LV hospitals (p=0.01).

**Conclusion:** Centralization of pancreatic surgery to high-volume centers results in decreased perioperative mortality and better long term survival. Centralization should be further encouraged.

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**P201**

**PANCREATIC PURE HEPATOID CARCINOMA: A REVIEW OF THE LITERATURE**

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**Introduction:** Hepatoid carcinomas (HCs) are uncommon extrahepatic neoplasms exhibiting features of hepatocellular carcinomas in terms of morphology and immunohistochemistry. Pancreatic forms of HCs can present in pure forms or in association with other morphological aspects, such as endocrine tumors or ductal adenocarcinomas.

**Aims/Objectives:** To evaluate demography, clinical presentation, cytological and histological findings before and after surgical excision. To discuss possible etiological pathways.

**Patients/methods:** Retrospective analysis of personal experience was performed. A literature review based on a Medline® search was undertaken.

**Results:** A total number of 19 pancreatic HCs, 9 of which as pure forms was found. Six patients were female (31.5%), 13 males (68.5%). Mean age was 51.4 years (range 21–80). Most common presenting symptoms were pain (33.3%), followed by weight loss (22.2%), nausea/vomiting (16.6%) and jaundice (16.6%). Elevated AFP serum levels were found in 55.5% of cases at time of diagnosis. 6 patients (33.3%) underwent preoperative cytological examination: in only one case (16.6%) a correct diagnosis was possible. Long term follow up after surgical excision shows divergent results.

**Discussion:** Demography and common presenting symptoms are typical of a slow growing mass forming tumor. Cytology is most of the times non diagnostic, while histology on specimen seems to be straightforward. Once complete surgical resection can be achieved, outcome seems to be related to the possible association with other pancreatic neoplasms. The common embryologic origin of the pancreas and liver, together with peculiar environmental factors, may explain their development.

**Conclusions:** Pancreatic HCs are extremely uncommon neoplasms presenting with non-specific clinical, laboratory and cytological findings. Further studies are needed to clarify pathogenesis and postoperative long-term outcome.
P202

EARLY DRAINAGE VERSUS DELAYED DEBRIDEMENT FOR FULMINANT NECROTIZING PANCREATITIS

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Introduction: Controversy still exists in surgical management of fulminant acute pancreatitis.

Material and methods: From 2000 through 2010, 21 patients with fulminant acute pancreatitis were managed surgically. All patients had severe clinical deterioration during initial period of treatment. 15 patients underwent early (during first 2 weeks) open drainage with delayed necrosectomy - group 1, others were operated on 3rd or 4th week of the disease (debridement with open packing or closed lavage) - group 2.

Results. Median (IQR) admission APACHE II score didn't differ between groups amounting 23,5 (18-26) and 20 (18-27) for gr. 1, 2 respectively. There were no any significant differences in local complications severity: gr. 1 Balthazar CT index - 7 (6-10) vs gr. 2 CT index - 7.5 (6-8). All 6 patients of delayed surgery group had infected necrosis at the time of operation. It was significantly more often then in gr. 1 - 26,7% (4/15), p<0.05. Among 15 patients managed with early drainage 7 died (46,7%). Mortality rate in gr. 2 reached 83,3% (5/6). Deaths in all patients were caused by sepsis-induced organ failure. Mortality rate differences between groups didn't reach statistical significance.

Conclusion: Widely accepted strategy: to delay surgery waiting for pancreatic necrosisdemarcation seems to be not as beneficial in fulminant pancreatitis as in case of severe acute pancreatitis.

P203

EARLY DRAINAGE VERSUS DELAYED DEBRIDEMENT FOR FULMINANT NECROTIZING PANCREATITIS

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Conclusion: Widely accepted strategy: to delay surgery waiting for pancreatic necrosisdemarcation seems to be not as beneficial in fulminant pancreatitis as in case of severe acute pancreatitis.

P203A

PANCREATIC INCIDENTALOMAS IMPLICATE A POTENTIALLY CURABLE DISEASE WITH FAVORABLE OUTCOME AND SHOULD THEREFORE ALWAYS BE CAREFULLY EVALUATED

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Background Asymptomatic “en passant” found pancreatic incidentalomas (PI) are increasingly being detected. They are usually treated according to guidelines for symptomatic pancreatic lesions (SPL) even though evidence is scarce.

 Aim To compare diagnoses, N-stage and outcome after resection of PI and SPL respectively.

Methods Primary pancreatic resections (indication chronic pancreatitis (CP) excluded) from 2004-09 were collected from our prospective registry. Histology, demographics, morbidity, mortality and survival analysis was done.

Results In all 360 cases were identified (PI = 35, 9.7 %). Compared to SPL, overweight was more prevalent in PI (63 vs. 36 %; p<0.01), but demographics, morbidity, mortality were not different. Cystic lesions were observed in 66 (18 %) and compared to SPL, cysts were more prevalent in PI (51 vs. 14 %; p<0.001) with a trend towards non-mucinous cysts (56 vs. 31 %; p=0.09). The diagnoses differed between PI and SPL: malignant 26 vs. 66 %; pre-malignant 29 vs. 13 %, pNET 17 vs. 8 %; benign 28 vs. 6 %, and CP 0 vs. 7 % (P<0.001). In malignant lesions there were no difference in N-stage (PI 57 vs. SPL 76%; p=0.4). Overall survival rate was better for PI compared to SPL (2 years 77 vs. 63 %, 5 years 74 vs. 46 %; p=0.02) but there were no differences in diagnosis related survival.

Conclusion Almost half of PIs are either pre-malignant or of non-exocrine origin. Incidental pancreatic lesions found “en passant” should therefore be carefully evaluated as they implicate a potentially curable disease.

P203B

BACKGROUND AND DESIGN OF MULTICENTER RANDOMIZED STUDY: PANCREATICOJEJUNOSTOMY VERSUS PANCREATICOGASTROSTOMY IN PATIENTS WITH SOFT RESIDUAL PANCREAS AND SMALL DIAMETER OF PANCREATIC DUCT

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Introduction Pancreateco-duodenectomy is the standards procedure for various disease of the pancreas and periampullary region. Pancreateco-jejunostomy (PJ) anastomosis is the most often used method of reconstruction after pancreateco-duodenectomy. Pancreatic fistula (PF) remains a common complication and the main cause of other morbidities and mortality. Several technique
modifications such as placement of the stents, reinforcement of anasomosis with fibrin glue, pancreatic duct occlusion and pancreatico-gastrostomy (PG) type of anastomosis was used in order to decrease PF rate. It was shown that the higher risk of PF was noticed in patients with soft residual pancreas and small diameter of pancreatic duct. Randomized multicenter controlled study (PanAm) was conducted to compare differences in morbidity between PG and PJ in these patients.

Patients and methods: Ninety-four patients with soft pancreas and small pancreatic duct will be randomly allocated to two groups: I) reconstruction of digestive tract using PJ anastomosis or II) reconstruction of digestive tract using PG anastomosis. Patients will be recruited from 5 hospitals during two years period. The primary endpoint is the total morbidity rate within hospitalization. Secondary endpoints are pancreatic fistula rate, mortality and duration of hospital and ICU stay. A total sample size of 94 patients was calculated to demonstrate that PG type of anastomosis can reduce total morbidity rate from 40% to 20% with 80% power at 5% alpha.

Objective: To share certain histological evidences. Merging different entities into one definition makes sense if their differentiation presents an unnecessary challenge and/or their detection entails applying the same therapeutic approach.


Results: No case of groove pancreatitis was revealed in 94 patients with soft pancreas and small pancreatic duct. Diabetes mellitus developed thrice after PD.

Conclusions: The term “paraduodenal pancreatitis” was proposed as an umbrella for cystic dystrophy in heterotopic pancreas (DD), paraduodenal cyst and groove pancreatitis, by reasoning that these conditions mimic pancreatic head tumors and share certain histological evidences. Merging different entities into one definition makes sense if their differentiation presents an unnecessary challenge and/or their detection entails applying the same therapeutic approach.

P130
LONG-TERM SURVIVAL AFTER WHIPPLE PROCEDURE AND TWO SUBSEQUENT MULTIORGAN RESECTIONS FOR PANCREATIC CANCER RELAPSES. CASE REPORT

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Background: Local recurrence of pancreatic adenocarcinoma (PA) is a typical reason for the denial of surgery based on the assumption that the survival time of this kind of patients is short.

Patient: Male, survived 4.5 years after three consecutive multiorgan resections for PA and its local relapses.

Results: Standard R0 pancreaticoduodenectomy (PD) was performed to 47-years old patient in 2007 for well-differentiated PA of the pancreatic head and followed by gemcitabine chemotherapy. A year and a half later excision of the pancreatic stump for recurring cancer and small bowel resection, right hemicolecctomy and extended lymphadenectomy for tumor recurrence in the pancreatic head bed were urgently performed against the acute cholangitis, caused by the efferent loop obstruction. There were no chemotherapy applied after that procedure. In 1.8 year PA relapse was revealed in retroperitoneal space, involving the celiac trunk, left adrenal gland and stomach. Taking into consideration the absence of distant metastases the tumor relapse with the celiac trunk, left adrenal gland, stomach and part of large bowel were excised followed by the common hepatic artery autovenous reconstruction. No tumor recurrence was detected 14 months later and the patient continued working at the time of the examination. Four years and a half after the first procedure the patient died due to diabetes mellitus decompensation.

Conclusion: Aggressive approach to PA local recurrency is justified in selected cases, prolonging survival with acceptable quality of life.

P131
ARTERIAL LIVER BLOOD SUPPLY AFTER MODIFIED APPLEBY PROCEDURE WITH EXCISION OF THE COMMON AND LEFT HEPATIC ARTERIES ON THE BACKGROUND OF MICHEL’S TYPE III ARTERIAL ANATOMY

Vishnevsky Institute of Surgery, Moscow, Russia

Background: Distal pancreatectomy with the celiac trunk excision (modified Appleby procedure, MAP) may be effective in selected cases of locally advanced pancreatic body cancer (PBC). We didn’t come across any description of left liver blood supply after MAP with excision of the common (CHA) and left hepatic (LHA) arteries.

Patients: Eight R0 MAP were performed on patients (48–67) with PBC (2008-2011). In seven cases the classical and in one case Michel’s type III arterial anatomy were revealed. In the latter case when the replaced right hepatic artery (rRHA) was originated from the SMA, the common and left hepatic arteries involved in tumor were excised. Liver blood supply was assessed in all cases by CT-angiography (CTA).

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Results. According to CTA data arterial liver blood supply takes place along the way “SMA - pancretoduodenal arcade - gastroduodenal artery (GDA) - proper hepatic artery (PHA) - LHA and RHA. After MAP with CHA and LHA excision in case of Michels’ type III right liver blood supply occurs through the rRHA and left liver – through the interlobar anastomoses between the branches of rRHA and LHA in the liver hilum. The sufficiency of the left liver blood supply was confirmed by intra- and postoperative color Doppler ultrasound. The stomach blood supply in all cases went through the way “GDA – right gastro-epiploic artery”.

Conclusion: Interlobar liver collaterals give the opportunity to sacrifice one of hepatic arteries during MAP if the other hepatic artery is preserved, liver hilum is intact and there is a possibility of Intraoperative US Doppler examination.
CLINICAL SCIENCE - BLOCK II
JUNE 22, 2012

P204

ECT DETECTION OF ACUTE POSTNECROTIC COLLECTIONS.

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

Objectives: To evaluate the ability of contrast-enhanced computerized tomography (CECT) to diagnose acute postnecrotic collections (APNC) over course of the disease.

Patients and Methods: Retrospective observation double centre study: performed to our patients with acute pancreatitis (AP) admitted in Gomel Regional Clinical and Mozyr City Hospitals in 2011. We studied the CT characteristics of APNC in various stages of the disease. Accuracy of CT differentiation we controlled by drainage and operation data.

Results: From 59 patients with AP collections were present in 23 (39%) cases and 9 (15%) of them were detected as APNC. CECT was performed within the first 10 days after admission and later on 20 - 71 day of necessity. In 5 patients collections were drained on mean 16,4 day and 3 of these were operated on mean 29,7 day. Necrotic masses in collection content detected by CECT were proved to be present perioperatively in all drained/operated patients and none of them had walls. We re-examined the density of APNC on preoperative CT scans and subjected obtained data to statistical analysis. The Hounsfield units’ analysis of CT images (Me [25%-75%]): early APNC HU=12,35 [9-16,2]; late APNC HU=18,4 [11,7-23,6]. According to Mann-Whitney analysis, the difference is statistically significant (p<0,001).

Conclusion: 1. Over the course of AP APNC becomes more homogenous, but the density increases.

P205

ACCURACY OF ENDOSONOGRAPHY FOR THE DIAGNOSIS OF PANCREATIC CYSTIC LESION BEFORE SURGERY

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Introduction: Cystic pancreatic lesions are of different origin and behavior but often have similar appearance during endosonography (EUS). Only part of them needs to be removed by surgery.

Aim: To describe ability of EUS to distinguish different types of cystic lesions

Method: All of the 57 patients (median of age 58, range 22-79) recommended to resection for cystic lesion between 2008 - 2011 were analyzed retrospectively. EUS findings, cytology, aspirate analysis were used to obtain preoperative diagnose. Finally, preoperative diagnoses were compared with postoperative pathological findings to establish level of EUS accuracy. The binary classification tests were used to evaluate the results.

Results: During 4 years 57 patients underwent resection for cystic lesion. We perform 14 (24 %) left-sided resection, 33 (58%) pylorus preserving pancreaticoduodenectomies, 2 (3%) duodenum preserving head resection and 2 (3%) total pancreatic resection. Palliative procedure was carried out in 7 cases (12%). Overall morbidity was 28%. 30 day mortality was 0%. 2 (3%) patients died after long lasting intensive care. Pathology revealed cystic lesion within chronic pancreatitis 37%, cystic tumor (38%), adenocarcinoma (14%) and the rest were unusual lesions. 19% were malignant and 81% benign. Sensitivity, specificity, positive and negative predictive value to identify tumorous noninflammatory lesions was 100%, 45%, 74%, 100%.

Conclusion: Low specificity of EUS can be cause of significant group of patients who undergo pancreatic resection for benign, inflammatory lesions as not potentially life threatening. Possible serious complications after pancreatic surgery are reason for precise selection of patients with cystic affections recommended to surgery.

P206

IN PANCREATIC SURGERY HEPATIC ARTERY VARIANTS DON'T AFFECT OUTCOME

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Introduction: Unexpected aberrant hepatic artery has an incidence of 10-20%.

Aim: to assess the incidence and type of hepatic artery variants in our series of pancreaticoduodenectomies and to investigate its relationship with the outcomes of the surgical procedure.

Patients and methods: from January 2010 to January 2012 we realized 106 consecutive pancreaticoduodenectomies for peripampillary tumors: 85 malignant, 6 neuroendocrine, 15 benign. We retrospectively analyzed operation reports and compared patients with arterial anomalies (group A) and without (group B).

Results: the group A consisted of 22 patients (20%), while group B of 84 (80%). Following Michels classification the group A is composed of: 2 patients belong to type 9, 17 to type 6, 2 to type 3 and 1 to type 8. Preoperatively CT scan revealed the arterial anomaly in 60% of cases in group A. Intraoperatively 96% of the patients had no injury of the aberrant artery during the dissection of the hepatic pedicle. The intraoperative data were: mean operative time 467±74 minutes in group A and 438±60 in B (p<0.05), mean blood loss 552±609ml and 409±594ml respectively (p=0.18). Surgical complications (37% in group A e 48% in B) and mortality rate were similar in both group. Radiality of resection in case of malignant disease was comparable (14% R1 in group A and 16% R1 in group B).

Conclusion: the presence of aberrant hepatic artery is observed in about 20% of cases and pre-operative recognized only in 60% of cases; its preservation significantly prolongs surgical time but doesn’t hamper radicality of resection.
P207

ENUCLEATION OF PANCREATIC HEAD TUMORS COMBINED WITH PRE-OPERATIVE WIRSUNG STENTING, INTRA-OPERATIVE ULTRASOUNDS AND ABSORBABLE FIBRIN SEALANT PATCH APPLICATION

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Introduction: enucleation of benign/low malignant tumors of the pancreatic head is technically demanding and often followed by high morbidity rates

Aim: to analyze the perioperative outcome of our series of enucleations for pancreatic head tumors.

Patients and methods: from February 2010 to February 2012 out of 119 resected pancreatic head/uncinate process tumors, 25 were cystic neoplasms and 14 neuroendocrine tumors (NET); in 10 of them (25.6%) an enucleation was performed. Enucleation was contraindicated in malignant lesions and when the tumor was deeply embedded in gland’s parenchyma involving the Wirsung duct. Endoscopic ultrasound was performed preoperatively in 9 patients. ERCP with Wirsung stenting was realized when the distance between the main pancreatic duct and the lesion was less than 3 mm (5 cases). Intraoperative US was performed in all the patients. At the end an absorbable fibrin sealant patch was placed on the area of enucleation.

Results: the mean diameter of the tumor was 2 cm (range 1-4.5); histology revealed 2 benign side branch IPMN, 7 G1 and 1 G2 NET. Mean operative time was 200.6±56.7 minutes, mean blood loss was 87±49.7 ml. No mortality was observed. Morbidity was 30%; 3 post-operative pancreatic fistula (2 grade B and 1 grade A). Mean length of hospital stay was 8±2 days. The reoperation rate was nil. Readmission regarded only 2 patients.

Conclusion: enucleation is a good alternative to pancreatectoduodenectomy in benign/low malignant tumors of the pancreatic head/uncinate. Pre-operative Wirsung stenting, intra-operative ultrasounds and fibrin sealant patch application can ameliorate the postoperative outcome.

P208

ARTERIAL VARIATIONS IN THE PANCREATIC REGION

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Introduction: The complex arterial system makes the pancreatic interventions technically challenging for surgeons, and interventional radiologists. The arterial variants may alter the tumor resectability, and cause complications in arterial embolization.

Aims: Data on the pancreatic blood supply in different countries are variable; therefore, we aimed to determine the frequency of pancreatic arterial variants in the Hungarian population.

Methods: Arteries of abdominal organ complexes (36) were injected with resin mixture, then corroded. Digital photos and CT images were taken.

Results: Classic anatomical variation occurred in less than 50%. Replaced and accessory right hepatic arteries were detected in 9.9% and 3.3%, respectively. In one case the proper hepatic artery branched off from the superior mesenteric artery (SMA). The gastroduodenal artery arose from the common hepatic in 94%, from the splenic in 3%, and from the right hepatic in 3%. Superior pancreaticoduodenal artery was found in 12.1%, while the anterior and posterior superior pancreaticoduodenal artery stem separately from the gastroduodenal artery in 69.7%. Inferior pancreaticoduodenal artery arose from the SMA in 42.8% and originated with the 1st jejunal in 25.7%. Anterior and posterior inferior pancreaticoduodenal arteries stem separately from SMA in 20%, from the accessory hepatic (from SMA) in 5.4%. Single transverse pancreatic artery occurred in 80%, and two in 20%. Except one case, multiple dorsal pancreatic arteries arose from the splenic.

Conclusion: Our results stress on the importance of the preoperative radiological analysis. Detection of replaced or accessory right hepatic artery is critical when performing pancreatectoduodenectomy, if not identified, may be injured.

P209

THE ROLE OF PREOPERATIVE EUS IN ADDITION TO CT IN PATIENTS SUSPECTED OF PANCREATIC OR PERIAMPULLARY CANCER

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Introduction: In patients suspected of pancreatic and periampullary cancer, abdominal computed tomography (CT) is the standard diagnostic modality to decide on laparotomy with curative intent. A supplementary endoscopic ultrasound (EUS) is often performed, without supportive evidence of added diagnostic value.

Aim: To evaluate the additional diagnostic value of EUS in deciding on exploratory laparotomy in patients suspected of pancreatic or periampullary cancer.

Methods: We retrospectively analyzed 86 consecutive patients who routinely underwent CT and EUS before exploratory laparotomy with or without resection for suspected pancreatic or periampullary carcinoma between 2007 and 2010. Outcomes were visibility of a mass and resectability (i.e. no locally advanced tumor or distant metastases) on CT/EUS, and resection with curative intent.

Results: A mass was visible on CT in 72/86 (84%) patients. In these 72 patients, EUS demonstrated a mass in 64 (89%) patients. Resectability was accurately predicted by CT in 64/72 (89%) and by EUS in 58/72 (81%) patients. In 14/86 (16%) patients no mass could be delineated on CT. EUS showed a mass in 12/14 (86%) of these patients. Overall, resectability was accurately predicted by CT and EUS in 90% (77/86) and 84% (72/86), respectively.

Conclusion: In patients with a discernible mass on CT, suspected for pancreatic or periampullary cancer, EUS has no obvious additional diagnostic value and does not influence
the decision to perform laparotomy. However, in patients without a visible mass on CT, EUS is useful to confirm the presence of a tumor.

P210

MINIMAL INVASIVE PROCEDURES IN PANCREATIC SURGERY - ARE THEY A GOOD OPTION FOR CYSTIC NEOPLASMS?

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INTRODUCTION: Cystic neoplasms of the pancreas don’t usually require operations. On average, 50% of those, which require surgical intervention, are situated in the tail. Their usually benign nature provides the opportunity to use minimal invasive surgery.

OBJECTIVES: The aim of the study was to analyse patients, who underwent surgery in our Department (especially laparoscopic resection) and whose histopathological examinations indicated cystic neoplasms of the pancreas.

PATIENTS & METHODS: Retrospective analysis covered 37 cases of patients (11M/26F) who underwent surgery in our Department between 2005 and 2011.

RESULTS: 445 major surgical procedures on the pancreas were conducted between 2005 and 2011. 37 patients were diagnosed with cystic neoplasms of pancreas, including 15 serious (1 cystadenocarcinoma serosum), 10 mucinous (5 adenocarcinoma mucinosum) and 12 IPMN (5 intraductal papillary mucinous carcinoma). 21 patients were diagnosed with solid tumors, 9 others with suspected cystic lesions, another 3 with mixed solid-cystic and 3 with IPMN. 18 Whipple procedures, 15 distal pancreatectomies and 3 total pancreatectomies were conducted on this group. 7 of the distal resections were conducted via laparoscopy. Compared with classic procedures, fewer complications were observed (28.6% vs 50%), less time was required for full rehabilitation (2 vs 4 days), and patients were discharged earlier (7 vs 8 days), with similar needs for painkillers. Postoperative deceases weren’t observed. The mean operating time was shorter in laparoscopy (87.14 vs 140.25).

CONCLUSION: As cystic neoplasms of the pancreas are tumors with good prognoses, well-differentiated and non-invasive laparoscopic distal pancreatectomy is usually a viable option for patients with lesions situated in the tail of the pancreas.

P211

INTRAPANCREATIC ACCESSORY SPLEEN MIMICKING A PANCREATIC NEOPLASM

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Accessory spleen is an anomaly affecting approximately 10% of the population. Usually diagnosed by radiologists and situated in the splenic hilum, it neither causes complications in examinations nor requires surgical intervention. Although the accessory spleen is common diagnosed, its intrapancreatic variety (IPAS) is rarely diagnosed correctly as mimicking a pancreatic neoplasm. In many cases, patients qualified for unnecessary pancreatic resection. A few cases of pancreatic resection of IPAS as a solid tumor have been recorded.

We present the case of a 54 year old female patient, who underwent surgery for a neuroendocrine tumor, with a large pancreatic tail mass, diagnosed by computer tomography. Laparoscopic distal resection of the pancreas was conducted. The perioperative period was complicated by an infection of the wound and suppuration. The patient was discharged on the 7th day after the operation. Postoperative histopathological examination revealed the intrapancreatic accessory spleen.

Accessory spleen mimicking a pancreatic tumor is difficult to diagnose. Some papers compare examination methods, but usually they are complicated, expensive and unavailable to patients. Moreover, in most of cases, EUS-FNA is impossible due to splenic vessels. In such cases, minimal invasive procedures appear to offer a good alternative to classic operations.

P212

FAST GROWING OF PANCREAS CANCER IN A PATIENT WITH FAMILY RISK: A CASE REPORT

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Background: A positive family history is a well defined risk factor for the development of pancreatic cancer. However, data is scarce regarding time of progression in these families and no clear guidelines are available about time interval and modality when to follow these individuals.

Clinical Case: A 47 year old male with two first-degree relatives dead of pancreatic cancer (mother 53 and sister 40 years respectively). In 2007 at the age of 43, the patient was included into a screening program by annual CT scans at a community hospital. In 2009, after two years of negative screening, it was suggested to increase the interval to biannual CTs. At the beginning of 2011 the patient was admitted due to abdominal pain and jaundice. Imaging showed a 3 cm large tumor in the head of the pancreas with encasement of a replaced right hepatic artery from the superior mesenteric artery. The patient underwent total pancreatectomy with en block resection of the right hepatic artery, rebuilt by a rotation end-to-end anastomosis to the splenic artery. Histology showed pancreatic ductal adenocarcinoma (pT3, pN1, pM0). At 12 months follow up no recurrence has been detected.

Conclusion: A positive familial history is a risk factor to develop pancreatic cancer. In this family, as suggested by the EUROPAC, two first-degree affected, with a cumulative age at the diagnosis less than 110 years, is an important risk factor. The current case suggests that an annual screening seems reasonable and safer than longer intervals of time.
P213

CLINICAL MANIFESTATION OF CHRONIC PANCREATITIS ASSOCIATED WITH SPINK1 MUTATIONS IN CHILDREN.

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Objectives: The reported paediatric experience with chronic pancreatitis is limited. The aim of our study was to evaluate frequency of SPINK1 mutations and their role as a cause of CP in children.

Methods: 204 children with CP, hospitalized since 1995 to 2011, were enrolled into the study. Medical records of these patients were reviewed for data on presentation, diagnostic findings and endoscopic treatment. All children were screened for SPINK1 mutations (MIM:167790).

Results: SPINK1 gene mutations were found in 37 patients (18%). 22 girls and 15 boys; mean age 11.6 years; range: 2.6-18. We detected N34S/- heterozygous in 29 patients. IVS3+2T>C/- heterozygous in 3 children, N34S/N34S homozygous in 3 patients and compound heterozygous IVS3+2T>C/N34S in 2 cases. In 9 patients we found coexisting gene mutations – CFTR in 8 and PRSS1 in 1 case. In 5 patients anatomic anomalies of pancreatic duct were observed: pancreas divisum - 3 and ansa pancreatica in 2 cases. Family history was positive in 14 cases (38%). There was no difference in age of the disease onset between SPINK1 group and group without SPINK1 mutations (9.2 years vs. 8.8 years;NS). In children with SPINK1 mutations ERCP had mean 1.70 Cambridge grade, vs. 1.60 in non-SPINK1 group; NS. There was no difference in the frequency of the calcifications in the imagine studies (32% vs. 35%;NS), pancreatic duct stenting (35% vs. 30%;NS) and surgical interventions (11% vs. 15%;NS).

Conclusions: SPINK1 mutations are common etiological factors in children with CP with similar clinical course as CP associated with other factors.

P214

AUTOIMMUNE PANCREATITIS IN BARCELONA AS ASSESSED BY THE HONOLULU DIAGNOSTIC CRITERIA. REVIEW OF A SERIES OF 16 PATIENTS.


Effective pharmacological treatment may avoid complications in autoimmune pancreatitis (AIP) but diagnosis remains challenging. According to the Honolulu consensus conference type 1 and type 2 AIP define differentiated histopathological and clinical modalities with therapeutic implications.

Aims: To describe clinical, imaging and histological features according to the Honolulu criteria in 16 Spanish AIP patients.

Methods: Histopathology (lymphoplasmocitic infiltrates, obliterative fibrosis, storiform fibrosis, IgG4+ cells, granulocytic epithelial lesions-GEL), imaging (diffuse or focal pancreatic enlargement with delayed enhancement, main duct strictures) and clinical features of 16 AIP patients were reviewed.

Results: 15 males and 1 female (17-73 years; mean 46,6) were studied. Ten patients were smokers and 5 alcohol abusers. Pancreatectomy was performed in 12 patients for suspected malignancy. Six had type 1 AIP and 10 patients type 2. Type 1 patients were older (56±4.8 vs 39±5.1 years). Presentation was (%) epigastric pain (75), weight loss (56), acute pancreatitis (50), jaundice (50), GI bleeding (37), fever (25), diabetes (19), diarrhea (19), dematiss (12), altered liver biochemistry (81), leukocytosis (50), antinuclear antibodies >1/160 (44), IgG4> 280 mg/dl (31) and raised CA19.9 (31).

Extrapancreatic involvement included chronic cholecystitis without gallstones (69), cholangitis (50), duodenitis (37), colitis (55), gastritis (31), hepatitis (19), and nextritis (19). Common imaging findings were focal (62) and/or diffuse (25) pancreatic enlargement, multiple main pancreatic duct stenosis and bile duct stenosis. Four patients had splenic vein thrombosis. Steroid therapy improved symptoms, IgG4 levels (523±143 to 181±16 mg/dl), extrapancreatic involvement and, occasionally, pancreatic function.

Conclusions: In Barcelona, 70% AIP have low IgG4 and 60% have type 2 features. Diagnosis is often made after pancreatic resection. Pancreatic biopsies should improve diagnostic yield and prevent unnecessary surgery.

P215

SHORT-TERM OUTCOME AND COST-BENEFIT ANALYSIS OF LAPAROSCOPIC LEFT PANCREATECTOMY: RESULTS OF A CASE-MATCH STUDY.

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INTRODUCTION To date, no RCT comparing laparoscopic (LLP) with open (OLP) left pancreatectomy is available. Existing data from single-institution series or heterogeneous multicenter comparisons reported shorter hospital stay after LLP, but no data regarding economic analysis have been published.

AIMS To compare short-term outcome and hospital costs of LLP versus OLP in a high-volume center.

METHODS Between 2009 and 2011, 53 consecutive patients underwent LLP. The first 10 cases were excluded as part of the learning curve. Each of the remaining 43 patients was matched with one control patient who underwent OLP, selected from our prospective electronic database. Match criteria were: gender, age (±5 years), ASA score (1-2, 3-4), BMI (<24, 24-30, >30), lesion site, type of disease. All patients were treated according to an enhanced recovery after surgery protocol. Hospital costs were calculated for each patient in both groups.

RESULTS No mortality occurred. Conversion rate in LLP group was 18.6%. Mean operative time(min) was 216±61 for LLP, 214±73 for OLP(p=0.885), blood loss(mL) was slightly reduced in LLP group(388±371 vs. 571±599, p=0.092) without affecting transfusion rate. No difference was found in overall morbidity (44.2% in both groups). Mean length of stay(days) was 7.37±3.0 in LLP group vs. 7.81±2.8 in OLP group(p=0.481). Median time(weeks) to return to preoperative performance was significantly lower in LLP group (3 vs. 5, p<0.001). Additional cost for laparoscopic instruments was €769 per patient. Overall savings in the LLP group were €168 (€155 due to shorter LOS, €13 due to reduced cost of complications). Net balance resulted in €599 extra-cost per LLP patient.

CONCLUSION Short-term outcome was similar in the two groups, however LLP was associated with a faster recovery of preoperative performance. The extracharge for LLP patients was almost equivalent to laparoscopic instrument costs.
**P216**

**SINGLE-CENTER EARLY RESULTS OF “DECOMPRESS” STUDY**

**(DECOMPRESSIVE LAPAROTOMY WITH TEMPORARY ABDOMINAL CLOSURE VERSUS PERCUTANEOUS PUNCTURE WITH PLACEMENT OF ABDOMINAL CATHETER IN PATIENTS WITH ABDOMINAL COMPARTMENT SYNDROME DURING ACUTE PANCREATITIS)**

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**Aims/Objectives:** To compare effects of decompressive laparotomy with temporary abdominal closure and percutaneous puncture with placement of abdominal catheter (“peritofix”) in patients with abdominal compartment syndrome (ACS) during severe acute pancreatitis (SAP).

**Patients and Methods:** Prospective study included 15 patients divided into two groups (8 with laparotomy, 7 with “peritofix”). APACHE II score, SOFA score, IAP, presence of sepsis were evaluated before and after procedures in all patients and comparison between two groups were assessed with ANOVA test.

**Results:** In the first group APACHE II score was 19.5±2.7 before and 15.7±3.1 after procedure, SOFA score 8±1.4 before and 6.4±1.7 after procedure, and IAP 22±1.4 before and 10±2.1 after procedure. In the second group APACHE II score was 19.7±3.9 before and 17.3±5.7 after procedure, SOFA score 8.4±1.4 before and 6.9±1.9 after procedure, and IAP 23±2.2 before and 14±3.2 after procedure. There was significant difference in APACHE II scores (F=16.964; p=0.001), SOFA scores (F=21.021; p=0.001) and IAP (F=137.932; p=0.001) before and after procedures, but no significant difference in APACHE II scores (F=0.776; p=0.394), SOFA scores (F=0.006; p=0.940) and IAP (F=2.423; p=0.144) changes between groups. In the first group sepsis was noted in one patient before and in 4 after procedure. Before procedure there weren’t patients with sepsis and sepsis was noted in 3 patients after procedure in the second group. Overall mortality was 53% (8 patients), 63% (5 patients) in the first group and 43% (3 patients) in the second group. There was no significant difference in mortality between groups (p=0.619).

**Conclusion:** Patients with ACS in SAP requires decompression procedure. Impact of procedures in reducing the systemic complications is similar, but lower incidence of sepsis and lower mortality rate is associated in patients with “peritofix”.

**Key words:** severe acute pancreatitis; abdominal compartment syndrome; decompression; outcome

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**P217**

**CORRELATION BETWEEN PROCALCITONIN AND INTRA-ABDOMINAL PRESSURE AND THEIR ROLE IN PREDICTION OF THE SEVERITY AND OUTCOME IN ACUTE PANCREATITIS**

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**Aims/Objectives:** Increased intra-abdominal pressure (IAP) can deteriorate compromised pancreatic perfusion and perfusion of abdominal viscera in early stages of acute pancreatitis (AP). Procalcitonin (PCT) can predict infection of pancreatic necrosis. The aim was to determine the correlation of PCT serum concentrations and IAP as prognostic markers in AP.

**Patients and Methods:** Prospective study included 51 patients, 29 with severe AP (SAP). At 24 h of admission patients were evaluated with APACHE II score, C-reactive protein (CRP) serum concentrations, PCT and IAP. PCT was measured three times in the first week of disease and three times after, while IAP was measured daily. The values of PCT and IAP were correlated between each other and compared with values of APACHE II score and CRP.

**Results:** Values of PCT, IAP, CRP and APACHE II score noted at 24 h of admission were significantly elevated in patients with SAP (p<0.001). There was noted a significant correlation between values of PCT and IAP measured at 24 h of admission (Δ=0.659, p<0.001), and between maximal noted values of PCT and IAP (Δ=0.692, p<0.001). In predicting the severity of AP at 24 h of admission, sensitivity and specificity was determined for APACHE II score (89%; 69%), CRP (75%; 86%), PCT (86%; 63%) and IAP (75%; 77%). The APACHE II scores and PCT serum values at 24 h of admission were significantly higher in nonsurvivors than survivors (p<0.001).

**Conclusions:** Increased IAP is accompanied with increased PCT serum concentration values, and could suggest a gut barrier dysfunction. PCT is a good marker for early assessment of the severity and outcome of AP. Elevated IAP and PCT values can be used as indicators of systemic complications.

**Key words:** intraabdominal pressure, procalcitonin, acute pancreatitis, severity, outcome

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**P218**

**SURGICAL TREATMENT OF PANCREATIC PSEUDOCYSTS**

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**Introduction.** A pancreatic pseudocyst is a circumscribed collection of fluid rich in pancreatic enzymes, blood, and necrotic tissue, typically located in the lesser sac of the abdomen, and are usually complications of pancreatitis.

**Objective.** Analysis of patients operated for pancreatic pseudocysts during 5 year period.

**Patients and Methods.** During the period from 2005 to 2010, a total of 101 patients were treated for pancreatic pseudocysts in our department at First Surgical Clinic, Belgrade, Serbia. They were retrospectively reviewed and followed up. There were 68% men, between 18 and 85-years-old (mean age 58.3 years).
Results. Dominating symptoms in most patients were epigastric pain, palpable mass, nausea, vomiting, fever and leukocytosis, and persistent elevation of serum amylase. Imaging studies, such as ultrasound, CT scan, and ERCP were used in establishing the diagnosis. Operative procedures consisted of external drainage (ED, 9 cases), internal drainage using cystojejunostomy (CJ, 85% cases) and cystogastrostomy (CG, 10 cases), and distal pancreatectomy (4 cases). The following complications were observed including recurrence of cyst (1 patient with ED and 1 with CJ), delayed massive bleeding (1 with CG), pancreatic fistula (3 with ED, 3 with CJ, 1 with CG), pancreatic abscess (1 with CJ) and persistent pain (1 with CG). Reintervention was needed to stop bleeding in 1 patient with CG. No deaths occurred.

Conclusion. Although complications do occur in surgical treatment, cystojejunostomy is still gold standard for treatment of pancreatic pseudocysts.

P219
EXTENDED DRAINAGE PROCEDURES IN SURGICAL TREATMENT OF CHRONIC PANCREATITIS - FREY PROCEDURE
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Introduction. Chronic pancreatitis is defined as a chronic inflammatory condition characterized by recurrent bouts of acute exacerbation which eventually results in a defective restitution after acute pancreatitis. Pain is the principle symptom although its exocrine/endocrine insufficiency are also equally important. A number of procedures have been developed in the 20th century to deal with it. There is no procedure evolved so far to provide a 100% cure to this condition.

Objectives. The outcome of the Frey procedure, postoperative complications, pain relief and preservation of endocrine and exocrine function of pancreas.

Methods and Patients. From 2002 to 2011, 45 patients with chronic pancreatitis underwent the Frey procedure at First Surgical Clinic, Belgrade, Serbia. The etiology was alcoholic in about 90%, and idiopathic in 5 patients. The majority of patients were male (82%), with mean age of patients about 47 years. The mean follow-up was 22 months. A scoring system was used for assessing the severity of pain and it consisted of a visual analogue scale, frequency of pain attacks, analgesic requirement and time of disease-related inability to work. Pancreatic exocrine function was assessed by the presence of steatorrhea. Pancreatic endocrine insufficiency was assessed using an oral glucose tolerance test.

Results. The most common postoperative complication was pancreatic leakage and it occurred in 10% of our patients. Complete pain relief was achieved in 92% of patients. Exocrine pancreatic function was not altered in any of patients. Endocrine pancreatic function was preserved in 89% of patients. One patient recurred reoperation, and one death occurred.

Conclusion. Frey procedure provides a good pain relief in majority of patients diagnosed with chronic pancreatitis. It also enables preservation of endocrine and exocrine function of pancreas.

P220
THE NON-DISAPPEARING PANCREATIC CYST AFTER DRAINAGE
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Background: The natural history of the cystic lesions of the pancreas is still uncertain. Since some of the lesions have higher potential for malignant transformation, their identification and treatment is substantial. However, the differential diagnosis could be challenging.

Clinical case: A 55-year old female patient with no history of pancreatitis was incidentally diagnosed with a 10-cm cyst with a single septation in the tail of the pancreas during hysterectomy. The cyst cytology and serology were normal and after confirming benign histology on intraoperative biopsy, diagnosis of congenital cyst was placed and cysto-gastrostomy was performed due to technical challenge to resect. During 10-year follow-up the cyst did not decrease in size and more septations appeared. The patient was referred to us 10 years later with a few-week history of recurrent cyst infections. She was operated due to suspicion of mucinous cyst neoplasm with distal pancreatectomy, splenectomy, left-sided nephrectomy and hemicolectomy, and a local gastric resection with uneventful postoperative course. The final pathology revealed a mucinous cystic neoplasm with foci of high-grade dysplasia, but no invasive cancer.

Conclusion: The differential diagnosis of cystic lesions of the pancreas should not rely on biopsy of the cystic wall. In cystic lesions without apparent association with pancreatitis, and particularly if initial treatment intention fails should the initial diagnosis be reassessed and without delay be further referred to highly-specialized centers for diagnosis and treatment.

P221
OUTCOMES AND PROGNOSTIC FACTORS FOLLOWING PANCREATICODUODENECTOMY FOR CHOLANGIOCARCINOMA
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Introduction: Distal cholangiocarcinoma has a UK incidence of approximately 200 cases/year. There are limited small studies identifying clinicopathological prognostic factors following pancreaticoduodenectomy for distal cholangiocarcinoma which report a 5-year survival of around 24%.

Objectives: To identify clinicopathological prognostic factors following pancreaticoduodenectomy for distal cholangiocarcinoma.

Methods: Patients with a histological diagnosis of cholangiocarcinoma following pancreaticoduodenectomy from 1997-2011 were identified from a prospectively maintained database. Perioperative blood tests, pathological findings and survival data were collected. Kaplan-Meier survival curves were produced, and differences assessed using the Log-Rank
test for univariate analysis. Multivariate analysis was performed using a Cox Proportional Hazard model. 

Results: 104 patients (60 male, 44 female) were identified with a median age of 65 years (IQR 57-70 years). There were 3 perioperative deaths (2.9%). Median overall survival was 17.9 months (95%CI 14.6-21.3 months) and 5-year survival was 18%. Univariate analysis revealed raised post-operative CA19-9 (p=0.014), tumour differentiation (p<0.001), tumour stage (p=0.002), lymph node involvement (p=0.002), positive resection margin (p<0.001) and number of positive margins (p<0.001) to be significant predictors of survival. On multivariate analysis, positive resection margin status (HR=2.27, 95%CI 1.32-3.85, p=0.003), raised post-operative CA19-9 (HR=1.93, 95%CI 1.13-3.25, p=0.013) and tumour differentiation (HR=2.04, 95%CI 1.20-3.50, p=0.009) remained significant independent prognostic factors.

Conclusion: This study is the largest of its kind in a European population and concurs with previous studies regarding the prognostic significance of resection margin status and tumour differentiation. These data suggest for the first time that post-operative CA19-9 levels are useful in predicting outcome following pancreaticoduodenectomy for distal cholangiocarcinoma.

P222

PROGNOSTIC FACTORS IN GEMCITABINE/CISPLATIN POLYCHEMOTHERAPY REGIMENS INPANCREATIC CANCER: XPD-LYS751GLN POLYMORPHISM STRIKES BACK

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Background: Recently the most relevant therapeutic progress in metastatic pancreatic cancer has come from the combination of several cytotoxics, such as the FOLFIRINOX, and the cisplatin-epirubicin-5-fluorouracil-gemcitabine, cisplatin-doxetaxel-capcitabine-gemcitabine (PDXG), and cisplatin-epirubicin-capcitabine-gemcitabine (PEXG) regimens.[Reni et al., Cancer Chemother Pharmacol 2012]. However the improved survival versus gemcitabine-alone did come at the cost of a significant increase in hematologic/extra-hematologic toxicities. Pharmacogenetic studies to identify patients who could benefit most from such therapies are urgently needed.

Aim/Methods: The Xeroderma-Pigmentosum-factor-D (XPD) polymorphism at codon-751 (XPD-Lys751Gln) emerged as the most significant independent predictor for death - and progression-risk in our previous pharmacogenetic study on 11 functional polymorphisms in 122 advanced pancreatic cancer patients treated with PDXG/PEXG.[Giovannetti et al, Pharmacogenomics 2011]. Therefore, we further evaluated the correlation of XPD-Lys751Gln with clinical outcome in 246 patients treated with the same regimens.

Results: Genotyping was successfully carried out in the vast majority of samples. Genotype frequencies followed Hardy-Weinberg equilibrium, and no correlations were detected with age, gender, performance-status, CA19-9 or stage. At univariate analysis, XPD-Lys751Gln was associated with differential progression-free and overall-survival, and the Cox model used for the multivariate analysis confirmed its prognostic significance. In particular, XPD-Gln751Gln was significantly associated with risk of death (hazard ratio, HR=1.7, 95%CI, 1.1-2.6, P=0.011) and risk of progression (HR=1.7, 95%CI, 1.1-2.5, P=0.013).

Conclusions: The increasing evidence of XPD-Lys751Gln impact on the outcome of gemcitabine/cisplatin-polychemotherapy leads to plan prospective studies. Ultimately, the validation of the role of this polymorphism will offer a new tool for optimization of currently available treatments in pancreatic cancer.

P223

AFTER PANCREATODUODENECTOMY, PANCREO-GASTROANASTOMOSIS PRODUCES A GREATER IMPAIRMENT OF RESIDUAL FUNCTION THAN PANCREO-JEJUNOSTOMY

-RESULTS OF AN 8 YEAR FOLLOW-UP.


Introduction. No long term comparison is available of residual pancreatic function after pylorus-preserving pancreatectoduodenectomy associated either with pancreateojunostomy (PGA) or pancreateojunostomy (PJA) anastomosis.

Methods. We recalled patients who 6 years ago had entered, in our high volume, referral Centre, a controlled, short term comparison of PGA and PJA. Studied parameters were RNM with secretin infusion (presence of atrophy and of impaired secretion), exocrine (faecal elastase-1, faecal fat balance, serum vitamin D) and endocrine function (Hb1C, fasting and postprandial glycaemic sticks), signs of malnutrition (decrease in body mass index, serum prealbumin levels) and quality of life (EORTC QLQ-C30 questionnaire).

Results. We studied 34 patients (16 PGA, 18 PJA; age 56.6±2.7 vs 57.5±2.5 years; time from surgery 81±5 vs 80±3 months). No difference was found in variation of BMI since operation, prealbumin and parameters of endocrine function. Quality of life was similar to normal values in both groups. On the contrary, exocrine function was more severely impaired after PGA (steatorrhoea 26.6±4.1 vs 18.2±3.6 g/day, nv<7; FE1 70.2±25.5 vs 121.4±6.7 mcg/g, nv>200; vitamin D 18.1±1.8 vs 23.2±3.1ng/ml, nv >28; p always <0.05). In PGA, RNM showed a higher proportion of pancreatic atrophy (81% of PGA patients vs 39% of PJA) and, after secretin infusion, of impaired secretion (42% vs 18 % respectively).

Conclusion. The anastomosis of pancreatic duct with the stomach is associated, in the long run, with more severe impairment of exocrine function than pancreateojunal anastomosis.
P224

PERCUTANEOUS DRAINAGE OF INFECTED NECROSIS IN SEVERE ACUTE PANCREATITIS

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Introduction: Infected necrosis (IN) in severe acute pancreatitis (SAP) represents a life-threatening complication, as the main indication for surgery.

Purpose: To assess the outcome of SAP patients with IN managed primarily by ultrasound guided percutaneous catheter drainage (PCD), and to find predictors for successful outcome.

Methods: The study is a retrospective review of 28 SAP patients with IN managed primarily by PCD in a tertiary referral center, from 2007 to 2011. Results of two groups were compared: Group 1 – 16 patients (semi-solid necrosis) drained during weeks 3-4 of evolution, and Group 2 (WOPN = walled-off pancreatic necrosis) - 12 patients managed after 4th week. There were no differences regarding the number of collections and extent of necrosis between the 2 groups. Logistic regression was used to determine predictors of PCD success.

Results: Eighteen patients (64.2%) were successfully treated with PCD alone: 8 (50%) from Group 1 and 10 (83.3%) from Group 2. Catheter drainage duration averaged 72.3 days in Group 1 (higher number of drains, continuous lavage, change of antibiotics) and 18.6 days in Group 2. Surgical treatment was necessary in 10 patients: 8 in Group 1 (2 deaths) for unsolved sepsis; 2 in Group 2 for external pancreatic fistula. Complete liquefication, extent of necrosis, and use of large catheters were independent predictors for successful outcome.

Conclusion: PCD should be considered as initial therapy in patients with WOPN, and as a staging method for resolution of sepsis prior to surgery during weeks 3-4 of SAP evolution. Selection of patients, time of PCD performance and a skilful technique with adequate size catheters insertion is of critical importance.

P225

THE RELATION OF METABOLIC SYNDROME WITH COMPLICATIONS IN ACUTE PANCREATITIS

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Introduction: Metabolic syndrome seems to increase the likelihood of cardiovascular diseases in general population, but has not been evaluated in AP.

Aims/Objectives: To determine whether or not there is a connection between the metabolic syndrome (MetS) and AP.

Patients & Methods: Medical histories of 178 patients diagnosed with AP during the years 2008 through 2010 were analyzed. The International Diabetes Federation (IDF) parameters were used in diagnosing MetS. The effect of MetS on AP was determined through the occurrence of local and/or systemic complications of AP, using the Atlanta classification system. The statistical analysis was performed using the Mann-Whitney U-Test and the χ2-test.

Results: Of the 178 patients, 93 patients suffered from MetS. The percentage of patients with distinct AP complications in the MetS vs. non-MetS group was 39.8±5.1% vs. 30.6±5.0% for local complications (p=0.20) and 30.1±4.8% vs. 16.4±4.0% for systemic complications (p=0.03). When the groups were subdivided according to the number of complications into two subgroups (first with only one and the second with multiple complications), it was noted that the MetS patients more often suffered from multiple complications compared to patients without MetS. Again, this was statistically significant for systemic complications (p=0.024), but not for local ones.

Conclusion: The presence of MetS seems to coincide with the occurrence of systemic complications of AP, especially in the case of multiple systemic complications.

P226

UP FRONT RFA FOR LOCALLY ADVANCED Pancreatic CANcer: SHORT AND LONG TERM RESULTS

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Introduction: In recent studies radiofrequency ablation (RFA) has been applied to treat locally advanced pancreatic carcinoma (LAPC). The right timing of RFA in order to achieve best results in survival has still to be defined.

Aim: We analyse short term results and survival after up front RFA.

Patients and Methods: All patients with a new diagnosis of LAPC were prospectively enrolled. RFA was performed as previously described by our group. Indications for RFA were: lack of diagnosis, need for palliative surgery or intraoperative finding of unresectable disease. Complications RFA-related were identified. Survival rate was calculated with Kaplan Meier.

Results: Between February 2007 and December 2011, 66 received RFA as up front treatment. M/F ratio was 39/27 and median age was 68 yrs. Tumor was located in the pancreatic head in 69,6% of cases and median preoperative value of Ca19.9 was 113U/mL (IQR 31-509). Postoperative course was uneventful in 68,7% of pts whereas abdominal complications occurred in 30,3% and were RFA related (thermal injuries) in 16% of cases. Mortality rate was 3%; one patients died for duodenal perforation and the other for infected pancreatic collection. Overall survival is 16 months (IQR 13-25) and at this time 28,5% of pts are alive with stable disease (15%), progression of disease (7,5%), partial downstaging (1,5%) and disease free (4,5%).

Conclusion: RFA is an option to consider when surgery is needed for LAPC. At this time the procedure does not seem to offer an advantage in ameliorating prognosis for these patients.
Patients with CEL-MODY were recruited by Stage III PDAC. Chemotherapy (CHT) followed by RFA in a population affected used for solid tumors and recently adopted for Stage III PDAC. Radiofrequency (RFA) is a well known local ablative technique disease even when diagnosis is made at early stages. We have, with physiological investigations, demonstrated a severely reduced pancreatic ductal and acinar function in CEL-MODY preceding diabetes.

**P227**

**CEL-MODY CAUSES BOTH DUCTAL AND ACINAR PANCREATIC INSUFFICIENCY**

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**Introduction** CEL-MODY is a novel autosomal dominant condition characterized by low fecal elastase from early childhood, eventually leading to steatorrhea and diabetes mellitus from early adult age.

**Objectives** To study exocrine pancreatic function in CEL-MODY patients.

**Patients/methods** Patients with CEL-MODY were recruited through the Norwegian MODY registry, and compared to healthy volunteers. Pancreatic exocrine function was examined by rapid endoscopic secretin test (REST) and secretin stimulated MRCP quantification (MRCPQ). Duodenal juice was analyzed for peak levels of bicarbonate, lipase, amylase, elastase and chymotrypsin.

**Results** Sixteen patients and 23 controls underwent REST, while 23 patients and 20 controls underwent MRCPQ. In duodenal juice mean bicarbonate levels were 52.0 ± 21.5 mEq/L in patients and 110.8 ± 34.6 mEq/L in healthy controls. Mean enzyme levels in duodenal juice in patients and controls were for lipase 2799 ± 4105 U/mL and 38280 ± 19850 U/mL respectively, for amylase 37.0 ± 21.4 U/mL and 377.6 ± 327.0 U/mL respectively, for elastase 0.003 ± 0.004 U/mL and 0.157 ± 0.101 U/mL respectively, and for chymotrypsin 0.07 ± 0.09 U/mL and 2.97 ± 1.63 U/mL. All differences were significant at the level p<0.001 except for amylase that was significant at the level p=0.008. Mean volume increase to duodenum measured by MRCPQ the first 12 minutes after secretin stimulation measured by MRCPQ was 4.7 ± 2.4 mL/min in patients and 6.9 ± 1.8 mL/min in controls, p=0.002.

**Conclusions** We have, with physiological investigations, demonstrated a severely reduced pancreatic ductal and acinar function in CEL-MODY preceding diabetes.

**P229**

**METASTATIC TUMORS OF THE PANCREAS: A SINGLE CENTRE STUDY**

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**Introduction:** The occurrence of metastatic tumor to the pancreas is low, the incidence is under 2% of all pancreatic malignancies. The role of a radical intervention is very questionable. Most of the patients with metastatic tumor in the pancreas has widespread metastatic disease, moreover the operativ risk of a radical pancreatic surgery can be high.

**The aim** of our study was to rewiev our surgical experience with surgical management of pancreatic metastases in the last 15 years.

**Patients and Methods:** In the period of January 1997 and February 2012, 49 patients with pancreatic metastases, 27 women and 22 men were examined. Patient’s ages ranged from 48-84 years with a mean age of 68.95 years.

**Results:** Primary malignancies were renal cell carcinoma 30.6%, lung carcinoma 14.4%, colorectal adenocarcinoma 8.2%, melanoma 6.1%, gastric cancer 4.1%, oesophageal cancer 4.1%, lymphoma 4.1%, small intestine 4.1%, moreover we had 1 cases from each of the following tumors: breast cancer, ovarian cancer, gall bladder and malignant paranglioma. Overall follow-up period was 12.8 months. Comparison of the survival rates of the different malignancies, significant better survival (p<0.05) was observed in renal cell carcinoma than in other cases. Only 53% of the patients underwent surgical intervention, that represents 46% radical resection and 44% palliative surgery.

**Conclusion:** The overall survival rate correlates with the primary disease, that partly explains the better survival rate in the renal cell carcinoma. Early diagnosis of the pancreatic metastasis and subsequent radical resection may result in a prolonged survival.

**P228**

**SHORT TERM CHEMOTHERAPY FOLLOWED BY RFA: A NEW PROTOCOL FOR STAGE III PANCREATIC CANCER?**

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**Introduction** Pancreatic carcinoma (PDAC) is a systemic disease even when diagnosis is made at early stages. Radiofrequency (RFA) is a well known local ablative technique used for solid tumors and recently adopted for Stage III PDAC. The right timing of its application is not clear.

**Aim** We want to evaluate the efficacy of a short neoadjuvant chemotherapy (CHT) followed by RFA in a population affected by Stage III PDAC.

**Patients and methods** All patients consecutively observed with a diagnosis of non metastatic and not resectable pancreatic carcinoma were sent to receive short chemotherapy (4-6 months). After therapy they undergo a re-stadiation and only patients with persistence of locally advanced disease were proposed for RFA. After discharge patients received external RT and follow up was carried on every three months with serum markers and CT scan. Time to progression (TTP) and overall survival were then calculated.

**Results** Between February 2007 and December 2011, 49 patients underwent RFA after receiving CHT for 4 months (median; IQR: 0-6.25). CHT was Gem based in 94% of cases. Eighty eight percent of treated patients had uneventful course but one patients died because of the procedure. Median survival was 17 months (IQR: 10-25) with a TTP of 11 months. At this time 43% of patients are alive with progression (14%), stable disease (24.5%) or disease free (4.5%).

**Conclusion** The combination of a short CHT followed by RFA and external RT can be an interesting multimodal option to treat Stage III PDAC.
P230

CLINICAL, MORPHOLOGICAL AND FUNCTIONAL ASPECTS OF PATIENTS SUFFERING FROM PANCREATITIS ASSOCIATED WITH MUTATIONS OF CFTR AND SPINK1 GENES.

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Background: Sporadic pancreatitis may be associated with mutations of CFTR and SPINK1 genes. The clinical and instrumental outcome of pancreatitis associated with gene mutations (GM) differ from pancreatitis not associated with GM. New data are present in literature about clinical, instrumental and functional profiles of pancreatitis associated with CFTR GM compared to those of pancreatitis associated with SPINK1 GM.

Aim of this study was therefore to compare patients suffering from pancreatitis associated with CFTR and SPINK1 GM. Patients and methods: Clinical, instrumental and functional data from our prospective database of patients suffering from pancreatitis associated with GM were selected. The diagnosis of GM was gathered by investigation on 35 more common CFTR GM and the 2 main SPINK1 GM (N34S and P55I) on leukocyte DNA extracted from anticoagulated blood specimens. Patients with clinical history strongly suggestive for cystic fibrosis underwent HPLC and, if abnormal, a complete sequence of CFTR gene was performed. Patients were divided in 3 groups: CFTR-S (single CFTR GM), CFTR-D (compound CFTR GM) and SPINK1 (single or double SPINK1 GM).

Results: 86 pts (54 M, 32 F, mean age at clinical onset 29.8 ± 15.3 yrs) were studied, 57 (66%) in CFTR-S group (35 M, 22 F, mean age 31±13.9 yrs), 12 (14%) in CFTR-D group (8 M, 4 F, mean age 24.2±15.8 yrs) and 17 (20%) in SPINK1 group (11 M, 6 F, mean age 30±19.2 yrs). 11 pts (13%) suffered from painless pancreatitis. No differences were observed, in episodes of pancreatitis, need for an endoscopic approach, evolution toward pancreatic insufficiency. However, a diagnosis of chronic pancreatitis (p=0.007) and onset of calcifications (0.002) were more commonly observed in SPINK1 group. 24 pts (27%) underwent surgery, 12 derivative-type and 12 demolitive -type. 6 pts developed a pancreatic neoplasia (4 adenocarcinoma and 2 IPMNs) at a mean age of 58 yrs (range 48-72), and 4 patients died for pancreatic adenocarcinoma.

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

P231

PREVALENCE OF PANCREATIC CANCER AMONG PATIENTS WITH NEWLY DIAGNOSED DIABETES MELLITUS

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Introduction: In a certain portion of patients, newly diagnosed diabetes mellitus (DM) is a symptom of otherwise asymptomatic pancreatic cancer (PC). A specific clinical profile has been proposed in literature to differentiate between ordinary DM and DM secondary to PC.

Aims: Endosonographic investigation (EUS) of a group of newly diagnosed diabetics with suspicious clinical profile to exclude underlying PC.

Patients and methods: A group of 64 newly diagnosed diabetics fulfilling a given clinical profile (sudden onset of DM in age over 55 years, rapid progression to insulinotherapy, unstable diabetes with severe insulinresistance etc.) was investigated with EUS to exclude asymptomatic PC.

Results: Abnormal EUS findings were described in 17 patients (26,6%). None of them were PC. Chronic pancreatitis (ChP) was discovered in 4 patients (6,2%), nonspecific changes not meeting ChP criteria in 7 (10,9%), cysts in 5 (7,8%), in 1 patient (7,8%) side branch IPMN was diagnosed.

Conclusion: A clinical profile did not prove helpful in defining high risk population for PC among newly diagnosed diabetics. Therefore, we did not confirm the results of other authors (Ogawa et al. 2002, Damiano et al, 2004) who found PC in over 7% of newly diagnosed diabetics in their groups. Differentiating factors other than the clinical profile are needed.

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P232

CORRELATION BETWEEN PANCREATIC NECROSIS AND ORGAN FAILURE IN PATIENTS WITH NECROTIZING PANCREATITIS

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Background: Developments of pancreatic necrosis and organ failure have a serious influence on the course of necrotizing pancreatitis (NP). The aim was to evaluate the relation between pancreatic infection, extent of necrosis and organ failure in patients with NP.

Patients and Methods: This prospective study included 71 patients with diagnosis of NP admitted to Clinic for Emergency Surgery between 1996-2000. Diagnosis of NP 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 extent of necrosis has a strong impact on the occurrence of organ failure in NP. 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.
P233
HEMOSTATIC ABNORMALITIES AND THE SEVERITY OF ILLNESS IN PATIENTS WITH SEvere NECROTIZING PANCREATITIS

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Background: Disturbances of coagulation and fibrinolysis are well-known systemic effects of severe acute pancreatitis (SAP). The purpose of this study was to find out whether changes within the hemostatic system are related to severity of illness.

Patients and methods: This prospective study included 41 patients with SAP. The coagulation, anticoagulation and fibrinolysis variables: prothrombin ratio, activated partial thromboplastin time, fibrinogen, antithrombin III (AT III), protein C, plasminogen activator inhibitor-1 (PAI-1), d-dimer, alfa-2 antiplasmin and plasminogen were measured on day of admission (day 1) and on days 3, 5, 7, 10 and 14. At the end of study, two groups were compared: 26 survived (group S) and 15 non-survived patients (group D).

Results: Protein C levels were low on days 1, 3, 5, 7 and 14, in nonsurvivors and on day 1 in survivors. On the day 3 the difference between both groups was statistically significant. AT III levels were decreased on days 1 and 3 in survivors and on days 1, 3, 5, 7, 10 and 14 in nonsurvivors. On day 5 levels in survivors and nonsurvivors became significantly different. The PAI-1 levels were high in both groups on days 1, 3 and 5. On day 7 the difference between survivors and nonsurvivors reached statistical significance. The d-dimer levels were high in group D on days 1, 3, 5, 7, 10 and 14 and on days 1, 3 and 5 in survivors. Values on day 7 were significantly different between groups.

Conclusion: Changes in protein C, AT III, d-dimer and PAI-1 levels indicate exhaustion of fibrinolysis and coagulation inhibitors in patients with poor outcome during the course of SAP.

P234
ROLE OF HEMATOCRIT IN THE EARLY PREDICTION OF SEVERITY OF ACUTE PANCREATITIS

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Background: The early and accurate prediction of the severity of acute pancreatitis (AP) and the assessment of prognosis of the disease are very important and can influence the course of disease and outcome. The aim of this study was to determine the relation between hematocrit level on admission and AP severity.

Patients and methods: This retrospective study included 91 patients treated in the Clinic for Emergency Surgery, Clinical Center of Serbia. Patients were divided into two groups: patients with severe (SAP) and patients with mild AP (MAP). Severity of acute pancreatitis (SAP) was defined according to Atlanta classification system. Patients main characteristics curves (age, gender), etiology and result of the treatment were determined, as well as value of hematocrit on admission. Receiver operation characteristics (ROC) analysis determined cut-off value, sensitivity and specificity of hematocrit level as parameters for prediction of severity of AP.

Results: Group with SAP consisted of 33 (36%) patients and group with mild AP consisted of 58 (64%) patients. Average hematocrit level on admission was: 44% for SAP and 41% for MAP patients. For hematocrit cut-off level on admission (44%), sensitivity and specificity for prediction of severity of AP were 63.5% and 85.7% respectively.

Conclusion: The assessment of AP severity can be based on hematocrit level on admission that is higher than 44%. Among all the variables available, the value of hematocrit on admission can be a useful and cost-effective marker which provides significant predictive power for clinical decision-making.

P235
EXPRESSION OF TLR2 IN MONONUCLEAR CELLS IN PERIPHERAL BLOOD OF PATIENTS WITH SEVERE ACUTE PANCREATITIS DURING THE TREATMENT WITH NSAID “LORNOXICAM”.

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Introduction: Severe acute pancreatitis (SAP) is accompanied by a systemic inflammatory reaction which may lead to multiple organ failure in a number of cases. Toll-like receptors (TLR) are an important component in development of an inflammatory cascade.

The purpose of this study is to analyze the expression of matrix RNA (mRNA) of TLR2 receptors of mononuclear cells in peripheral blood of SAP patients.

Materials and methods: 19 patients at the age of 20 to 60 years with SAP caused by dietary factors were examined. The group 1 included 10 patients receiving the standard treatment alone. The basic treatment of patients in the group 2 (19 patients) also included a NSAID “Lornoxicam” which was introduced by intravenous dripping within the first five days after admission. Peripheral blood was sampled for tests on days 1, 3, 7 and 14 after the admission. The group of healthy donors included 20 subjects at the age of 20-45.

Results: The expression level for TLR2 mRNA in mononuclear cells of SAP patients was significantly higher (p) than that of healthy donors (p) on the first day of the disease. Further increase of TLR2 mRNA expression was observed on days 3 and 7 in the first group. Their insignificant decrease as observed on day 14. In the 2 group, TLR2 mRNA expression was significantly lower on days 3, 7 and 14 as compared to patients in the 1 group.

Conclusion: The TLR-2 system should be considered a marker for SAP severity, which may also be used for assessment of efficacy of the treatment performed. Administration of Lornoxicam permitted to decrease TLR2 mRNA expression in mononuclear cells in peripheral blood of SAP patients.
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**PANCREAS RESECTION DUE TO RENAL CANCER METASTASIS TO THE PANCREAS—REPORT OF A CASE**

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**Introduction:** Distant spread from renal cell carcinoma is commonly found to the liver and lungs. Metastatic involvement of any other gastrointestinal organ (duodenum, other kidney, adrenal gland) is unexpected. Clear cell renal carcinoma however is known to cause pancreatic metastasis.

**Objectives:** The authors present an 82 year old male patient, who was successfully operated because of a metastatic tumor localised in the pancreas.

**Patient and methods:** Eight years prior to the current hospitalization, left sided nephrectomy was performed due to clear renal cell carcinoma. Because of subileus, upper abdominal pain and weight loss CT scan was performed that revealed a tumor localised in the pancreatic tail. Distal pancreas resection was performed with splenectomy.

**Results:** In the postoperative period a reoperation was performed because of adhesion small bowel obstruction. The patient was discharged on the 12th, postoperative day. The histological examination revealed clear cell renal carcinoma metastasis. On the 22nd month control the patient was free from any complaints and evidence of any recurrence.

**Conclusions:** In most of the cases pancreatic tumors are primary alterations. Renal cell carcinoma generally give hepatic and pulmonary metastases. However, clear cell renal carcinoma is known to give pancreatic metastasis that are candidates for resection with good results.

P236

**AUSTRALASIAN EXPERIENCE WITH HEREDITARY PANCREATEATIS (HP) TESTING.**

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For the past five years this laboratory has offered screening for the known missense mutations associated with hp. Screening involves sequencing of PRSS1 exons 2-5, SPINK1 (exons 1 and 3), and exon 3 of CFTR. The majority of referrals come from Australia, although 3 kindreds with pathogenic mutations have been detected in Christchurch (popn. 400,000). The usual indication for referral is recurrent pancreatitis in an adult, or clinical evidence of pancreatitis in a child. A common experience is physician failure to provide adequate clinical evidence for reason-to-test. The number of tests is highly variable, with just 7 in 2009, and 37 during the past 12 months. Two relatively unusual mutational defects identified include a triplication of the cationic trypsinogen gene (confirmed by microarray analysis) and a SPINK1 intron 1 splice-site substitution. The serendipidous finding of PRSS1 R122C heterozygosity in a middle-aged Caucasian male with a 30-year history of chronic pancreatitis resulted in an illuminating and instructive clinical study.

P237A

**NEUTROPHIL - LYMPHOCYTE RATIO - A NEW SCORE FOR PREDICTING COMPLICATIONS IN PATIENTS WITH ACUTE PANCREATEATIS**

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**Background:** According to the available literature, most of the scoring systems used in predicting the severity of acute pancreatitis (AP) use total white blood counts as one of their components. We tried to asses whether recently developed neutrophil-lymphocyte ratio (NLR) could predict complications in patients with AP and which cut-off values are useful for predicting local and/or systemic complications.

**Methods:** We retrospectively analyzed 169 patients with AP who were hospitalized in our Department during the period from January 2007 to September 2010. The primary outcomes were local complications and/or systemic complications of AP. To assess diagnostic accuracy of each parameter, ROC curve analysis was performed. The results are presented as AUC ± SD error. The p value was calculated and a cut-off of 0.05 used as level of significance.

**Results:** Of 169 patients with AP, 57 had local complications, while 38 had systemic complications. After comparison of areas under the curve (AUC) of the receiver operator characteristics (ROC) of NLR, NLR score ≥ 5.09 had the sensitivity of 87.8% and specificity of 90.2% (AUC=0.82; p=0.0026) in predicting local complications, while NLR score ≥ 6.8 had the sensitivity of 76.3% and specificity of 48.9% (AUC=0.64; p=0.0054) for predicting systemic complications n patients with AP.

**Conclusion:** Our results imply that NLR score could be used in predicting the development of complications in acute pancreatitis patients and that considered cut-off values for predicting local and/or systemic complications are higher than in those recently published.