AISP - 28th National Congress. Verona (Italy). October 28-30, 2004

(The abstracts are published as submitted by the authors)

ORAL COMMUNICATIONS

Somatostatin and Gabexate Are Ineffective in Preventing Post-ERCP Complications

Andriulli A, Solmi L, Loperfido S, Festa V, Belmonte A, Leo P, Spirito F, Silla M, Forte G, Terruzzi V, Mescia P, Ciliberto E, Mauro M, Monica F, Perri F, on behalf of the Italian Group for Prevention of Acute Pancreatitis (GIPPA 2 study)

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Background The issue whether it is possible to prevent pancreatic damage by the prophylactic administration of somatostatin (SS) or gabexate (GM) is still debated.

Aim Aim of this study was to assess the efficacy of these drugs for prevention of post-ERCP pancreatitis.

Methods A double-blind, multicenter, placebo-controlled trial was conducted in 966 patients who randomized received an intravenous infusion of SS (750 µg, n=290), GM (500 mg, n=327), or placebo (saline, n=349) that was started 30 minutes before endoscopy and continued for 6 hours afterward. Patients were evaluated clinically and serum amylase levels determined at 4 and 24 hours after endoscopy.

Results No significant difference in the occurrence of pancreatitis, hyperamylasemia, or abdominal pain was observed among placebo (6.9%, 33.5%, and 4.0% respectively), SS (7.6%, 26.6%, and 2.8% respectively), and GM (6.1%, 32.7%, and 4.0% respectively). At univariate analysis of patients characteristics and endoscopic maneuvers, the Freeman' score for difficult cannulation (P<0.001), more than 3 pancreatic injections (P<0.001), an intradiverticular papilla (P=0.01), and bile duct diameter less than 8 mm (P=0.04) were associated to post-ERCP pancreatitis. At multivariate logistic analysis only more than 3 pancreatic injections (OR=1.72, 95%CI: 1.15-2.59), and the Freeman' score (OR=1.41, 95%CI: 1.08-1.86) were predictive of post-ERCP pancreatitis.

Conclusion Long-term (6.5 hours) administration of SS or GM is ineffective for prevention of post-ERCP pancreatitis. Pancreatic injury is related to maneuvers used to obtain biliary access rather than any patient characteristics.

Cell-Mediated Immune Functions Before and After Chemotherapy in Advanced or Metastatic Pancreatic Carcinoma Patients

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Background The survival rate for patients with pancreatic carcinoma is among the poorest for all cancers. Host defense against tumor does not appear to be induced effectively, suggesting potential impairment of cell-mediated immunity. NK and T cells both play a critical role in the effector phase of immunologically mediated tumor rejection, and their development and expansion depend on the cytokines produced by T helper cells.

Aim The study investigates the cell-mediated immune status of advanced or metastatic pancreatic carcinoma patients before and after chemotherapy.
Methods We studied 12 patients (age range 51-84); 6 underwent treatment with 5-FU continuous infusion for 6 weeks, cisplatin weekly and gemcitabine on days 1, 8, 28, and 35. Check-ups were programmed every two months. Peripheral blood mononuclear cells (PBMC) were obtained from patients and normal subjects. Lymphocyte subsets were determined by flow cytometry. Interleukin (IL)-12 and IL-10 was determined by ELISA in lipopolysaccharides (LPS)-stimulated PBMC culture supernatants, while Interferon (IFN)-gamma was measured in anti-CD3-activated lymphocyte culture supernatants. NK and LAK-mediated cytotoxicities were investigated against K562 and Daudi cells, respectively.
Results No difference in either absolute number or surface phenotype of T (CD3, CD4 and CD8) or NK cells (CD56) was observed in patients versus healthy subjects. LPS-stimulated PBMC from patients produced higher levels of IL-12 total p40 (P=0.03) and IL-10 (P=0.02), and lower levels of bioactive IL-12 p70 (P=0.006) than in normal individuals, while IFN-gamma levels produced by activated T cells from patients were found to be significantly lower (P=0.03), both NK and LAK-mediated cytotoxicities were also defective. From 2 to 4 months after the end of chemotherapy, in 75% of patients CD4+ cell percentage had significantly increased (P=0.009) and there was a slight decrease in IL-12 p40 production but no significant changes in IL-12 p70, IL-10 or IFN-gamma. While NK cell activity had not altered after chemotherapy, in 50% of treated patients LAK activity was enhanced.
Conclusions The results suggest that an altered balance between anti- (IL-10) and pro-inflammatory (IL-12, IFN-gamma) cytokines might be responsible for the defective cell mediated anti-tumor immunity in advanced or metastatic pancreatic carcinoma patients. Additional larger studies are required to correlate changes in cellular immune functions and clinical response to therapy.

Three Hypervascularized Lesions of Duodenal and Jejunal Tract in a Patient with von Recklinghausen's Disease: An Exceptional Triade?

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Case report DD, a 47-year-old man, was admitted in our hospital on April 2004 with the diagnosis of duodenal carcinoids in a patient with von Recklinghausen's disease. The medical history starts on September 2002 with melena. Based on a gastroduodenal endoscopy with biopsy, a Barret disease was diagnosed and a specific medical treatment was started. Colonoscopy was negative for bleeding lesions. On December 2003, due to the recurrence of melena and to transitory diarrhea, the patient was admitted to another hospital. He was submitted to an enteroscopy until 100 cm from Treitz ligament with evidence of two sub mucosal ulcerated lesions on Papilla major e minor; diagnosed at microscopic examination as carcinoids. The diagnostic suspicious was turned toward a hypothetical duodenal gastrinoma. However, laboratory findings, even if high gastrin level were found, showed a negative secretin test. Aspecific endocrine tumor markers were within the normal values (NSE 8.5 ng/mL, normal values <12.5 ng/mL; CgA 50 ng/mL, normal values 19-98 ng/mL) as well as for laboratory routine tests. No mutations for MEN I gene was observed. An intestinal contrast medium X-ray and an abdominal CT raised the suspicion for another lesion on ileal site, whilst octreoscan was negative for all the

aforementioned lesions. The patient was sent to our Department for a surgical approach. On April 2004 he underwent to laparotomy which demonstrated multiple liver metastases, as new element. A frozen section of one of them was positive for hepatic met of endocrine carcinoma. After an intra-operative US assessment all the liver lesions were judged as completely resectable. Moreover, intestinal examination confirmed at 50 cm from Treitz a brownish lesion, 6 cm in size with exophytic growth. The patient was operated upon of pancreaticoduodenectomy (Whipple procedure) with jejunal resection up to the distal lesion, extensive lymphadenectomy, and multiple metastasectomies. Procedure was considered with radical intent. Final pathological assessment established the presence of a papilla major and minor "somatostatinoma" (well differentiated endocrine neoplasm) with strong immuno-hystochemical expression of somatostatin, ki67 <1%, 6 out 73 positive nodes, 4 solid localization in peripancreatic tissue, 6 endocrine liver hepatic mets, a jejunal GIST with uncertain behavior (c-kit ++; ki67 <1%).
Conclusions Even if gastrointestinal tract involvement is not rare in von Recklinghausen's disease, at our knowledge, this is only the third report of synchronous association between the disease, jejunal GIST and ampullary endocrine tumors.

Case Report of an Intraductal Papillary Mucinous Neoplasm of the Uncinate Process

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Context Intraductal papillary mucinous neoplasms (IPMNs) are usually identified by imaging findings such as the ectasia of the main pancreatic duct (central IPMNs) with a possible involvement of the side branches of the ductal system (branch-side IPMNs). Clinical and demographic criteria should also be considered: patients older than 60 years with pancreatitis-like pain, weight loss, diabetes, jaundice and elevated CA 19.9 level could be related to malignancy of the neoplasm. IPMNs may led to chronic pancreatitis (CP); moreover, in some cases, a distinction between these two diseases can be difficult, in particular when the IPMN involves the entire gland.
Case Report We report the case of a 68-year Caucasian male admitted at the Department of Surgery of the University of Verona for obstructive jaundice. His medical history includes a right colectomy for cancer in 1984 and pulmonary lobectomy for metastasis 3 years later, a cholecystectomy for gallbladder stones in 1994 and an endovascular exclusion of aortic aneurysm in February 2004. The patient presented with vague and intermittent upper abdominal pain and a significant weight loss (25 kg in 4 months). At admission the bilirubin serum level was 22.63 mg/dL, CEA 8.3 ng/mL and CA 19.9 level 184 U/mL. ERCP showed a regular ampulla and a stenosis of the intrapancreatic bile duct associated with a dilation of the intrahepatic bile ducts; the main pancreatic duct was seen only 2 cm far from the papilla of Vater. CW MR showed dilation of the main pancreatic duct and of the side branches of the pancreatic head. These findings suggested the presence of an IPMN located in the head of the pancreas.
The patient underwent surgery and submitted to pylorus-preserving pancreaticoduodene-ctomy. The postoperative course was uneventful and the patient was discharged in 10th postoperative day. The pathologic findings showed the presence of a large intrapancreatic pseudocyst (diameter 3 cm) involving the head of the pancreas between the main bile duct and the Wirsung and of CP in the pancreatic remnant.
Discussion We reported a case of clinical, laboratory data including tumor markers level

and imaging findings suggesting the preoperative diagnosis of a pancreatic head malignant IPMN. Histology examination of the surgical specimen revealed the presence of intrapancreatic pseudocyst associated with CP without any evidence of neoplasm.

Conclusion Even if the etiology of chronic pancreatitis is still unknown this patient represents in our experience the first case of misdiagnosis between branch-side IPMNs and CP.

May an Experimental Model of Intraductal Papillary Mucinous Neoplasm of the Pancreas Have a Clinical Meaning?

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Background In the last decade intraductal papillary mucinous neoplasms (IPMNs) have turned from a rare entity to a continuously increasing disease. While their clinical knowledge and management have been consequently improved, the biology of IPMNs and their behavior to malignancy, however, are still largely unknown. Being surgery the only curative approach, resection is mandatory, but its indication in early stages or in elderly patients and its extent in multifocal disease is still a matter of debate. Finally no further treatment is effective in unresectable patients.

Aim and Methods In our opinion, the availability of an experimental model could be helpful in better understanding the biological features of IPMNs. With this purpose, we implanted in nude mice surgical samples from a 66 years-old female submitted to Longmire-Traverso procedure for pancreatic head IPMN.

Results The tumor was successfully implanted. The xenograft was then established in five following steps, all reproducing the primary pattern, and grew as a large burden with peritoneal diffusion. The pathological assessment of invasive IPMN confirmed preoperative diagnosis and the patient is still alive and free of disease 6 years after surgery. So we are able to report the first experimental model for IPMN. No mutations in K-ras, p53 and p16 typical of ductal carcinoma were found neither in primary nor in implanted tumor, this furthermore proving the xenograft derived from the invasive component of IPMN. We are about to characterize the phenotypic profile.

Conclusions A real and stable experimental model for IPMN appears to be an effective tool in investigating the genetic and biological features of this tumor and in understanding its behavior in the progress to malignancy. A deeper knowledge of these aspects brings at last on a clinical impact, since it may help us to better manage the patients suffering from IPMN and select those undergoing surgery. Finally, the availability of such an experimental model enable us to test in preclinical studies chemotherapeutic drugs and adjuvant treatments for unresectable patients.

Margins Involvement in Pancreatic Cancer Resection

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Background The achievement of radicality in pancreatic cancer resection is considered one of the main determinant of survival.

Aim The aim of this study was to define the incidence of margins involvement (stratifying patients in microscopic and macroscopic

involvement), the pattern of failure after non-radical resections and the relation between margins invasion and postoperative survival.
Patients and Methods From 1990 to 2002, 296 patients underwent resection for non-metastatic ductal pancreatic adenocarcinoma. Patients were classified according to the UICC-R classification: R0: no margins involvement; R1: microscopic involvement, R2: macroscopic residue. Statistical analysis was performed by the chi-square test, log-rank test and Cox regression analysis (covariates stage, grading and nodal status).
Results One-hundred and 75 patients (59%) underwent R0 resection, 68 patients (23%) and 53 patients (18%) underwent R1 and R2 resection, respectively. The most frequently involved margin was the posterior one (69%). Follow-up was considered adequate to define the pattern of failure in 202 out of 296 patients. Local relapse (LR) was found in 52 patients (40%) after R0 resection, 15 patients (39%) after R1 and 18 patients (53%) after R2 (P NS). IORT was applied in 127 patients. IORT had no protective effect on LR: in R0 patients LR was found in 42% of patients receiving IORT and 41% of patients who did not (P NS); in 56% of R1+2 patients receiving IORT and 45% of R1+2 patients who did not (P NS). The difference between survival curves of patients with different margin status was significant when considering R0 versus R1+2 ($P<0.01$). However, the survival difference was not significant when considering R0 versus R1 resection ($P=0.2$). Also the multivariate analysis confirmed that radicality was an independent prognostic factor when considering R0 versus R1+2 patients; however, the microscopic margins involvement (R0 versus R1) was not a significant determinant of survival.
Conclusion Margin invasion is found in about 40% of patients. R0 resection does not warrant for a reduction of LR nor for a significant prolonged survival when compared to R1. R2 resections have a worse prognosis, but they can offer a good palliation. IORT did not reduce LR in non radical resection.

Effect of Different Therapies on the Survival of Pancreatic Neuroendocrine Tumors

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Aim To evaluate the efficacy of different therapies in patients with pancreatic neuroendocrine tumors (NET).
Patients Eighty-three (37 M, 46 F) consecutive patients with pancreatic NET diagnosed in our Department from 1978 to 2003.
Main outcome measures Clinical check-up and abdominal US were carried out every 3 months during the first year after diagnosis and every 12 months thereafter. Survival was estimated by means of the Kaplan-Meyer, and the Mantel-Cox model was applied to identify putative factors affecting the survival.
Results The median age of patients at diagnosis was 55 years (range 19-81) and the median age at the last observation was 60 years (range 29-82). The median follow-up period was 36 months (range 3-264). Fifty-two patients (62.7%) had non-functioning NET, 16 (19.3%) had functioning NET and 15 (18.1%) had MEN 1 disease with pancreatic involvement. The tumor was localized in the pancreatic head in 31 cases (37.3%), in the body in 24 cases (28.9%), in the tail in 21 cases (25.3%) and was diffuse throughout the gland in 7 cases (8.4%). In 55 patients, the median size of the tumor

evaluated at imaging techniques was 4.1 cm (range 1.0-11.3) and, in 41 patients, the median size at surgery was 5.0 cm (range 1.0-13.0). Twenty-seven patients (32.5%) had liver metastases at the time of diagnosis and 43 (51.8%) developed liver metastases during the follow-up period. Involvement of the lymph nodes was found in 47 out of 79 patients (59.5%). The median Ki67 evaluated on 29 histological specimens was 2.9% (range 1.0-84.1). Forty patients (48.2%) had radical surgery, 20 (24.1%) had debulking surgery and 23 (27.7%) were treated medically. Of the latter 23 patients, 19 (82.6%) underwent at least one of the following treatments: somatostatin-analogs in all cases, interferon in 3 (15.8%), chemotherapy in 2 (10.5%) and chemoembolization in 2 (10.5%). Forty-nine patients (59.0%) were still alive at the time of the study; the median survival time was 90 months (95% CI 29-151) and the 5-year survival was 55.3%. Survival was significantly related to: age of patients at diagnosis (OR per 10 years 1.38, 95% CI 1.04-1.83; P=0.026), presence of metastases (liver metastases at diagnosis: OR 5.42, 95% CI 2.63-11.17, P<0.001; presence of lymph node involvement: OR 4.97, 95% CI 1.91-12.90, P=0.001), type of the tumor (overall P=0.033; functioning vs. MEN: OR 7.63, 95% CI 1.64-35.51, P=0.010; non-functioning vs. MEN: OR 4.65, 95% CI 1.07-20.13, P=0.040) and type of treatment (overall P<0.001; no surgery vs. radical surgery: OR 5.20, 95% CI 2.12-12.72, P<0.001; debulking vs. radical surgery: OR 4.29, 95% CI 1.76-10.48, P=0.001). Survival was not significantly related to: sex (P=0.151), age of patients (P=0.965), localization of the tumor (P=0.646), size of the tumor both at imaging techniques (P=0.222) and at surgery (P=0.325), and Ki67 determination (P=0.341).
Conclusions Radical surgery continues to have a central role in the therapeutic approach to NET of the pancreas.

3D Respiratory Triggered MRCP Versus Conventional MRCP in the Evaluation of Branch Duct Intraductal Mucinous Papillary Tumors

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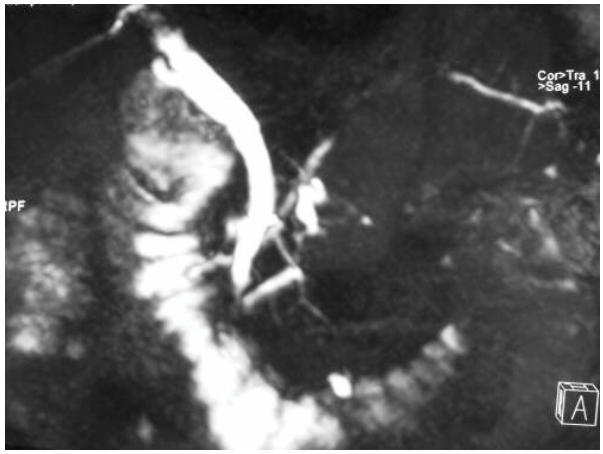
Background Branch duct intraductal mucinous papillary tumors (IMPTs) are reported increasingly often. MRCP has replaced ERCP for the diagnosis.
Aim To compare the utility of 3D respiratory triggered HASTE and thick-slab RARE sequences in the demonstration of the communicating duct of pancreatic IPMTs of the collateral branches.
Methods Thirty-six consecutive patients with an ERCP diagnosis of branch duct IPMT were referred for MRCP, which was performed with both 3D respiratory triggered HASTE and thick slab RARE sequences. In 14 patients secretin was administered in order to better visualize the MPD, after 2 mL of gadolinium to improve the image quality. Images were viewed by two independent observers, blinded to the real nature of the cystic lesion.
Results 3D MRCP images of diagnostic quality were obtained in 34/36 patients: in 31/34 (91%) the communicating duct was visible. 2D RARE images of diagnostic



quality were obtained in 36/36 patients: in 25/36 (69.5%) the communicating duct was visible.

Conclusions Thanks to its superior spatial resolution, 3D MRCP is better suitable for establishing a diagnosis of branch duct IPMTs than RARE sequences and almost equals the diagnostic accuracy of ERCP in demonstrating the communicating duct. RARE sequences maintain their fundamental role in the dynamic evaluation of pancreatic function.

Acute Pancreatitis Due to Simvastatin Therapy: Increased Severity After Re-Challenge

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Introduction Statins are generally well-tolerated and acute pancreatitis has been reported in only a few cases treated with this drugs. However, there have not been many cases reported regarding the re-challenge evidence.

Case report A 64-year-old man presented at the Emergency Room of our Hospital complaining of epigastric pain of 16 hours duration accompanied by nausea and vomiting. There was no history of alcohol ingestion or previous abdominal surgery. He had had an acute myocardial infarction 6 months before. The patient had been treated for the previous 6 months with simvastatin 20 mg once daily for hypercholesterolemia and with beta-blockers and aspirin for ischemic heart disease. No other medication was used regularly. On physical examination, the abdomen was distended with hypoactive bowel sounds and diffuse tenderness which was maximal in the epigastrium; no rebound tenderness was present. Laboratory data on admission showed increased serum amylase and lipase activity (amylase: 2,884 IU/L, reference values: 0-220; lipase 3,245 IU/L, reference values 0-270). Serum values of urea, creatinine, AST, ALT, alkaline phosphatase, triglycerides, cholesterol, calcium and bilirubin were normal. Abdominal ultrasound revealed parenchymal alterations compatible with pancreatic edema; the biliary tree was not dilated and no gallstones were seen. The patient was conservatively treated and simvastatin was discontinued. In December 2003, the patient reintroduced simvastatin 20 mg once daily, on his own initiative, and seven days later, he felt epigastric pain. Laboratory examination revealed increased serum amylase and lipase activity (1,814 IU/L and 4,504 IU/L, respectively), and C-reactive protein concentration (27.3 mg/dL, reference values: 0-0.8). Abdominal ultrasound carried out on admission revealed an enlargement of the pancreas, there was also a dilation of the main pancreatic duct, whereas the gallbladder and the common bile duct were normal. A contrast-enhanced CT scan was carried out two days after admission and revealed a dishomogeneous enhancement of the pancreatic head with a small necrotic area and peripancreatic fluid collection. The patient was treated conservatively, and clinical and laboratory parameters progressively ameliorated. Two months later, an endoscopic ultrasound was carried out and no alterations of the bile duct system were seen.

Conclusion As the use of statins increases, the diagnosis of acute pancreatitis is being made more frequently in patients who develop abdominal pain of unknown etiology while taking these medications. When the pancreatitis is clinically confirmed, the drug should be stopped and replaced to reduce the possibility of further episodes of pancreatitis, especially in the form of more severe disease; the patient should also be aware of the risk involved in the reintroduction of the drug on his own initiative.

TAP and Acute Pancreatic Damage. A Pilot Study Using a New Technique for TAP Determination

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Aim To evaluate the clinical value of a new immunoassay for serum and urine TAP determination in assessing the diagnosis and the severity of acute pancreatitis.

Patients Thirty-four patients with acute pancreatitis (AP) (22 mild pancreatitis and 12 severe disease); 12 patients with non-pancreatic acute abdomen (AA), 11 healthy subjects (HS) and 16 patients who underwent therapeutic ERCP (ERCP).

Methods Serum TAP (optical density, OD), amylase (reference range 64-92 IU/L) and lipase (reference range 46-67 IU/L) were determined in AP, AA, and HS at their initial observation; AP patients were also studied for six consecutive days from admission. In ERCP patients, serum TAP, amylase and lipase, as well as urine TAP and amylase (upper reference limit 460 IU/L), were determined before and 6 hours after ERCP.

Results Mean±SD serum TAP levels on admission were 0.35±1.60 OD in AP patients, 0.005±0.001 OD in AA patients, while HSs had no detectable serum TAP levels. ERCP patients had no detectable serum TAP levels before and 6 hours after the execution of ERCP, whereas urine TAP concentrations before the execution of the endoscopy were 1.72±3.43 OD (mean±SD) and decreased 6 hours after ERCP (mean±SD: 0.75±1.49 OD) (P=0.249). Using a cut off range of 0.013-0.020 OD for TAP, 138-142 IU/L for amylase, 67-98 IU/L for lipase, the sensitivity and specificity of the three markers in assessing the diagnosis of AP were 23.5% and 91.7%, 94.1% and 100%, 97.1% and 100%, respectively. Using a cut off range of 0.005-0.008 OD for TAP, 409-448 IU/L, for amylase and 375-406 IU/L for lipase, the sensitivity and specificity in assessing the severity of AP were 29.9% and 73.5% for TAP, 38.8% and 81.2% for amylase, 28.4% and 83.6% for lipase, respectively.

Conclusions TAP is of limited value in assessing the diagnosis and the severity of acute pancreatic damage.

The Orphan Receptors COUP-TFs Are Required for Pancreatic Stellate Cells Transdifferentiation and Modulate the Mitogenic Responses in Activated Cells

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Background Pancreatic stellate cells (PSC) has been identified as the precursor cell type mainly responsible for the development of pancreatic fibrosis. The orphan receptors chicken ovoalbumin upstream promoter transcription factors (COUP-TFI and COUP-TFII) belong to the nuclear receptor superfamily and play an important role in development and differentiation. They bind to cis-actin element either as homodimer or as a heterodimer with retinoid X receptor (RXR). There are evidences that COUP-TFs modulate the activity of other nuclear receptor including retinoic acid receptors (RAR) and peroxisome proliferator activated receptor (PPAR).

Aim In consideration of the role of nuclear receptors in PSC activation we analyzed the

expression and transcriptional activity of COUP-TF during PSC transdifferentiation in vitro.

Methods Espression of COUP-TFs was evaluated by western blot and RT-PCR. Transcriptional activity was evaluated by transfection experiment using a luciferase reporter plasmid specific for COUP-TF (-841/-800 NHE-1 promoter). PSC proliferation was evaluated by cell counting and H^3 Tymidine incorporation.

Result Both COUP-TFI and II was rapidly up regulated during PSC transdifferentiation in vitro. In freshly isolated cells both receptors was undetectable but after 24 h the II isoform was significantly increased. In parallel, transcriptional activity was induced during cell activation. Increased levels of these receptors in activated HSC by transfection induced cell proliferation and potentate the response to mitogens such as PDGF and EGF. In addition COUP-TFs antagonized PPAR and RAR mediated signaling in PSC and regulate collagen and fibronectin gene expression.

Conclusion These data suggest that members of the COUP-TF family play a role in modulating profibrogenic response in pancreatic stellate cells.

Chromosomal Unbalance in a Cell Line from Pancreatic Ductal Carcinoma by Multicolor FISH

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Introduction Genetic alterations occurring in pancreatic ductal carcinoma are not limited to gene mutations of K-*ras* oncogene and suppressor genes *p53*, *p16*, *Smad4*, but also to genomic unbalance with loss or gain of entire chromosomal arms of the same genes.

Materials and methods One pancreatic adenocarcinoma cell line was derived from primary culture and analyzed (passages 7, 20, 40, 60, 80 and 100) to evaluate the physical status of chromosomes 3, 7, 9 and 17. Multicolor FISH allowed to probe the centromeric regions of chromosomes 3, 7 and 17, together with region 9p21.22 by using four differentially labeled probes (CEP®3SpectrumRed™, CEP®7SpectrumGreen™, CEP®17SpectrumAqua™, and LSI 9p21.22 SpectrumGold™, respectively). Cultured cells were grown on slides for 48 h and fixed for 5 min in Carnoy solution (methanol/acetic acid 3:1). Probe hybridizations were carried out overnight at 39°C in a humidified chamber. Following hybridization, specimens were washed using a solution of 0.1% NP-40 in 2X SSC, stained with DAPI, and submitted to FISH analysis.

Results Cultured adenocarcinoma cells were analyzed at passages 7, 20, 40, 60, 80 and 100. In all cases the chromosomic profile was found to be altered. In particular, an increase in copy number of chromosomes 3, 7 and 17 was observed. Deletion of the short arm of chromosome 9 (9p21.22) was identified precociously (passages 7 and 20).

Conclusions Mutation studies in pancreatic adenocarcinoma cannot be limited to the analysis of point mutations of K-*ras* oncogene and the suppressor genes known to be involved in adenocarcinoma tumor development. Attention must be focused also on the gain of chromosomal centromeric regions that we found associated to extracopies of chromosomes 3, 7 and 17. Chromosome 17 is particularly relevant due to the presence of suppressor gene *p53*, which appeared to be mutated in the cell line under study. We also identified a precocious deletion of the short arm of chromosome 9

(9p21.22) that can be associated to the loss of one copy of suppressor gene *p16*. Such pattern of mutations is frequently found in pancreatic carcinoma. A more detailed genome mapping will better define the chromosomic alterations identified in the cell line under study.

The Role of Procalcitonin in Predicting Complications and Prognosis in Severe Acute Pancreatitis: A Prospective European Trial

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Background Early, accurate and reliable staging and diagnosis of infectious complications in acute pancreatitis (AP) is important in the clinical practice. Procalcitonin (PCT), the 116 amino-acid precursor of calcitonin, is the first biochemical parameter for predicting infection and sepsis in various inflammatory diseases; in AP the clinical value of PCT determinations still remains controversial.

Aim To assess whether PCT play a role in predicting complications and prognosis in AP.

Methods From December 1999 until September 2003 a total of 103 patients with severe AP were included in 5 European Centres within 96 h of disease onset. CRP was determined routinely, PCT was assessed by a chemoluminescent immunoassay over a maximum of 21 consecutive days.

Results Ninety-three (90%) patients had CT-proven intra-and/or extra-pancreatic necrosis of whom 16 (15.5%) developed infection (IN). Single organ failure was observed in 39 (38%) and MODS in 29 (28%) patients, 7 patients (6.8%) died. Median PCT concentrations revealed an early and significant increase in patients who developed infected necrosis which was not observed for CRP. If IN was associated with MODS or patients subsequently died median PCT values reached highest concentrations which already peaked at the third day after onset of symptoms, whereas CRP values did not differ.

Conclusions Prediction of complications is already possible on the 3rd day after onset of symptoms with high sensitivity and specificity. Monitoring of PCT is a non-invasive and reliable method to predict IN and associated systemic complications as well as overall prognosis in severe acute pancreatitis. This single test parameter significantly contributes to an improved stratification of patients at risk to develop major complications in AP and deserves routine clinical application.

The Severity of Secretagogue-Induced Acute Pancreatitis is Reduced in Mice Lacking Phosphoinositide 3-Kinase Gamma

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Background PI3K-gamma is an intracellular signalling molecule expressed in white blood cells and in other tissues, including exocrine pancreas. PI3K-gamma regulates chemotaxis

of leukocytes and, in dispersed pancreatic acini, modulates the sustained rise in free cytosolic Ca^{2+} concentrations, and the activation of trypsinogen and NF-Kappa B after CCK hyperstimulation.
Aim Using mice lacking PI3K-gamma, we studied the function of this enzyme in pancreatic acini, and in a murine model of acute pancreatitis (AP).
Methods Amylase secretion was measured in acini after incubation with varying concentrations of cerulein. To elicit AP, mice were administered 6 or 13 hourly i.p. injections of a supramaximal dose (50 µg/kg) of cerulein. The severity of AP was evaluated measuring the extent of acinar cell injury/necrosis, pancreatic water content, serum amylase activity, and neutrophil infiltration. The TUNEL method was used to detect apoptosis of pancreatic acinar cells.
Results *In vitro*, the pattern of secretion in isolated acini was identical in PI3K-gamma null and wild-type mice. *In vivo*, after 6 cerulein injections, PI3K-gamma deficient mice showed a significant reduction in acinar cell necrosis, but not in pancreatic water content, serum amylase levels, and neutrophil infiltration (although this was minimal in both groups). In agreement with a protective role of apoptosis in AP, PI3K-gamma deficient pancreas showed an increased number of apoptotic acinar cells. Prolonged administration of cerulein for 13 hours further increased all of the parameters of AP damage, with evident sequestration of neutrophils within the pancreatic tissue and the appearance of small foci of coagulative necrosis. At 13 hours, pancreatic damage and neutrophil infiltration resulted significantly reduced in PI3K-gamma$^{-/-}$ compared to wild-type mice.
Conclusions Genetic ablation of PI3K-gamma significantly reduced the severity of secretagogue-induced AP. This protective effect was associated with preserved exocrine secretion from isolated pancreatic acini, increased apoptosis of acinar cells, and decreased neutrophil infiltration within the pancreatic tissue.

Optical Coherence Tomography to Detect Early Stage Malignant Epithelial Lesion of the Main Pancreatic Duct

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Introduction Adenocarcinoma of the pancreas is a disease often detected in an advanced stage when most of patients are judged unresectable. Optical coherence tomography (OCT) is a new medical device able to generate high-resolution real time imaging of tissue microstructure by a micro-probe optical-fibre inserted through the endoscope operative channel. Resolution is approximately 10 µm and penetration-depth of about 2 mm. To our knowledge, there are no studies on the utility of the OCT to detect malignant or inflammatory pancreatic lesions.
Aim To assess the ability of OCT to detect epithelial malignant lesions of the main pancreatic duct (MPD).
Methods We have studied multiple sections of 10 consecutive surgical pancreatic specimens obtained from patients (mean age 61.3 years; 6 males, 4 females) affected by pancreatic head adenocarcinoma who have undergone duodenocefalopancreasectomy (DCP). We inserted OCT probe into the MPD, within 1 hour from resection and before the pathological handling. A similar number of pancreatic specimens judged

tumor-free by pathologist, with normal histological pancreatic architecture, was used as control.
Results In normal specimens, the normal OCT pattern, as confirmed by histopathology, was defined and appeared reproducible in all cases. It was possible to visualize the epithelium, the connective tissue and the acinar parenchyma below with regular architecture and homogeneous back-scattered signal. In all adenocarcinoma specimens involving MPD, instead, a subverted architecture, with loss of parietal MPD layers and an heterogeneous back-scattered signal was observed.
Conclusions OCT allowed to identify the normal and the pathological MPD layer structure and appeared to be a reproducible technique. During endoscopic retrograde cholangio-pancreatography (ERCP) OCT mini-probe could be used to diagnose early MPD changes and to differentiate between malignant ductal lesions and normal ductal appearance.

Frequency of Post-ERCP Pancreatitis in a Single Tertiary Referral Center Without and With Routine Prophylaxis with Gabexate: A Six-Year Survey

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Background post-ERCP pancreatitis and its prevention have been the topic of several investigations in recent years. Several drugs have been tested, administered either before or during the procedure, but results are still conflicting and no data referring to the routine use of a pharmacological prophylaxis for post-ERCP pancreatitis have been published up to now.
Aim The aim of the present study was to evaluate the frequency of post-ERCP pancreatitis in a series of consecutive patients undergone ERCP procedures before and after the introduction of a routine prophylaxis with gabexate in all cases.
Methods Data from a total of 2,461 consecutive patients, 1,312 who underwent ERCP procedures without gabexate prophylaxis and 1,149 with 1 g i.v. gabexate, were retrospectively evaluated during a 6-year period. Patients were also subdivided in standard- and high-risk subjects, on the basis of patient- and technique-related risk factors: 984 subjects (39.9%) had one or more conditions that placed them at high risk for post-ERCP pancreatitis.
Results Post-ERCP pancreatitis was reported in 76 out of 2,461 patients (3.1%). In the pre-gabexate period pancreatitis was recorded in 51/1,312 patients (3.9%), it was severe in 11 cases (0.8%; 21.6% of all pancreatites). In the gabexate period pancreatitis was recorded in 25/1,149 patients (2.2%), it was severe in 3 cases (0.3%; 12.0% of all pancreatites). The incidence of pancreatitis in the gabexate period appeared significantly reduced in overall cases (P=0.019) and in high-risk patients (P=0.019).
Conclusions Routine gabexate prophylaxis can be proposed to reduce the frequency of post-ERCP pancreatitis in all cases and in high-risk patients.

Smoking and Pancreatic Cancer: A Bench Exercise Aiming to a Nutragenomic Intervention

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Background Smoking is a known risk factor for pancreatic cancer and nutrigenomic may act as new therapeutic strategies also in pancreatic carcinogenesis.

Aim The project was to test the potential of a novel phytotherapeutic compound, i.e. DTS (Denshichi-To-Shusei, Kyotsu Co., Tokyo, Japan) as a protective agent against smoke-induced DNA damage in rat pancreas.

Methods Wistar rats were exposed to sidestream cigarette smoke (27±3 mg total particulate matter/m^3) for 6 h/day for 6 weeks. Rats were allocated into 3 groups: A) supplemented with DTS 200 mg/kg/day since 1 week prior smoke exposure; B) standard food; C) healthy smoke-free as control. After sacrifice lungs, trachea and pancreas were excised and lipophilic DNA adducts were analyzed by ^{32}P-postlabeling technique followed by computerized visual quantification.

Results Qualitative smoke-induced DNA adducts pattern was similar in lung, trachea and pancreas. However, while lungs mainly expressed adduct n. 5, the major adduct in trachea and pancreas was n. 3, the levels (10^{10} nucleotides) being 279±67, 88±11 and 71±14, respectively ($P<0.001$ vs. group C). Group C rats showed a low baseline level of similar DNA adducts. DTS-treated rats showed a statistically significant decrease of major adducts in all tissues with an inhibition ranging from 36% to 48% ($P<0.05$). However, DTS did not affect the baseline level of DNA adducts in healthy rats.

Conclusions Such *in vivo* data follow prior in vitro findings of tobacco-specific genotoxic amines damaging also the pancreatic tissue. A nutrigenomic intervention, amenable to routine dietary use, with DTS showed to significantly lower the carcinogenesis risk. Although the pathogenesis of pancreatic cancer and its interplay with environmental factors still remain unfolded, the present nutraceutical, by acting via mechanisms such as antioxidative and/or enhancement of carcinogen-detoxyfying activity, may be worth taking into consideration for future research development with an eye on clinical application.

Substance P mRNA Expression in Pancreatic Tissue Correlates with Substance P Serum Levels in Patients with Chronic Pancreatitis

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Background Pain is the leading symptom in chronic pancreatitis (CP) and often surgical management is necessary in cases with medically intractable pain. The patho-physiology of pain in CP is still incompletely understood. Recent data suggest a role for neuropeptides, such as substance P (SP), and the neuroimmune interaction in the inflammatory process of the pancreas. SP is involved in pain transmission and we already demonstrated an increased expression of this neuropeptide in CP. However no data are

available about the possible correlation between tissue and serum levels.
Aim To investigate a possible correlation between SP mRNA expression in pancreatic tissue and serum levels of SP in patients undergoing surgical procedures because of chronic pancreatitis to confirm the hypothesis of neuroimmune inflammation as patho-genetic factor in CP.
Patients and Methods SP mRNA levels were analyzed by quantitative RT-PCR in pancreatic tissue specimens from 30 patients with CP undergoing pancreatic resection and 10 healthy organ donors. In addition, SP serum levels were determined before surgical procedure by using enzyme immunoassay (ELISA).
Results Quantitative RT-PCR demonstrated increased SP mRNA expression in CP tissues ($P<0.05$). Before undergoing surgical procedure patients with CP exhibited significantly higher SP serum levels in comparison to control group.
Conclusions The present data confirm an increase of SP expression during chronic inflammation of the pancreas. Furthermore, the SP mRNA tissue expression correlates with increased serum levels in CP patients. SP acting essentially as a proinflammatory neuropeptide seems to be not only localized into the inflamed pancreas but also influences the systemic environments as suggested by our findings. Based on these consideration, SP might represent a reliable marker of neurogenic inflammation in CP patients. The long term postoperative control of SP serum levels will be object of further studies.

Timing of Antibiotic Prophylaxis of Septic Complications in Acute Pancreatitis: Results of a Controlled Randomized Study with Meropenem

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Background Recent studies clearly show that antibiotic prophylaxis improves the outcome of severe acute pancreatitis (AP); the starting time for an appropriate treatment is not well understood as some authors suggest to begin as soon as possible, others only when necrotic process is demonstrated. On the other hand, experimental studies show an early bacterial translocation from the gut into the pancreas within the first hours of AP.
Aim The aim of the present study was to investigate this topic in a randomized controlled trial using the same antibiotic with a different starting time of administration.
Methods A group of 175 patients suffering from AP were enrolled. Inclusion criteria were: age greater than 18 years, diagnosis of AP, admission within 48 hours from onset of abdominal pain, and no intake of antibiotics over the 3 days before admission. Patients were randomly assigned to group A (n=88), who started antibiotic therapy (meropenem 500 mg i.v. tid) at admission, and group B who received the same schedule after the demonstration of necrosis at contrast-enhanced CT scan. CT was performed in both groups at least after 48 hours of hospitalization. The clinical outcome was compared in the two groups.
Results Twenty-six patients in group A and 24 in group B showed necrosis at CT scan; these two groups resulted well matched as concerns demographic and clinical characteristics. Antibiotic treatment was started after 4.7±1.4 days from hospitalization in group B and after 1.04±0.7 days in group A ($P<0.001$). Pancreatic infection occurred in 3 patients in group A (11.5%) and 7 in group B (29.2%; P NS); extra-pancreatic infections occurred in 4 patients in group A (15.4%) and

in 11 patients in group B (45.8%; P<0.03). Need for surgery and length of hospitalization were also higher in group B (P NS vs. group A); mortality rate was similar in the two groups, but all 3 patients with infected necrosis in group A and only 2 out 7 in group B died.

Conclusions The results of the present study suggest that very early administration of antibiotic treatment (meropenem) is associated with a slight improvement in the prognosis of severe AP; a study involving larger series of patients is clearly justified to better address this important topic.

Sporadic Pancreatic Ductal Carcinoma in Patients Aged Less Than 40 Years

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Introduction Pancreatic ductal carcinoma is extremely rare before age 40 years.

Aim The aim of this study was to evaluate the pathological and molecular features of this tumor in patients aged less than 40 years.

Materials and Methods Two hundred and ninety three pancreatic ductal carcinomas were collected from 1976 to 2004 at our Institution. Six specimens from patients (3 males and 3 females) with a mean age of 36 years (range: 32-39) were included in the study. Familial history of pancreatic cancer was excluded by the anamnestic analysis. The mutation analysis of BRCA2 gene on frozen samples from 2 patients is under way. The tumor grade and stage were assessed according to the WHO and pTNM classification. Molecular analysis included the study of K-*ras* and *p53* mutations on laser microdissected tumor paraffined samples. The expression of *p53*, EGF-R, E-cadherin, beta-catenin, and microsatellite instability (MLH1, MSH2) was performed by immunohisto-chemistry.

Results Pathological status was similar to that occurring in elderly patients. K-*ras* mutation was found at codon 12 only in 1/5 cases; no mutations were found at codon 61 in 6/6 cases. One sample was not amplifiable due to degradation of nucleic acids. *p53* mutations were detected in 3/6 patients. *p53* over-expression was evidenced in 4/6 cases. EGF-R expression on the tumor cell membrane was present in 3/6 cases. E-cadherin at cell membrane was found in 3/6 cases. Abnormal accumulation in the cytoplasm and nucleus of beta-catenin, was observed in 5/6 cases. No microsatellite instability was found as documented by the MLH1 and MSH2 positivity in all 6 cases.

Conclusions Sporadic pancreatic ductal carcinoma in young patients is extremely rare and shows similar pathological and biological aspects with respect to the older ones. The frequent stabilization of beta-catenin in the cytoplasm and nucleus indicates an higher transactivation activity. Furthermore, the low incidence of K-*ras* mutations could suggest a different cancerogenic mechanism in sporadic pancreatic cancer of young patients.

Intraductal Papillary Mucinous Neoplasms Involving the Entire Main Duct Always Need Total Pancreasectomy?

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Background Intraductal papillary mucinous neoplasms (IPMNs) secrete large quantities of thick mucus into the lumen, partially obstructing it and causing both proximal dilation and attacks of obstructive pancreatitis. IPMN involving the main pancreatic duct is nearly the most exclusive indication for total pancreasectomy (TP), also considering the high biological impact on the patient. We need a clear preoperative indication for surgery.
Aim To analyze patients with IPMN who underwent TP (also in two times) in order to estimate how many times the neoplasm is associated with obstructive chronic pancreatitis (OCP) or really involve all the main duct.
Methods We analyzed all the patients undergone TP for IPMN which involve the entire pancreas; histopathology report have been analyzed in order to find signs of OCP. The patients have been therefore divided in adenomas, borderline, carcinomas in situ and infiltrating carcinomas.
Results From 1994 to 2003 we underwent 33 patients to TP, 20 for IPMN; in 5 cases TP was performed in 2 times. Pathology reports 7 cases of moderate dysplasia (borderline), 4 for carcinoma in situ and 9 for invasive carcinoma. The presence of OCP in the residual parenchyma was present in 15 patients (75%): in all patients undergone TP *d'emblée*, in 2 patients who underwent TP with increasing resections and other 2 submitted to TP in 2 times. The total median survival was 110 months (US 95%: 57;104) from surgery. Five patients dead during the follow up: 4 IPMIC and one IPMB 9 months after for AMI. The greater survival of patients with associated PCO is statistically significant ($P<0.05$) than the real IPMN.
Conclusions IPMNs involving the entire main duct are only the 25% of the analyzed population; in the other 75% the ductal dilation is due to an associated OCP. Another evidence is a better overall survival in patients with histological diagnosis of OCP. Concerning diffuse main duct ectasia, the real extension of the neoplasm should be carefully evaluated and so it is mandatory to verify all the malignancy clinical, laboratory and radiological findings before performing TP.

X-Ray Cross-Complementing 1 Gene Polymorphisms, not X-Ray Cross-Complementing 3 or Cytochrome p450, Might Predispose to Pancreatic Cancer

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Background An individual predisposition to cancer might be searched in polymorphisms of genes involved in DNA repair, as X-ray cross-complementing (XRCCs), or involved in carcinogens activation, as cytochrome p450 (CYP1A1).

Aims 1. to ascertain whether there was any association between the XRCC1+22163 C/T (Arg194Trp), XRCC1+24011 G/A (Arg399Gln), XRCC3+16064 C/T (Thr241Met) or CYP1A1+4889 A/G (Ile462Val) polymorphisms and pancreatic cancer (PC); 2. to verify any

correlation between the serum levels of vitamins A and E and PC cancer diagnosis, staging, grading and survival.
Methods We studied 91 PC patients and 29 chronic pancreatitis (CP). Survival was available for 44 PC. The genetic polymorphisms were analyzed by RFLP. Serum vitamins A and E were measured by an HPLC procedure.
Results XRCC1+22163 C/T, XRCC3+16064 C/T and CYP1A1+4889 A/G were not correlated with diagnosis. None polymorphism was correlated with tumor stage, tumor grade, or the onset of metastases after surgery. Survival was influenced only by stage (Log rank=12.4, P<0.01). In patients with less than 60 years, not in those with more than 60 years, XRCC1+22163 CT was significantly correlated with PC (Fisher's exact test: P<0.05). Vitamins A and E levels did not significantly differ between PC and CP. Vitamin A was significantly lower in stage III-IV (556±53 nmol/L, mean±SE) than stage I-II PC (896±112) (t=3.08, P<0.01). The lowest serum levels of vitamin E were in PC patients who developed liver or local metastases after surgery (10.7±1.4 μmol/L, mean±SE), with respect to those who developed lung metastases (22.2±2.9) (F=8.41, P<0.01).
Conclusions XRCC1+22163 CT genotype seems involved in favoring PC in subjects with less than 60 years; these effects might be consequent to an altered protein efficiency in DNA repair; the antioxidant vitamins A and E might partly counteract tumor growth and spread.

Artificial Neural Networks for the Prediction of Diabetes Mellitus Occurrence in Patients Affected by Chronic Pancreatitis

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Background A number of clinical variables have been related to the occurrence of diabetes mellitus in patients affected by chronic pancreatitis, but at present, in the single patients we are not able to predict the occurrence of diabetes mellitus. Artificial neural networks (ANNs) allow to discover hide and complex relations between variables, and to solve complexes problems.
Aim Artificial neural networks have been used to identify the variables predictive of diabetes in patients suffering from chronic pancreatitis (CP), and to predict the presence of diabetes in these patients.
Methods The analyzed data base consisted of 92 patients, 36 of which were female, in age between 20 and 83 years. In all patients, chronic pancreatitis was diagnosed by clinical history, imaging and functional pattern. The variables used as neural networks input were: sex, age, family history, illness onset, alcohol consumption, smoking, gallstone disease, dyslipidemia, dyspepsia, pain, serum enzymes rise, calcifications, exocrine insufficiency, other pathologies, genetic mutations (CFTR, SPINK-1, POLY-T). Diabetes mellitus represented the target to be predicted. Three research protocols were used, all based on supervised neural networks: 1) random research protocol implemented by utilization of back propagation neural networks and linear statistical model; 2) optimized protocol with "artificial organisms" Training & Testing (T&T) and Input Selection (I.S.) (Semeion®); 3) heuristic protocol based on the variables most frequently selected by I.S.
Results The best classification was achieved by the heuristic protocol with the 92.6% of accuracy. The variables that resulted predictive of diabetes were: age, family history, alcohol, other pathologies, genetic mutations.
Conclusions Artificial neural networks provide an important help in clinical practice.

Their use has permitted to identify the variables related to diabetes and predicted the presence of diabetes with an accuracy higher than 92% in single patients affected by chronic pancreatitis.

Causes of Asymptomatic Hyperamylasemia

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Background Elevated levels of serum pancreatic amylase have been observed in asymptomatic patients. Hyperamylasemia (HA) may be related to many clinical conditions, such as celiac disease, dyslipidemia, macroamylasemia, hepatitis C, renal failure.

Aim The aim of the study was to identify the causes of HA and to find out any pancreatic disease during the follow-up.

Patients and Methods We enrolled asymptomatic patients referring to our Center over the period 1994-2004, with at least 2 documented abnormally elevated serum levels of pancreatic amylase. We retrospectively evaluated clinical history, blood analysis and instrumental findings of these patients at the first observation of HA and during the follow-up.

Results We studied 49 patients (33 males, 16 females; mean age 46.3±13 years) with a mean follow-up time of 4.4±3.5 years. Four out of 42 patients (9.5%) had at least one family member with a documented HA. Seventy-eight percent of patients were teetotalers and 22% drank less than 40 g of alcohol/day; 26% of patients were smokers (13.4±5.9 cigarettes/day). At first observation of HA, the increase over the upper normal serum level was 2.7±1.6 fold for amylase, and 2.1±1.6 fold for lipase. During follow-up, enzyme concentrations remained elevated, although wide fluctuations were observed and 10 patients (20.4%) had transient normalization. Twenty-seven out of 44 patients (61.4%) had cholesterol levels higher than 200 mg/dL and 8/35 (22.9%) triglyceridemia higher than 160 mg/dL. At abdominal US, we found hepatic and pancreatic steatosis in 28.6% and 37% of patients, respectively. Macroamylasemia was found in 12 patients (25%). Celiac disease was diagnosed in 5/15 patients (33.3%) and all had macroamylasemia. Biliary lithiasis was detected in 12/35 patients (34.3%), a slight increase of CA 19-9 in 3/16 (18.7%) and one patients was HCV positive. Pancreas divisum was diagnosed in 2 patients and renal diseases in 2 patients. No possible cause of HA was found in only 6 patients (12%). No pancreatic diseases were observed during the follow-up.

Conclusions We may recognize a possible cause of asymptomatic HA in the majority of patients. Dyslipidemia, in particular hypercholesterolemia, is frequently associated with HA.

Quality of Life in Patients with Chronic Pancreatitis

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Introduction Health-related quality of life is becoming a major issue in the evaluation of any therapeutic intervention in patients with chronic or hard to cure diseases.

Aims To assess the quality of life in a large group of patients with chronic pancreatitis, the majority of whom have had the disease for a long time, and to evaluate which factors linked to the disease are able to influence the quality of life.

Subjects and methods A total of 190 consecutive patients (157 M, 33 F; mean age 58.6 years, range 18-92) with proven chronic pancreatitis were enrolled in the study from January 2003 to June 2003. The mean age of onset of the pancreatitis was 42.3±14.8 years and the mean time interval between diagnosis and admission to the study was 201±141 months (range 0-629 months). The etiology was alcohol abuse in 147 patients (77.4%), due to other causes in 11 (5.8%) (hereditary pancreatitis in 5, associated with pancreas divisum in 2, cystic dystrophy of the duodenal wall in 2, CFTR gene mutation in 1, autoimmune pancreatitis in 1); in the remaining 32 patients (16.8%), the pancreatitis was idiopathic. Fifty-two patients of the 147 drinkers (35.4%) continued to drink alcohol after the diagnosis of chronic pancreatitis. One hundred and forty-seven patients (77.4%) were smokers and 89 of them (60.5%) continued to smoke at the time of the study. One hundred and twenty-four patients (65.3%) had pancreatic calcification, 75 (39.5%) had pseudocysts, and 133 (70.0%) had a dilatation of the Wirsung duct. Fecal elastase and/or fecal chymotrypsin were evaluated in 94 patients; 80 of them (85.1%) had pancreatic insufficiency. One-hundred patients (52.6%) had diabetes secondary to pancreatitis. Eighty patients (42.1%) had had pancreatic surgery for chronic pancreatitis and 16 (8.4%) underwent endotherapy. A histological diagnosis of chronic pancreatitis was available in 79 patients (41.6%). Sixty-five patients (34.2%) had pancreatic pain in the month before the study enrollment. The SF-36 questionnaire was used for assessing the health-related quality of life.

Results The z-scores of the 8 domains of the patients with chronic pancreatitis were significantly negative indicating an overall impairment of the quality of life when compared to the Italian normative sample. Pancreatic pain was the unique clinical variable able to significantly impair all 8 domains of the SF-36, while Wirsung dilation and diabetes were negatively related to some physical and mental domains. Body mass index was the unique variable positively related with some SF-36 domains.

Conclusions Pain may be considered the most important factor affecting the quality of life of chronic pancreatitis patients; moreover, alimentary and metabolic factors deserve more attention in improving the quality of life of these subjects.

Distal Pancreatic Neoplasms: Is There a Role for Minimally-Invasive Surgical Procedures? Indications, Technique and Results on 32 Consecutive Patients Treated by the Same Surgical Team

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Background Distal pancreatic laparoscopic resection procedure is feasible and safe with results comparable with open resections even though post-operative fistula complication remains the most challenging problem.
Aim The aim of the study is to review our experience in order to confirm the feasibility and the safety of the procedure and to highlight the technique.
Methods Between May 1999 to May 2004 we performed 32 distal pancreatectomies for benign or border line cystic or solid tumors, 22 (69%) "spleen preserving" and 10 (31%) "spleen including". The technique includes supine decubitus, infragastric access, retrograde pancreatectomy in order to spare pancreatic healthy tissue and to preserve the splenic vessels, pancreatic section with endoGIA, drainage of the stump by a soft drain.
Results The mean operative time was 148 minutes (range 75-200) with no conversion rate and no blood transfusion. Eighteen out of 22 spleen preserving procedures were with splenic vessels preservation. There were 6 minor complications (18.7%): one trocar bleeding and 5 pancreatic fistulas resolved within 30 days without invasive procedures; 5 major complications (15.5%): one pancreatic fistula requiring CT guided drainage, one splenic infarction requiring splenectomy, 3 abdominal abscesses requiring re-operations. The overall reoperation rate was 12.5% with three open procedures and one laparoscopy. The mean hospital stay was 9 days (range 7-20) with no mortality.
Conclusion This experience of the same surgical team, the largest in the world to our knowledge, confirms that distal laparoscopic pancreatectomy is feasible and safe. The issue of the pancreatic stump management remains the most strong challenge for the surgeon either laparoscopic or open.

Results of Treatment of Distal Pancreatic Carcinoma

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Background Cancer arising in the left pancreas are thought to have a worse prognosis than those found in the head of the pancreas for their later diagnosis.
Aim To define tumor features, surgical outcome and long-term survival in tumors of body and tail of the pancreas in comparison with cancer arising in the head.
Methods Data were prospectively collected in our pancreatic surgery data-base. Fifty-two patients with ductal adenocarcinomas of the distal pancreas and 248 with ductal adenocarcinomas of the head of the pancreas underwent surgical resection from 1990 to 2002. Chi-square test, long-rank test and Cox regression analysis have been used for statistical evaluation.
Results Tumors of the left body and tail of the pancreas were larger than tumors of the head (4.1 vs. 2.8 cm; $P<0.001$). Radicality and grading did not show any statistical difference. Number of removed nodes was higher in pancreaticoduodenectomy (PD) than in distal pancreatectomy (DP) (20.8 vs. 10.8

nodes; P<0.001), but N1 rate were similar in the two groups. Mortality and relaparotomy were 0% and 1.9% after left pancreatectomy and 2.8% and 7.2% after pancreaticoduodenectomy, respectively (P NS). Incidence of pancreatic fistulas was higher in distal pancreatectomy (33% vs. 16%; P<0.01), whereas postoperative hospital stay was significantly lower in pancreatico-duodenectomy (12.6±4.5 days vs. 19.5±9.7; P<0.001). Also survival did not show any difference between the two groups of patients (median: 17 months after distal pancreatectomy and 19 months after pancreaticoduodenectomy). Multivariate analysis confirmed that site of the tumor did not influence prognosis, while diameter, grading and radicality were independent prognostic factors.

Conclusions Tumor arising in the body and tail of the pancreas have greater diameter than tumors of the head, even if this finding does not worse prognosis. Pancreatic fistulas are more frequent after DP but they are less (no mortality and less length of hospital stay).

Diffuse Carcinoma with "Jump" Lesion and Neuroendocrine Tumor of the Pancreas: Intraoperative Trap

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Case report We report a case of a diabetic patient submitted to surgery because of pancreatic cancer. A preoperative CT scan showed a 35 mm tumor limited to the head of the pancreas. A Whipple procedure was planed. During surgery a 4 mm suspect nodule of the liver was diagnosed by intraoperative ultrasonography. The intraoperative frozen sections excluded a metastasis. After duodeno-pancreatectomy the resected pancreas was controlled by the pathologist showing that free margins were only 3 mm but otherwise the pancreas remnant appeared macroscopically normal. Other 20-mm pancreas were anyway resected to increase the negative margin. The distal margin was controlled again by the pathologist but resulted surprisingly invaded by adenocarcinoma. A total pancreatectomy was then performed. The definitive pathology showed a microcystic mucinous carcinoma involving the whole pancreas (pT3N1M0), characterized by some "jump" lesion alternating normal pancreas and carcinoma, showing also diffuse neuroendocrine proliferation and a 4-mm neuroendocrine tumor.

Conclusions This rare association of neuroendocrine tumors with carcinoma of the pancreas is exclusively described for the serous type of adenoma/adenocarcinoma. To our knowledge this is the first report concerning the association of a neuroendocrine tumor with a microcystic adenocarcinoma of the mucinous type. Retrospectively analyzing this case about the suspect liver nodule together with the rare association of two different cancers with different prognostic significance we would like to stress out the importance of intraoperative pathological examination specimen to avoid strategical mistakes. There is also the risk to leave cancer in the pancreatic remnant estimating R0 a resection that is unfortunately R1. The possibility of the "jump" of the cancer, and of the association of different cancers underlines also the possible multifocal and multiclonal origin and/or development of pancreatic cancer that we believe should be better investigated.

Acute Pancreatitis in Pediatric Age: A Case Report

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Context Acute and chronic pancreatitis are uncommon in pediatric age. North American epidemiological studies showed that acute pancreatitis ad cystic fibrosis are common in children. The most important factors for the development of pancreatitis are: abdominal trauma, infectious diseases, and particularly systemic diseases, malformations of biliary tree, some drugs. Diagnosis in pediatric age could be difficult and there are not standardized protocols about follow-up in children with acute, recurrent or chronic pancreatitis.

Case report A 4-year old girl was admitted to hospital because she presented incoercible vomit, diarrhea and important abdominal pain. She presented pathologic values of lipase, amylase and C reactive protein, associated to cholestasis. The ultrasonography of pancreatic region showed peripancreatic necrosis The patient performed a therapy with antibiotics and somatostatin. After some days there is the resolution of clinical symptoms, the reduction of pancreatic enzymes and the improvement of the ultrasonography finding. After two months she underwent to endoscopic retrograde cholangiopancreatography (ERCP), that showed the fusiform dilatation of choledochus with long biliary-pancreatic duct. The ERCP permitted to drain and to disinfect the biliary tract. After one month, the patient underwent to cholecystectomy, choledochectomy with, hepatic-jejunostomy. In the last five months after the surgery the girl was always asymptomatic.

Conclusions The cyst of choledochus, and the "pancreas divisum" are the most frequent anatomic malformations in children with acute pancreatitis, however capable of surgical correction.

Prevalence of CFTR and SPINK1 Gene Mutations in Chronic Pancreatitis Patients

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Background Three genes are involved in chronic pancreatitis: CFTR (cystic fibrosis transmembrane conductance regulator), PRSS1 (cationic trypsinogen) and SPINK1 (trypsin inhibitor) but the prevalence of mutations varies in different populations.

Aims To determine the prevalence rate of CFTR and SPINK1 gene mutations in patients with chronic pancreatitis from North-West Italy.

Methods We evaluated 128 patients with chronic pancreatitis (age between 19 and 83 years, 65 males). The diagnosis was established by clinical symptoms, imaging and laboratory tests. Patients with a diagnosis of cystic fibrosis were excluded. All patients were analyzed for the most frequent CFTR mutations by OLA (Cystic Fibrosis Assay, Perkin Elmer) and screening for all 27 exons was performed with denaturant gradient gel elettrophoresis (DGGE) analysis. The N34S mutation in the SPINK1 gene was analyzed by amplification of the exon 2 of the gene with specific oligonucleotides and HindII

Restriction Enzyme digestion.
Results We found 14 out of 128 patients to carry mutations in the CFTR gene. Two new mutations (N187K and I497V) were identified. Two patients were compound heterozygotes (R1162X/F1052V and R334W/2183AA>G respectively) while the other 12 patients were heterozygote for one mutation. The 5T allele was identified in 10 of 128 patients (7.8%), all heterozigous for this gene variant. A SPINK1 N34S mutation was present in 5 patients (3.9%), in a patient in combination with a 5T allele.
Conclusion These results confirm previous reports of a low frequency of the N34S mutation in Italian patients, while about 2% of patients with chronic pancreatitis carry two mutations in the CFTR gene. These patients carrying mild mutations of CFTR gene, could develop later in their life multiorganic manifestations of cystic fibrosis. A screening for CFTR mutations in chronic pancreatitis patients can identify these CF patients, and change our clinical approach.

High MUC1 Concentrations Predict Adverse Outcome: Study of 155 Patients with Histologically Confirmed Pancreatic Cancer

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Background MUC1 is a polymorphic, highly glycosylated, type I transmembrane protein expressed by ductal epithelial cells of many organs including pancreas. MUC1 is overexpressed and differentially glycosylated by pancreatic ductal adenocarcinomas and there are evidence *in vitro* that it could contribute to invasive and metastatic potential by cell surface adhesion properties modification and by dendritic cell function modulation.
Aim The aim of this investigation was to investigated the prognostic impact *in vivo* of MUC1 in patients with pancreatic cancer.
Methods MUC1 concentrations were measured prospectively in 155 patients with histologically confirmed pancreatic cancer at the diagnosis. MUC1 concentrations were related to patient outcome by both univariate and multivariate analysis.
Results Patients with high concentrations of MUC1 (H-MUC1 >25 units/L; 31.6% of patients) had a significantly shorter overall survival pattern than those with low concentrations (L-MUC1) (median survival: 175±32 vs. 350±44; P=0.0017). As a prognostic factor, MUC1 was independent of tumor size, presence of metastasis, surgery treatment, and patient age. MUC1 was also predictive of outcome irrespective of the type of therapy administered, i.e., whether chemotherapy, or radiotherapy was administered. As well as being prognostic in the total population of patients, MUC1 also predicted outcome in different subgroups of patients, including those submitted to resective surgery, node-negative and node-positive disease, high and low grading.
Conclusion Assay of MUC1 is a relatively inexpensive, convenient, and noninvasive method for evaluating prognosis in newly diagnosed pancreatic cancer patients.

The Pituitary Adenylate Cyclase-Activating Polypeptide Pathway is Activated in Human Chronic Pancreatitis

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Background Pituitary adenilate cyclase-activating polypeptide (PACAP) is a multifunctional neuropeptide released by enteric nervous system and synthesized by immune cells during chronic inflammatory conditions. Recent reports have shown that PACAP acts essentially as a potent anti-inflammatory mediator stimulating the release of interleukin 10 (IL-10) from macrophages. IL-10 is a cytokine that reduces the magnitude of inflammatory response. Up to day no data are available about the protective role of PACAP in human chronic pancreatitis (CP) and its relationship with IL-10 production.

Aim In the present study the genetic expression of PACAP, PACAP specific receptor type 1 (PAC-1) and the gene encoding IL-10 were evaluated in patients with CP.

Patients and Methods Pancreatic tissue specimens obtained from 14 patients with chronic pancreatitis and 8 healthy organ donors were analyzed. PACAP, PAC-1 and IL-10 mRNA expression levels were studied by quantitative RT-PCR. In addition, PAC-1 receptor and IL-10 were analyzed with Western Blot. Respective proteins were localized with immunohistochemistry.

Results RT-PCR analysis showed that PACAP and IL-10 mRNA expression levels were increased in CP tissue samples compared with normal controls ($P<0.05$). In contrast, PAC-1 mRNA levels were expressed at low levels in chronic pancreatitis tissue samples. Using immunohistochemistry, PACAP protein was localized mainly in pancreatic enlarged nerves, immune cells, vessels and in atrophic pancreatic parenchyma. Faint PAC-1 receptor immunoreactivity was present in CP samples showing similar tissue distribution of PACAP. Increased IL-10 immunoreactivity was seen mainly in atrophic pancreatic parenchyma and immune cells in CP. Western Blot analysis demonstrated an increased expression of PAC-1 and IL-10 proteins in CP tissues compared with controls.

Conclusion In the present study we show for the first time quantitative tissue changes of PACAP protein, PAC-1 receptor and IL-10 expression in human CP. Taken together, these findings indicate an activation of PACAP pathway: on the other hand, the reduction in PAC-1 mRNA expression suggests an impairment of PACAP/IL-10 anti-inflammatory action. This might in part explain the perpetuation of chronic painful inflammation in CP.

18-FDG PET in Differentiating Malignant From Benign Pancreatic Cystic Lesions: A Prospective Study

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Background Differential diagnosis between benign and malignant pancreatic cystic lesions remains difficult. After reporting that 18-FDG PET was useful to discriminate

malignant from benign cystic lesions in 56 patients (Ann Surg 2001; 134:675-80), we tried to confirm the reliability of 18-FDG PET in a further large cohort of patients.
Materials and Methods From February 2000 to June 2003, 50 patients with suspected cystic neoplasms (n=33) or intra ductal papillary mucinous tumors (IPMN, n=17) were prospectively investigated with 18-FDG PET, abdominal computed tomography (CT), serum CA 19-9 assay and, in some instances, with MRI. The validation of diagnosis was based on pathologic findings after surgery (n=33), percutaneous biopsy (n=3), and according to follow-up in 14 patients (follow-up range: from 1 to 3 years). The 18-FDG PET was analyzed visually and semi quantitatively using the standard uptake value (SUV). It was considered positive when a focal uptake occurred with a SUV of at least 2.5. The accuracy of 18-FDG PET and CT was determined for differential diagnosis between benign and malignant cystic lesions.
Results Seventeen patients had malignant tumors; 16 patients (94%) showed 18-FDG uptake with a standard uptake value ranging from 2.5 to 7.0, including two patients with carcinoma in situ. Eleven patients (65%) were correctly identified as having malignancy by computed tomography. Thirty patients had benign tumors: two patients showed increased 18-FDG uptake of 2.6 and 3.0 (a partially intra splenic pseudocyst and a pancreatic localization of Tangier's disease, respectively). Four patients with benign cystic tumors showed CT findings of malignancy. Sensitivity, specificity, positive and negative predictive values, and efficiency for 18-FDG PET and CT scanning in detecting malignant tumors were 94%, 94%, 89%, 97%, 94%, and 65%, 88%, 73%, 83%, and 80%, respectively.
Conclusions 18-FDG PET is accurate in identifying malignant pancreatic cystic lesions and should be routinely used in combination with CT in the preoperative evaluation of patients with cystic lesions of the pancreas.

Laparoscopic Pancreatic Resection: Preliminary Experience

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Aim To evaluate the results of laparoscopic pancreatectomy for pancreatic tumors.
Methods Four women and three men underwent laparoscopic pancreatectomy and were collected retrospectively from June 2002 to February 2004.
Results Pancreaticoduodenectomy (n=4), intermediate pancreatectomy (n=1) and distal pancreatic resection with splenectomy (n=2) were successfully performed. Operative mortality was nil. The postoperative morbidity included two low-output pancreatic leaks. The mean operating time, blood loss and hospital stay was 342 minutes, 289 mL and 14 days, respectively. Pathological diagnosis were ductal adenocarcinoma in one, neuroendocrine tumor in five and metastatic melanoma in one. All patients remain well at a median follow-up of 7 months (range 1-20).
Conclusions Patients appear to benefit from laparoscopic pancreatectomy for pancreatic tumors. Minimally invasive approach ensures an adequate treatment despite it requires the expertise of highly skilled laparoscopic surgeons.

Pancreatic Cancer Resection in Elderly Patients

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Background Pancreatic resections continue to be associated with significance post-operative morbidity and occasionally mortality. In patients aged 70 years or older these procedures are considered high risk operations.
Aim To establish the feasibility of pancreatic cancer resection in elderly patients.
Methods This study retrospectively compares two groups of patients observed in our Institute between 1998 and 2003: group A includes 25 pancreatectomies performed in patients aged 70 years or older; group B includes 25 pancreatectomies in patients younger than 70 years old. The two groups were similar regarding sex, pathology, type of resection and stage.
Results Mean age was 75 years (range 70-88) in group A and 59.8 (range 30-68) in group B. Post-operative mortality rate was 8% (2 patients, one of which over 80 years) in group A, 4% (1 patient) in group B (P NS). Post-operative morbidity rate was 40% in group A and 36% in group B (P NS). In particular, incidence of pancreatic fistula was similar: 7/25 (28%) in group A and 6/25 (24%) in group B. Mean hospital stay was 18 days (range 8-38) in group A and 20 days (range 8-46) in group B (P NS). In group A, 5 patients (20%) were alive free of disease (mean follow-up: 10 months, range 2-20 months); 1 (4%) is alive not free of disease (follow-up: 11 months) and 19 (76%) are dead of disease (mean follow-up: 15 months, range 1-48 months). In group B, 4 patients (16%) were alive free of disease (mean follow-up: 25 months, range 2-58 months); 2 (8%) are alive not free of disease (mean follow-up: 20 months, range 16-23 months), and 19 (76%) are dead of disease (mean follow-up: 13 months, range 1-37 months). Survival was not statistically different between the two groups (P NS).
Conclusions Our experience suggests that age is not a contraindication for pancreatic cancer resection. It is very important, however, to establish the upper age limit above which a pancreatic resection should not be performed. Thus, exhaustive pre-operative work-up and carefully patient selection are both fundamental.

POSTER SESSION

Neuroendocrine Pancreatic Cancer: Diagnoses and Characterization with Spiral Computed Tomography and Nuclear Magnetic Resonance

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Background Neuroendocrine pancreatic cancer are neoplasms not so frequent and they are very difficult to diagnose and to differentiate from other solid pancreatic masses.
Aim To evaluate the computed tomography (CT) and nuclear magnetic resonance (NRM) accuracy, using specific protocols, looking features of functioning and non-functioning neuroendocrine tumors of pancreas.
Methods From 1990 till today, 72 consecutive patients affected by neuroendocrine pancreatic cancer were examined. The first patients analyzed were

studied with angiography, the recent ones with spiral CT and NMR.
Results The study of the pancreas with dedicate CT protocols and dynamic sequences is able to characterize neuroendocrine tumors and to differentiate them from other pancreatic cancer, based on the different contrast enhancement of the masses after infusion of iodate contrast agents. Neuroendocrine tumor are solid mass, well marginated, with expansive and not infiltrative growth and dilated vascular thromboses; sometimes they present signs of more aggressivity: necrotic or hemorrhagic degeneration and intralesional calcifications. The three-phasic study with NMR after infusion of paramagnetic contrast agents can help to recognize pancreatic neuroendocrine tumor and sottoglissonian hepatic micrometastases that are not visible with CT sequences.
Conclusions The gold standard for diagnosis of pancreatic neuroendocrine tumors is ^{111}In scintigraphy with octreotide. The above mentioned imaging techniques are useful for staging and sometimes for characterizing neuroendocrine tumors, even if clinical information is in any case very important. The pathologists, using immunohistochemistry are the only ones that can distinguish all the pancreatic masses.

Has Distal Bile Duct Cancer a Better Prognosis than Pancreatic Cancer?

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Background Pancreatoduodenectomy is the standard treatment for all the malignancies of periampullary region. In our experience, the most frequent malignancy of this region is represented by pancreatic adenocarcinoma (65%), followed by ampullary carcinoma (13%), distal bile duct cancer (10%) and duodenal cancer (3%).
Aim To compare outcome of patients undergoing to pancreatoduodenectomy for distal bile duct cancer or for pancreatic cancer.
Methods Since 1990 to 2002, 464 pancreatoduodenectomies for malignancies were performed in our Department. Among these, 303 were performed for pancreatic cancer (group 1) and 46 for distal bile duct cancer (group 2). These two groups were compared, with a *post-hoc* analysis, by postoperative complications and overall survival.
Results We observed a mortality rate of 2.6% in group 1 and 6.8% in group 2 (P NS). Reoperation rate was 7.9% in group 1 and 8.7% in group 2 (P NS). The incidence of pancreatic fistula was 16.1% in group 1 and 30.4% in group 2 ($P<0.05$). Median overall survival was 18 months in group 1 and 17 months in group 2. Patients affected by small distal bile duct (without invasion of pancreatic parenchyma; T1-T2 stage) showed a median survival of 60 months versus a median survival of 12 months ($P<0.01$) in patients with more advanced cancer (T3 and T4).
Conclusions Morbidity of pancreato-duodenectomy for distal bile duct cancer is higher than for pancreatic cancer. Distal bile duct cancer has the same dismal prognosis of pancreatic cancer. Only early stage bile duct cancers have a better prognosis.

Early and Late Results of Surgical Treatment of Insulinomas

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Background Wide series on early and late results of surgery in the treatment of pancreatic insulinoma are lacking.
Aim To assess post-operative and long term results after surgical treatment of insulinomas.
Results In the last 23 years we observed 91 patients with pancreatic insulinoma (51 females and 42 males); mean age was 42 years. According to WHO histopathological classification, 62 tumors were classified as having a benign behavior (66.6%), 19 (20.4%) as uncertain behavior, 4 as well differentiated carcinoma. We identified 5 individuals affected by MEN-1. Preoperative imaging techniques correctly identified 82/86 insulinomas. Endoscopic ultrasonography and MR showed the higher sensitivity (87.5% and 80.0%), followed by ultrasounds (72.2%), angiography (63.5%) and CT scan (53.4%). Intraoperative handling and ultrasounds allowed to identify 2/4 occult insulinomas. Surgical procedures were: 54 enucleations (1 laparoscopic), 22 distal pancreatectomies (2 laparoscopic, 2 with splenectomy), 7 median pancreatectomies, 6 pancreatoduodenectomies. No mortality was observed. Morbidity was 36.3%, with a relaparotomy rate of 3.2%. The most frequent complication was pancreatic fistula (22.1%): all of them, except one, underwent spontaneous closure after 1-3 months. We observed 8 deaths (mean follow-up of 93 months): 2 of them related to disease progression in patients with malignant tumors, whereas the other 2 patients with malignant insulinoma are still alive with metastatic stable disease. Six patients died of unrelated diseases. No recurrence of symptoms was observed in any patient. Overall 5- and 10-year actuarial survival rates were 93.7% and 86.8% respectively.
Conclusions Careful preoperative and intraoperative evaluation are able to correctly localize the most of insulinomas. Pancreatic fistula is a frequent complication of this type of surgery, but it can be easily managed. Surgery allows satisfactory late results, both for survival and symptoms resolution.

Role of Fecal Elastase 1 in Pancreatic Cancer: A Pilot Study

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Background Fecal elastase 1 (E1) is an indirect test of pancreatic function. Few study investigated the role of E1 in pancreatic cancer.
Aims 1) To evaluate fecal elastase levels in normal healthy subject in comparison to patients with pancreatic cancer; 2) to assess the relationship between fecal elastase 1 and tumor topography in patients with pancreatic cancer.
Methods Twenty-six consecutive patients (15 male, 11 female, mean age 72±21 years) admitted in our GI unit between January 2003 and February 2004 with first diagnosis of pancreatic cancer were enrolled in the study. Clinical, laboratory, histologic and imaging data were prospectively collected. Cancer topography was as follow: 14 patients had head cancer; 5 patients had body-tail cancer; 7 patients had head-body cancer. The head-

body group of patients was removed from the study when we analyzed the relationship between fecal elastase levels and pancreatic cancer topography. Control group was composed of 165 normal healthy subject (70 male, 95 female, mean age 68±27 years). All patients and controls gave their informed consent. Stool elastase level was measured by an immunoenzymatic method (Meridian Bioscience Europe). According to our normal control group, we considered abnormal E1 values lower than 200 μg/g. Mann-Whitney rank-sum test was used fot data analysis.

Results Fecal elastase 1 levels were significantly decreased in pancreatic cancer patients (276.2±234.4) in comparison to normal subjects (504.5±145.3) (P<0.0001). A correlation between E1 levels and cancer topography was found: patients with pancreatic head cancer showed lower E1 levels (189.4±180.7) in comparison to patients with pancreatic body-tail cancer (421.2±229.1) but did not achieve significant level (P=0.078) because of low power of the test.

Conclusions Fecal elastase 1 is significantly decreased in patients with pancreatic cancer in comparison to normal healthy subject. Moreover, fecal elastase 1 could have a significant correlation with pancreatic cancer localization.

Preoperative Administration of Interleukin-2 Increases Natural Killer Cells Count in Operable Pancreatic Cancer Patients

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Background Natural killer (NK) cells are large granular lymphocytes, which exhibit natural cytotoxicity against a broad range of human tumors, playing an important role in host anticancer defense mechanism. High levels of NK cells count and/or NK cell activity in peripheral blood of cancer patients are associated with a lower incidence of metastases and a better prognosis. Furthermore, major surgery impairs natural citotoxicity and this may facilitate the dissemination of tumor cells in the peri-operative period. Interleukin-2 (IL-2) is a cytokine with pleiotropic immunobiological activities, which include stimulation of the innate immunity against cancer cells, by expanding the number of circulating NK cells and activating their cytotoxic activity.

Aim The aim of this study is to investigate the influence of preoperative administration of high doses of recombinant IL-2 (rIL-2) on NK cells blood count in the peri-operative period in patients with pancreatic adenocarcinoma.

Methods Nine consecutive patients with resectable pancreatic adenocarcinoma (6 males, 3 females; mean age: 67 years) received 12 millions UI/day of rIL-2, divided in 2 daily subcutaneous injections of 6 millions UI, for 3 consecutive days prior to surgical radical resection (R0). NK cells (CD16+/CD56) count in peripheral blood was measured by flow cytometry before administration of rIL-2, and in 7^{th} and 14^{th} post-operative day. Seven patients underwent pancreaticoduodenectomy, 1 splenopancreat-ectomy and 1 total pancreatectomy.

Results Toxicity related to rIL-2 treatment was mild (grade 1-2 of WHO). The basal count of NK cells was 208±97 mm^{-3}. In the post-operative period, we observed a significant increase of NK cells count both in 7^{th} (318±129 mm^{-3}, P<0,01) and in 14^{th} day (299±60 mm^{-3}, P<0.03).

Conclusions This preliminary study shows that preoperative subcutaneously rIL-2 administration at high doses (12 millions UI/day) abrogates surgery-induced decline of NK cells in patients affected by pancreatic cancer. The high NK cells count obtained with rIL-2 immunotherapy could have a prognostic impact on the course of the disease, because of the important role of NK cells in anticancer defense.

Five-Year Results of Extended Vs. Standard Lymphadenectomy in Pancreatic Cancer

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Background The role of lymphadenectomy in pancreatic cancer (PC) is still matter of debate.

Aim To analyze short and long term results of pancreatic resections associated to standard (SL) vs. extended lymphadenectomy (EL) in PC.

Methods We retrospectively analyzed the data of 87 patients diagnosed with locally non advanced PC undergoing pancreatectomy at our Center between November 1987 and January 1998. Overall, 44 patients (50.6%) received a SL and 43 (49.4%) EL. There were not significant differences between the two groups regarding demographics and other baseline characteristics. Actual survival was estimated after a minimum follow-up of 5 years.

Results The mean number of lymph nodes retrieved were 9.8 in SL group as compared to 25.3 in EL group. Mortality (SL: 4.5% vs. EL: 2.3%; P NS) and morbidity rates (SL: 31.8% vs. EL: 44.2%; P NS) were similar irrespective of the type of lymphadenectomy. Overall, the incidence of diarrhea was significantly higher in EL vs. SL (78.9% vs. 22.7%; P<0.001). One, 3 and 5-year survival rates were similar in both groups (SL: 56.8%, 14.6% and 7.8%; EL: 70.7%; 25.2% and 14.0%; P NS), even considering the subgroups of patients with metastatic lymph nodes (SL: 52.2%; 10.4% and 5.2%;. EL: 60.9%; 23.6% and 14.0%: P NS). However, 1, 3, and 5-year survival rates of node positive patients undergoing EL (60.9%; 23.6% and 14.0%) equaled that of node negative patients undergoing either SL (65.2%; 20.7% and 13.8%) or EL (83.3%; 26.9% and 14.0%). Node positive patients treated by SL achieved clearly lower survival rates at the same time points (52.2%; 10.4% and 5.2%), although the difference was not statistically relevant.

Conclusions EL does not increase morbidity and mortality of pancreatoduodenectomy, but it seems to negatively affect the quality of life since this treatment is plagued by a high incidence of severe diarrhea. According to this study EL does not offer a statistically significant survival advantage, even if it seems to eliminate the negative prognostic implications of lymph node metastasis on long-term survival.

Surgical Approaches to the Treatment of Pancreatic Neuroendocrine Tumors with Synchronous Hepatic Metastases

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Background Pancreatic tumors with liver metastases are traditionally considered non-surgical diseases. Nevertheless some histological types of tumors - such as neuroendocrine tumors - because of their less aggressive biological behavior as compared to ductal adenocarcinoma, can be considered surgical diseases even when locally advanced or metastatic.

Aim To analyze short- and long-term results in a series of patients undergoing concurrent resection of primary pancreatic neuroendocrine tumor (PPNT) and multiple liver metastases (MLM).

Materials and Methods Between November 1987 and January 2004, 14 out of 48 patients diagnosed with PPNT were also found to harbor concurrent MLM (32.6%). There were 7 males and 7 females; ranging in age between 27 and 74 years (mean age 59.6 years). Prior to referral to us, 8 patients (57.1%) had already received palliative procedures for either obstructive jaundice or upper gastrointestinal obstruction in the absence of histological demonstration of tumor type. The mean time interval between palliation and second-look resection was 8±2.2 months.

Results Resection of PPNTs required pancreaticoduodenectomy in 6 patients (42.8%) and distal pancreatectomy with en-bloc splenectomy in the remaining 8 patients (57.2%). Synchronous MLM metastases were treated by enucleation in 10 patients (42.9%), segmentectomy in 2 patients (14.4%), left hepatectomy combined with right lobe enucleations in 1 patient (7.1%) and wedge resection in 1 patient (7.1%). Mean post-operative stay was 16.3±2.8 days. No patient died and post-operative complications occurred in 3 patients (21.4%), without need to repeat surgery. Overall, 1-, 3- and 5-year survival rates were 100%, 80% and 60%, respectively. All the 7 patients without residual tumor (R0) survived the 5-year period while 1-, 3-, and 5-year survival of those with residual tumor (R1 or R2) was 100%, 80% and 40%, respectively (P NS).

Conclusions In this series simultaneous extirpation of PPNT and MLM resulted in low morbidity and valuable long-term results. Radical tumor clearance (R0) should definitely be pursued since it is associated with excellent long-term survival.

Cooperative Inhibition of Pancreatic Carcinoma Cell Lines Growth in Nude Mice by Gemcitabine and Trichostatin A

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Background The availability of more effective adjuvant treatments is a goal standard in pancreatic carcinoma, but currently even the most active chemotherapeutic agents, like gemcitabine, show a response rate less than 20% in clinical studies. Therefore the research has been focused, rather on the detection of new drugs, on substances able to enhance the efficacy of the previously tested chemotherapeutics. The histone deacetylase inhibitors, like trichostatin A (TSA), promote histone hyperacetylation and induce a high degree of apoptosis both in *p53* positive and *p53* negative tumor cells.

Aim Starting from the previous *in vitro* results on several cell lines (data in press), we evaluated the effectiveness of a combined treatment with TSA and gemcitabine on *in vivo* pancreatic cancer cells growth.

Methods A $5x10^6$ suspension of T3M4 pancreatic cancer cells were subcutaneously implanted in four groups of five nude mice, respectively. Seven days after each group was randomly treated with a twice weekly injection of DMSO (control), TSA (0.25 mg/kg), gemcitabine (2.5 mg/kg) or TSA plus gemcitabine. Tumor growth was daily monitored and the animals were sacrificed after a 4 week treatment.

Results We reported neither drug related toxicity nor mortality in any of the treated groups. TSA or gemcitabine alone did not significantly reduce the tumor burden, compared to control group, as shown by the mean tumor weight at the end of treatment. Instead, combined treatment reached an about 50% reduction in mean tumor weight, if compared both to control and single treatment groups. Higher doses treatments (i.e. TSA 1

mg/kg and/or gemcitabine 25 mg/kg) did not increase either growth inhibition or toxicity.
Conclusions These *in vivo* results seem to confirm a significant effectiveness in reducing the pancreatic cancer cell growth by a combined treatment with TSA and gemcitabine. The advantage in scheduling a phase 2 clinical trial from these data has to be evaluated.

Contrast Enhanced Ultrasonography vs. Spiral CT in the Detection of the Vascularization of Solid Pancreatic Lesions

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Aim To compare contrast enhanced ultrasonography (CEUS) vs. spiral CT in the detection of the vascularization of solid pancreatic lesions.
Methods 43 resected lesions of the pancreas were studied with CEUS, by using i.v. injection of Sonovue (Bracco, Milan, Italy) and microbubble-specific harmonic mode (Coherent Contrast Imaging) with low mechanical index (MI<0.2) on a Sequoia 512 (Acuson, Mountain View, CA, USA), and biphasic Spiral CT. The lesion enhancement was scored in comparison to the normal parenchyma and to the precontrastographic characteristics of the lesion as: 1=less, 2=equal, 3=little more, 4=more. All the lesions underwent pathological examination using hematoxylin-eosin and CD34 markers stains with an evaluation of the microvessel density (MVD) scored in comparison to the normal parenchyma as: 1=less, 2=equal, 3=little more, 4=more. The correlation of CEUS and spiral CT with the MVD of the lesions was established with the Spearman's test.
Results The correlation of CEUS with the MVD of the lesions was significantly superior (r_s=0.915; P<0.001) to that of Spiral CT (r_s=0.675; P<0.001).
Conclusions CEUS is better than Spiral CT in the detection of the vascularization of solid pancreatic lesions.

Clinical Finding in Patients Suffering from Pancreatitis Associated with Gene Mutations (CFTR, SPINK1, K8)

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Background In the last decade, CFTR, SPINK1 and K8 gene mutations have been described in patients suffering from pancreatitis. Little data are available on clinical and instrumental findings of these patients.
Aim To evaluate the clinical aspects and outcome of patients suffering from pancreatitis associated with gene mutation.
Patients and Methods We studied patients with one or more mutations on CFTR, SPINK1 and K8 gene referring to our Center between 1998 and 2003.
Results We studied 46 patients (27 males, 19 females; mean age 46.3±16.9 years), 33 patients with CFTR gene mutations (18 males, 15 females; mean age at onset of pancreatitis 35.5±17.9), 9 patients with

SPINK1 gene mutations (6 males, 3 females; 41.4±21 years) and 6 with K8 gene mutations (5 males, 1 female; 45.3±18.3 years). In one patient we documented mutations in all three genes investigated (deltaF508 on CFTR, N34S on SPINK1 and G61C on K8). The mean follow-up time from the clinical onset of pancreatitis was 10.2±8.1 years. Family history of pancreatitis was found in 4 patients (8%). Only 3 patients (6%) drank more than 80 g/day of alcohol and 24 (48%) smoked 18.2±10.0 cigarettes/day. Two patients (4%) were asymptomatic, whereas 44 patients had 5.8±3.6 recurrences of pancreatitis during the follow-up. We observed 8 episodes of severe acute pancreatitis in 7 patients (15%). Thirty-one patients (67%) had a definitive diagnosis of chronic pancreatitis (CP) after 4.3±5.4 years. Calcifications were observed in 22 CP patients (71%), diabetes in 11 (37%) and steatorrhea in 12 (39%). Eighteen out of 31 CP patients (58%) underwent surgery, (12 derivations and 6 resections). Endoscopic sphincterotomy was performed in 18 patients, 8 of whom underwent more than 1 procedure. Three patients died, one of whom for pancreatic adenocarcinoma.

Conclusions Pancreatitis associated with gene mutations is characterized by numerous recurrences and by evolution into CP. Exocrine and endocrine insufficiencies are frequent and appear after few years from the diagnosis of CP.

Multislice CT in the Staging of Pancreatic Adenocarcinoma: State of the Art

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Background New therapeutic horizons of pancreatic cancer give the possibility to study pancreatic masses with innovate imaging techniques.

Aim To demonstrate that multislice computed tomography (MSCT) is the gold standard to study the tumor dimensions (T), the infiltration of the major peripancreatic vessels using post-processing multiplanar reconstruction, the identification of metastases and the lymph node dimensions and characteristics.

Methods One-hundred and 7 consecutive patients with pancreatic tumors underwent assessment with MSCT. The T parameter, the infiltration of peripancreatic vascular structure, the metastases, the localization and the dimensions of lymph nodes (N) were evaluated.

Results Our study demonstrated that MSCT in the staging of pancreatic cancer, has an high diagnostic accuracy: sensitivity 98% and specificity 80%.

Conclusion The metastases, an important involvement and longitudinal extension of vascular infiltration, are basic parameters in decision of therapeutic strategy. We re-evaluated the N parameter comparing CT results with pathology that considered either the dimensions than the existence of metastases. The dimensions of lymph nodes (less or greater than 1 cm) is not predictive of metastatic ones: nodes under 1 cm can be positive N+ (45.5%) or negative (N-). In conclusion, MSCT has an high accuracy in staging of pancreatic adenocarcinoma, giving to surgeons a specific lymph node map for partial lymphoadenectomy.

Total Lymphocyte Count Predicts Pancreatic Cancer Survival

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Background An impaired host immunity might concur in determining the tremendous prognosis of pancreatic cancer (PC).

Aim To ascertain whether the pattern of blood lymphocyte immunophenotype in PC correlates with: 1) tumor stage; 2) tumor grade; 3) the development of metastases after surgery; 4) survival.

Methods We studied 46 PC patients. Staging was: stage I=2%, stage II=11%, stage III=48%, stage IV=39%. Grading was: G1=19%, G2=40%, G3=41%. Survival was available for 32 patients (min=1, max=24, median=19 months). Metastases were found after surgery in 76% of these patients. Lymphocyte immunophenotype was determined by FACS analysis. The following were considered: CD16/CD56+ (natural killer); CD19+ (B lymphocytes); CD3+ (T lymphocytes), CD4+ (T helper), CD8+ (T cytotoxic).

Results Tumor stage did not correlate with lymphocyte immunophenotype or total lymphocyte count. CD16/56+ were lower in patients with (14.7±1.14%, mean±SE) than in those without lymphnode metastases (25.4±4.9%)(t=9.83, P<0.05). CD4+ were lower in patients with undifferentiated (47.6±2.1%) than in those with well differentiated PC (55.6±2.1%) (Mann Whitney U=56.5, P<0.05). Tumor stage, not grade (squared chi=3.55, P NS), correlated with the development of metastases after surgery (squared chi=12.75, P<0.01). Total lymphocyte count discriminated patients who developed from patients who did not develop distant metastases after surgery with a sensitivity of 83% and a specificity of 80% (cut-off=$1.5x10^9$/L). The overall survival of patients correlated with tumor stage (Log rank=12.4, P<0.01), but also with total lymphocyte count (Log rank=13.7, P<0.001). The association between survival and total lymphocyte count was confirmed when stage III (Log rank=10.2, P<0.005) or stage IV patients (Log rank=3.0, P=0.08) were considered singly.

Conclusions The presence of lymphnode metastases at diagnosis or the development of metastases after surgery are significantly associated with a reduction of natural killer cells and total lymphocyte count. A reduction in the latter at diagnosis could predict patients' survival, independently from tumor stage.

Laser Microdissection on Primary Cell Cultures of Pancreatic Adenocarcinoma

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Background Setting up of primary cultures from pancreatic adenocarcinoma is a delicate and complex procedure with very low chances of succeeding. One of the major issues is represented by the difficulty to separate epithelial cells from fibroblasts,

which are very abundant due to the marked desmoplastic reaction associated to pancreatic adenocarcinoma.
Aim Aim of the present study was to expand the epithelial cell population by using laser microdissection on primary cultures derived from pancreatic adenocarcinoma.
Materials and methods Forty-six samples from pancreatic adenocarcinoma (collected between December 2001 and June 2004) were selected to set up primary cultures. Cells were grown in RPMI 1640 (10% FCS, 1% L-Glu, 1% antibiotics) at 37°C in 5% CO_2 humidified atmosphere. Four primary cultures (PP109, PP117, PP147, and PP161) and 1 cell line (PP78) were obtained. Line PP78 and primary culture PP117 were sown (passage 105 and 45, respectively) on poly-ethylene tereftalate (PET) coated Petri dishes, specifically designed for laser microdissection (Leica ASLMD), and 4.000 cells, where microdissected from both cultures, transferred on chamber slides and incubated as above. We also cultured with same modalities epithelial cells from PP219, a culture composed by epithelial and fibroblast cells.
Results Microdissected cells from PP78 and PP117 culture grew to form a single layer. Cells were then transferred to a fresh flask and passaged 10 additional times, up to passage 115 and 55 respectively. Epithelial cells from PP219 culture are still under study.
Conclusions Cell growth and migration on PET coating were comparable to those on standard solid supports used for cell cultures. Laser microdissection allowed successful isolation and expansion of cell cultures. If the epithelial cells microdissected from PP219 will show the same behaviour of PP78 and PP117, this new method could offer several advantages: 1) reduced primary culture time setting, by isolating a target cell type from the original mixed cell population; 2) isolation of different cell populations within a single primary culture.

Mutational Study of K-*ras* Oncogene in Pancreatic Ductal Carcinoma

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Background K-*ras* mutations are a frequent event in infiltrating pancreatic carcinoma. They are to be considered a precocious event in tumour development, given their presence in pre-neoplastic lesions (PanIN). K-*ras* mutations found in pancreatic carcinoma are most frequently located at codons 12 and 13, with reported frequencies ranging between 70% and 80%. Rare mutations at codon 61 have also been reported.
Materials and methods Eighty-nine cases of pancreatic ductal carcinoma (samples collected between December 2001 and June 2004) were collected. Fresh sections from 52 selected tumors were laser micro-dissected (Leica ASLMD) and DNA extractions performed. Cell cultures from 46 tumor samples were attempted. Four primary cultures (PP109, PP117, PP147, PP161) and one cell line (PP78) were established. K-*ras* mutational analysis was carried out on primitive tumor samples as well as on corresponding cell cultures with reference to codons 12, 13 (exon 1), and 61 (exon 2) by PCR and automated sequencing.
Results Mutational analysis of codon 12 and 13 showed mutations in 43/52 tumors (82.7%). Primary cultures all showed mutated at codon 12 (PP109 GGT -> GTT, PP117 GGT -> GAT, PP147 GGT -> CGT, PP161

GGT -> GAT). Line PP78 was mutated at codon 61 (CAA -> CAC), while codons 12 and 13 were unaltered. Three out of 9 primitive tumors unaltered at codons 12 and 13 were mutated at codon 61 (2 CAA -> CAC and 1 CAA -> CTA) No histological differences were observed between these 3 tumors and primitive tumors mutated at codons 12 and 13. In the set of samples examined K-*ras* mutation frequency was 88.5%. The cell culture mutational profile was identical to the one evidenced in the original primitive tumor. Preliminary post-genomic analysis, bi-dimensional protein electrophoresis and mass spectrometry, carried out on primary cultures mutated at codons 12 (PP117) and 61 (PP78), revealed different protein maps.

Conclusions In our study mutation analysis of K-*ras* gene gave a total mutation frequency of 88.5%, a proportion of which (5.7%) was attributable to codon 61. Alterations at codon 61 are infrequently reported in pancreatic carcinoma, with only one study on a cultured cell line (T3M4). The two protein maps corresponding to two different mutations could reveal a different functional status of K-*ras* oncogene.

Development of a Novel Anti-TAP Cross-Species Reactive Immunoassay for the Detection of Acute Pancreatitis

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Background The pathological activation of trypsin activating peptide (TAP) within the pancreas constitutes a critical step in the initiation of acute pancreatitis.

Aim We describe the generation of a new anti-TAP antibody which is reactive across animal species (rat, mouse, dog, monkey, man) and has a very high affinity for its antigen.

Methods The 8-amino-acids TAP antigen FPLEDDDK was synthesized and used for covalent coupling to keyhole limpet hemocyanin (KLH) as a *carrier* protein via an added C-terminal cysteine residue appended after a small glycine spacer (FPLEDDDKGGC). The molecular weight of the derived immunogen is equal to 1,195 Da. Three rabbits were immunized following the procedure for the generation of anti-idiotypic antibodies to enhance immunogenicity of the peptide. The rabbits generated a potent humoral response which proved specific to the peptide in a quantitative ELISA. The developed antibodies were purified using an affinity column where the TAP peptide had been immobilized. Yields of the purified antibodies varied between 23 and 88% of bound and recoverable antibodies. The antibodies were further characterized for their potency, specificity and functional dynamic range of TAP detection using diverse immunoassays such as Western or Dot-blotting and direct or competitive ELISAs.

Results When comparing the performance of our best antibody (563) to a commercially available one (Biotrin) in a competitive immunoassay format, we found that our assay provides a similar dynamic range but better sensitivity at lower TAP concentrations. Developing reverse phase protein arrays from the plasma of treated animals, we show that the assay can be easily miniaturized and requires as little as few microliters volume of samples.

Conclusion The antibody can be efficiently used to identify and quantify the levels of TAP in body fluids, both in experimental animals as well as in clinical samples from human donors.

Quality of Life After Total Pancreatectomy. Ten-Year Experience

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Background Though extremely rare, surgical indication for total pancreatectomy (TP) may play a role both in case of multifocal and low-grade malignant diseases and for intra-operative complications or difficult management of pancreatic stump. A careful preoperative assessment has always to be performed, but little is still known about quality of life (QoL) in patients operated on.

Aim To evaluate QoL and health status score in patients submitted to TP in our series.

Methods All the patients operated on TP in our Department from 1994 to 2003 were evaluated by means of the EORTC QLQ-C30. Health status and QoL, with a score between one and seven, and further queries about the endocrine/exocrine balance were assessed.

Results We submitted to TP 33 patients, 18 males and 15 females. Over a median follow of 34 months (range 1.5-112) eight patients died (25%) for progression of the underlying disease, 3 patients are dropped out (9.4%) and 22 (65.6%) are still alive. The latter group of patients was submitted to the questionnaire. A median of 30.5 IU/day insulin (range 18-53) is required in order to control glycemia; one patient requires subcutaneous insulin infusion. The latest HbA1 level was normal (less than 7%) in 18 patients (85.7%). Fifteen (72%) patients claim hypoglycemic episodes with a daily and weekly appearance in 30% and 70% of cases, respectively. Neither one of the patients followed up died for endocrine failure nor developed signs of diabetic peripheral neuropathy. The exocrine function is replaced by a mean of 90,000 IU/day of lipases (50,000-130,000); even though, 42% patients still complain a certain degree of steatorrhea. The median QoL score was 5.5 (range 3-7) and the median health status score was 5 (range 3-7).

Conclusions In most of the patients who underwent a TP, QoL and the health status appear to be acceptable. Instead of the replacement therapy, the most frequent complication seems to be hypoglycemic episodes and steatorrhea. Nevertheless, TP, whenever indicated, appears a safe procedure with acceptable QoL in long-term survivors.

A "Shotgun" Proteomic Approach Identify Versican and MAC25/Angiomodulin as Novel Molecules Released by Pancreatic Cancer Cells: A Preliminary Characterization

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Background With the development of shotgun approaches such as multidimensional protein identification technology (MudPIT), proteomics is gaining efficiency as a tool for detection and analysis of proteins from complex mixtures, allowing the identification of new biomarkers which are critical for better understanding the biology of cancer and to improve its early and non invasive detection.

Aim We concentrated our investigation on proteins secreted by SUIT-2, a pancreatic cancer cell line, in order to get a first indication of proteins produced and released

by pancreatic cancer cells. The presence of the most relevant proteins identified should be assayed on a broader spectrum of samples.
Methods We analyzed small amounts of serum-free supernatant, produced by cultured SUIT-2 cells, with MudPIT; the analysis was broadened using RT-PCR in a series of adenocarcinoma cell lines and xenografts. In addition, immunohistochemistry in both primary pancreatic cancers and in SUIT-2 cells embedded in MATRIGEL® and implanted in nude mice was used to confirm the production and release of the proteins in the extracellular matrix.
Results We identified 47 major secreted proteins, some of which had never been described as released by pancreatic adenocarcinoma cells. This is the case for chondroitin sulfate proteoglycan 2 (CSPG2/versican), which can be produced in four isoforms due to alternative splicing, and angiomodulin (MAC25/IGFBP-rP1/IGFBP7). Nine of 19 (47%) cell lines were positive for CSPG2 and seven (37%) for MAC25 mRNA. Fourteen of 15 (93%) xenografts were positive for CSPG2 mRNAs, and 12 (80%) were positive for MAC25. Immunohisto-chemistry in both primary pancreatic cancers and in MATRIGEL®-embedded SUIT-2 cells confirmed the production and release of the proteins in the extracellular matrix *in vivo*.
Conclusions We show that CSPG2/versican and MAC25 are synthesized and secreted by pancreatic adenocarcinoma cells, both *in vitro* and *in vivo*. Therefore, CSPG2/versican is not only a product of the stromal reaction that is a typical feature of pancreatic adenocarcinoma but is actively produced by cancer cells which contribute to its accumulation in the extracellular milieu. The role of MAC25 in pancreatic adenocarcinoma is still unknown and requires further investigations.

Ten-Year Experience of Intra-Arterial Chemotherapy in Pancreatic Adenocarcinoma

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Background Before introduction of gemcitabine (GEM), standard treatment for unresectable pancreatic carcinoma was "best supportive care". Now GEM is the treatment of first choice and is generally included in every kind of chemotherapic regimen. However overall survival has not significantly changed. Another way of investigation is intra-arterial chemotherapy (IAC) based on a strong pharmacological and biological rationale.
Aim To identify the significance, the results and the influence of IAC on natural history of pancreatic adenocarcinoma (PA).
Methods From January 1994 to January 2004 we have treated 197 patients with FLEC regimen (5FU 1,000 mg/m^2, leucovorin 100 mg/m^2, epirubicin 60 mg/m^2, carboplatin 300 mg/m^2) administered into celiac axis by bolus infusion through an angiographic catheter. In adjuvant setting the doses were decreased of 25%.
Results Patient characteristics: M/F = 119/78; median age 62 years (range 38-78); stage III/IV 80/82 and radically resected 35; location head/body/tail 130/52/15; histology adenocarcinoma/mucinous type/undifferentiated 185/8/4. A total of 696 cycles were administered. Grade III/IV toxicities were: alopecia 24%, hematological 16%, nausea-vomiting 8%, diarrhea 2%, 1 sudden death, 1 preinfarction angina, 2 transitory ischemic attacks, 1 iliac intimal dissection. Clinical benefit was observed in 36/162 (22%); CT-scan response: PR 22/162 (14%); CA 19-9 PR 42/162 (26%); median overall survivals: III/IV/resected 9.2/5.6/32.5 months. In univariate analysis survival was found to be affected by radical surgery, stage, basal value of CA 19-9, clinical benefit,

decrease of CA 19-9 more than 50% and number of administered cycles (more than 3). Significant prognostic factors in multivariate analysis were: radical surgery and number of administered cycles.
Conclusions PA needs an integrated approach and up to now only surgery is potentially curative. A three-departments disease (pancreatic, peritoneal and hepatic) where IAC might be considered, but only in a global strategy of cure. FLEC regimen is active and well tolerated and after radical surgery showed a very interesting median survival of 32.5 months with 2 and 3-year survival of 54% and 48%, respectively.

Main Pancreatic Duct Structure: Comparison Between Optical Coherence Tomography Images and Histological Specimen

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Background Optical coherence tomography (OCT) is a new medical device able to generate high-resolution real time imaging of tissue microstructure by a micro-probe optical-fibre, inserted through the endoscope operative channel. Resolution is approximately 10 μm and penetration-depth of about 2 mm. To our knowledge, there are no studies on the utility of the OCT to assess pancreatic duct anatomical pattern.
Aim To assess the ability of OCT to define the normal pattern of the main pancreatic duct (MPD).
Methods We have studied a number of multiple sections of pancreatic specimens judged tumor-free by pathologist, with a normal histological pancreatic architecture, obtained by 10 consecutive surgical pancreatic specimens of patients (mean age 61.3 years; 6M, 4F) affected by pancreatic head adenocarcinoma who have undergone duodenocefalopancreasectomy (DCP). The OCT probe has been inserted into the MPD within 1 hour from resection and before the pathological handling.
Results In all the specimens judged to be normal by histology OCT has shown a superimposed layers architecture in which from the surface of the duct we can recognize the epithelial cells layer (reflective), the fibro-muscle layer (hyper-reflective) and the acinar structure (reflective). The thickness of the ductal wall measured by OCT was similar (0.5 mm) to the correspondent histological specimen.
Conclusions In this preliminary experience OCT has shown to be able to characterize the histological appearance of the main pancreatic duct wall. This ability could be used to study *in vivo*, during endoscopic retrograde cholangiopancreatography (ERCP) the MPD to recognize early pathologic changes in duct wall.

A Comprehensive *in Vitro* Characterization of Pancreatic Ductal Carcinoma Cell Line Biologic Behavior and Its Correlation with the Structural and Genetic Profile

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Background There are a large number of stable pancreatic ductal carcinoma cell lines (PDCL) that are used by researchers worldwide. Detailed data about their differentiation status and genetic alterations are present in literature but a systematic correlation with cell biologic behavior are often lacking.
Methods Twelve PDCL were clustered by source of tumor cell (ascites, primary tumor, metastasis) and the data of functional cell biology were correlated with the reported structural and genetic profiles.
Results MHCI expression, chemosensitivity and aneuploidy, appeared related to the source of PDCL and proliferative capacity appeared related to the grade of differentiation. No correlation between genetic/structural features of PDCL and biologic behavior was found. All the cell lines appeared generally insensitive to *in vitro* treatment with 5-fluouracil and showed variable degree of susceptibility to gemcitabine, raltitrexed and oxaliplatin. All the PDCL showed resistance to Fas-mediated apoptosis but were significantly sensitive to the pro-apoptotic effect of inflammatory cytokines (IL-1beta, TNFalpha and IFNgamma). PDCL were characterized for the secretion of several factors relevant to the tumor-immune cross-talk. VEGF, CCL2, CCL5 and TGFbeta were the factors most frequently released; less frequent was the secretion of CXCL8, CCL22, IL-6 and sporadically CXCL12, IL-10 and HGF. The cytokines IL-1beta and TNFalpha were always undetectable.
Conclusion A clear correlation between structural/genetic features and function could not be detected suggesting the weakness of a "morphologic" classification for the *in vitro* studies of pancreatic cancer.

Palliative Treatment of the Pancreatic Carcinoma: What Surgical By-Pass?

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Background The palliative treatment of the neoplastic obstructive jaundice foresees two possibilities: the position of endoscopic biliary stents or the surgical biliary by-pass. The digestive-biliary by-pass are differentiated in cholecystojejunostomy and hepatic-jejunostomy.
Aim The aim of the study is to evaluate the results after the cholecystojejunostomy.
Methods In the period from 1998 to June 2003, we have retrospectively evaluated 31 patients with jaundice from inoperable pancreatic neoplasia: 18 patients were treated with position of endoscopic stent; 13 patients underwent the palliative intervention of cholecystojejunostomy. The preoperative evaluation was made evaluating the following parameters: instrumental evaluation (US/CT) of the increase of the gallbladder volume; notice of the neoplastic lesion; intraoperatory evaluation: patency of the cystic duct; cholecystojejunal anastomosis on a Roux en Y jejunal loop (by means of stapler or manual).

Results We have evaluated: operative time length (mean: 60 minutes), reduction of the jaundice in all patients; specific morbidity: no anastomotic dehiscences, mean patient mobilization equal to 2 days, mean resumption of the alimentation in the fourth day in, mean hospital dismissal in the seventh day, one bronchopneumonic infiltrate. The distant results confirm the reduction of the jaundice at a follow-up of 6 and 8 months.
Conclusions The cholecystojejunostomy was safe, because of the very low postoperative morbidity and effective, to control the jaundice even after distant time from the intervention, in the palliative treatment of the pancreatic carcinoma.

Mangafodipir Trisodium Enhanced MRI and Pancreatic Neuroendocrine Tumors: Is There a Role?

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Background Mangafodipir trisodium (Mn-DPDP) is an intracellular paramagnetic contrast medium uptaken by the normal liver, pancreatic, cardiac and adrenal tissue. The enhanced normal pancreatic tissue increases detectability of focal solid lesions, that are relatively hypointense.
Aim To report our experience regarding the Mn-DPDP enhancement of primary neuroendocrine pancreatic tumors.
Methods Among 51 patients with focal pancreatic lesion who had had a Mn-DPDP-enhanced MR examination (1.5T magnet), we retrospectively reviewed 7 cases with a pathological diagnosis of neuroendocrine tumor. For each lesion we calculated contrast to noise ratio (C/N) and contrast index (CI) before and after Mn-DPDP infusion.
Results Among the 7 tumors 5 were insulinomas; 1 was a somatostatinoma and 1 was indeterminate. All these tumors were visible on plain T1w GRE images as hypointense nodules within the pancreatic gland. After Mn infusion 3 lesions increased C/N and CI; 4 lesions (57%) enhanced as much as to decrease C/N and CI determining a reduction of lesion detectability.
Conclusions Neuroendocrine tumors enhance after Mn-DPDP infusion and the enhancement can decrease lesion detectability. Therefore Mn-DPDP should be used carefully or should not be used when a pancreatic neuroendocrine tumor is suspected.

Role of Surgery in Complications of Severe Acute Pancreatitis

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Background Severe acute pancreatitis is still associated with significant morbidity and mortality, related to early and late complications of the disease.
Aim To evaluate the role and timing of surgery in early and late complications of severe acute pancreatitis.
Methods A retrospective study through records of patients admitted to our Institution from 1994 to 2004. Search criteria included either a diagnosis of severe acute pancreatitis or of late complications of a previous severe acute attack.
Results Sixty-five consecutive patients met our criteria. Forty-four patients were admitted for severe acute pancreatitis (group A); twenty-one for a late sequela (group B). In group A the mean hospital stay was 47 days; 18 days in group B. The overall hospital mortality was 4.5% (3 deaths in group A).

Twenty-three (52%) patients of group A developed an early systemic complication; only one in group B. All the patients in group A developed early or late local complications during hospitalization; 25 patients (57%) underwent a surgical procedure; 19 patients (43%) were treated by a conservative approach (two underwent a late surgical procedure). The surgical procedures performed were as follows: necrosectomy and/or drainage of infected necrosis 23; cholecystectomy 16; cysto-jejunostomy 7 and cysto-gastrostomy 1; external biliary drainage (T-tube) 6; nutritional jejunostomy 4; cholecystostomy 3; colonic and/or ileal resections with ileostomy 4; gastro-enteral anastomosis 2. In group B 4 patients (19%) were treated by a conservative approach, 17 (81%) by surgery.

Conclusions Whereas surgery for early local complications can only be recommended in selected cases, the surgical treatment is the first choice when late local complications occur. A multi-disciplinary and single patient-tailored approach are important in order to reach low mortality rate and better prognosis.

Scoring-System Utility in Management of Severe Acute Pancreatitis

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Background There is considerable controversy about timing for surgery in acute pancreatitis. It is generally accepted that patients with infected pancreatic necrosis should receive surgical management. Scoring systems are widely used in intensive care units but they are usually used in order to assess the severity of diseases but not for decision-making.

Aim In this study, modifications of clinical conditions, identification of pancreatic infection, scores and time for surgery are analyzed.

Methods Twenty-one patients with infected pancreatic necrosis are studied in a retrospective study with prospective collected data. The Atlanta's criteria were used to evaluate severity of pancreatitis. Necrosis was identified with dynamic contrast-enhanced CT scan. Ultrasound or CT guided fine needle aspiration was used to recognize infected necrosis. All patients need intensive care and all were submitted to open-packing. Nine patients were referred from other Hospitals because of previous unsuccessful surgical treatments. APACHE II, SAPS II and SOFA were computed, daily or every other day, before and after surgery respectively. Two particular phases of disease were observed: the day of ICU admission and the day of surgical treatment.

Results Mean age was 60.8 years. They all suffered from severe acute pancreatitis: mean Ranson score was 6.2 (range 3-8), mean APACHE II was 14.9 (range 4-28). In all cases the extent of necrosis exceed 50%. Infection was documented before any surgical treatment. Open-packing was performed in all patients and was done after two weeks from the beginning of disease. Multiple organ dysfunction was present in nine (43%) and seventeen patients (81%) on day of ICU admission and day of surgical treatment, respectively. Six patients died, three because of persistence of sepsis (mortality rate 28.5%). Patients who died had higher APACHE II, SAPS II and SOFA scores. In patients who died at ICU admission day the mean SOFA score was 5.0±3.0 while at day of open-packing the mean SOFA score was 8.5±3.0. The difference between SOFA scores, in these particular moments of disease, is significant.

Conclusions In patients who died a progressive deterioration was noticed during pre-operative period despite intensive medical

management. Clinical derangement was associated with scores increasing. This condition could indicate "a not controlled inflammation" or an "unrecognized sepsis". In our opinion, score systems are particularly useful when cultures are negative and clinical condition are critical. At the second or third weeks, when a very sick clinical condition are present, high SOFA score could contribute to identify the "best" surgical timing even without identification of pancreatic infection.

Intraductal Papillary Mucinous Neoplasms. Personal Experience and 10-Year Literature Review

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Background Preoperative differential diagnosis among intraductal papillary mucinous neoplasms (IPMNs: benign, borderline, in situ and invasive carcinoma) is still very difficult in several cases.

Aim We reviewed 31 our patients and patients reported in the last 10 years.

Materials and Methods Thrity-one patients with IPMN were treated between 1991 to October 2003 in our Surgical Department; 21 were prospectively investigated also with 18-FDG PET. It was considered positive when a focal uptake occurred with a standard uptake value (SUV) of at least 2.5. A literature review of the last 10 years allowed us to collect 1,037 patients.

Results Among our patients there were 20 males and 11 females with a mean age of 62 years (range 46-78). An adenoma was diagnosed in 7 patients, a borderline tumor in 5, a carcinoma in situ in 3 and an invasive cancer in 9 patients. Twenty patients underwent resection, 1 patient underwent palliative surgery, and 10 patients did not undergo surgery. 18-FDG PET resulted negative in 5 adenomas (A) and 5 borderline (B) IPMNs, while resulted positive in 3 carcinomas in situ (CiS) and in 8 invasive carcinomas (IC). Among the 1,037 IPMNs there were 326 A, 67 B, 162 CiS, 317 IC, 54 A/B, 48 CiS/IC, 22 B/CiS/IC, and 41 were undefined. Malignancy was reported in 77% of 223 main duct IPMNs and in 38% of 225 branch duct IPMNs. Three-hundreds and 93 patients underwent pancreatoduodenectomy, 126 left pancreatectomy, 112 total pancreatectomy, 49 limited resection and 15 did not undergo surgery. Data were missing for 342 patients. Two out of 159 A relapsed and both DOD. Two out of 28 B relapsed and 1 DOD. Four out of 82 CiS relapsed and 3 DOD. One-hundred and 8 out of 227 IC relapsed and 89 DOD. Four out of 62 A/B relapsed and all DOD. Nineteen out of 109 CiS/IC relapsed and 16 DOD. Seven out of 114 A/B/CiS relapsed and 1 DOD. Survival data of 277 patients were not reported.

Conclusions 18-FDG PET is very accurate in distinguishing benign from malignant IPMNs. Adenomas, borderline tumours and in situ carcinomas have a quite similar survival rate. Invasive carcinomas have a high relapse rate and a poor prognosis. Finally a thorough examination of the surgical specimen is needed to avoid an under evaluation of the disease.

Elevated Serum Levels of Insulin-Like Growth Factor-I Are not Associated with Pancreatic Cancer

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Background Insulin-like growth factor-I (IGF-I) is the major endocrine and paracrine mediator of the effects of the growth hormone; it thus has a strong influence on cell proliferation and differentiation. Due to its mitogenic and proangiogenic action, it plays a critical role in the development and progression of human cancer. High serum concentrations of IGF-I are indeed associated with an increased risk of breast, prostate, colorectal and lung cancers. Particularly, IGF-I has been implicated in the pathogenesis of pancreatic cancer.

Aim The aim of this study is to assess possible variations in the serum levels of IGF-I in patients with pancreatic cancer as compared to a healthy control group.

Methods Serum levels of IGF-I were measured by RIA in 11 patients (6 males, 5 females; mean age: 69 years) with histological diagnosis of pancreatic adenocarcinoma and compared to those of 20 age-matched healthy control subjects (11 males, 9 females), from September 2002 to January 2004. In 8 of the 11 patients the cancer was in the head of the pancreas, in 2 patients in the tail and in 1 in the body. The disease's stage was the same for all the patients (T3N1M0), with histopathologic grading ranging from G1 to G3.

Results IGF-I levels obtained from the serum of the patients with pancreatic adeno-carcinoma were not significantly different from the levels of the control group (124.3±83.0 ng/mL vs. 136.8±61.5 ng/mL, $P>0.6$).

Conclusions Despite the high levels observed in patients with different solid neoplasms, IGF-I serum values in pancreatic cancer patients are not higher than the levels obtained in healthy subjects, probably because of its predominant paracrine action, through high peritumoral concentrations. Therefore IGF-I in pancreatic cancer is still to be investigated, particularly its local and endocrine role.

The ELISA Fecal Elastase-1 Polyclonal Assay Reacts with Different Antigens than Those of the Monoclonal Assay

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Background The measurement of fecal elastase-1 concentrations by means of an ELISA based on monoclonal antibodies (Elastase-1 Schebo Diagnostic, Giessen, Germany) is highly specific for human elastase-1 and it has become an accepted indirect test of exocrine pancreatic function. Its usefulness has been demonstrated in various clinical studies including comparison with direct function tests and ERCP morphology. Recently, a new ELISA kit for elastase-1 determination (Elastase-1 ELISA, Bioserv Diagnostics, Rostock, Germany) based on polyclonal antibodies is commercially available.

Aim To compare the results of these two different measurements of fecal elastase-1.

Patients and methods Six subjects (2 pancreatic endocrine non-functioning tumors, 1 pancreatic adenocarcinoma, 1 chronic

pancreatitis, 1 liver cirrhosis, 1 healthy subject; 2 males and 4 females; median age 58 years, range 38-76 years) were included in the study. Six replicates for each sample were measured. The stools of these patients were collected and stored at -20°C until analysis. The stool samples were then processed according to the manufacturers instructions and were determined in duplicate using the two assays. Furthermore, 3 standards of the monoclonal ELISA assay (St50: 50 μg; St150: 150 μg; St500: 500 μg) were processed in duplicate by using the polyclonal ELISA kit. Finally, chymotrypsin using a colorimetric methods (Chymo, Roche Diagnostics GmbH, Mannhein, Germany; low reference value 6.0 U/g) was also determined in the feces of the six patients (median 14.0 U/g, range 2.1-19.9 U/g). The Spearman rank correlation test was applied.

Results The median polyclonal elastase-1 determination was 293 μg/g (range 82-564 μg/g) and the median monoclonal elastase-1 determination was 242 μg/g (range 33-482 μg/g) in the 6 subjects. Both kits showed a good intra-subject coefficient of variation (polyclonal: median 6.9%, range 2.0-8.6%; monoclonal: median 2.0%, range 0.6-9.0%), whereas no significant relationship was found between the two ELISA kits (r_s=0.771, P=0.072); the differences of the concentrations evaluated by using the polyclonal assay vs. the monoclonal assay ranged from -31% to +351% (median +27%). Polyclonal elastase-1 assay alone was significantly related to fecal chymotrypsin determination (polyclonal: r_s=0.829, P=0.042; monoclonal: r_s=0.543, P=0.266). The results of the measurement of the standards of the monoclonal assay with the polyclonal kit were highly different than those expected (St50: 3 μg, St150: no detectable; St500: 6 μg).

Conclusion The ELISA polyclonal determination seems to react with different antigens than elastase-1. Therefore, accurate cross-reactivity studies comparing the two elastase-1 assays are required and the reference value of polyclonal ELISA kit should be specifically re-evaluated.

Pancreatic Elastase-1 in Stools - a Marker of Exocrine Pancreas Function - Correlates with Both Residual Beta-Cell Secretion and Metabolic Control in Type 1 Diabetic Subjects

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Background A strict correlation between endocrine function, in particular for what concerns insulin, and endocrine secretion has been demonstrated. In patients affected by Type 1 diabetes mellitus, low concentration of pancreatic elastase in stools, are related to a poor metabolic control, but a relation between this protein and residual beta cell function has not been shown.

Aim We evaluated the correlation between stool elastase, the residual beta cell activity and glycemic control in patients affected by type 1 diabetes mellitus.

Methods We studied 37 consecutive patients, affected by diabetes mellitus type 1 (16 males, mean age 34±2 years) and 20 healthy controls. In the patients we excluded causes of malabsorption or gastroenterological disease. We dosed stool elastase, C-peptide, HbA1c. In patients with stool elastase less than 200 μg/g of stools, 24 hours fecal fat were obtained.

Results The fecal elastase level in subjects affected by type 1 diabetes mellitus resulted significantly lower than controls (263±36 vs. 438±38 μg/g stools; P=0.0004). 21 patients out of 37 had fecal elastase values less than the normal, and among these, 4 presented steatorrhea (24 hours fecal fats greater than 6 g/24 hours). Of the 21 patients with abnormal values of fecal elastase, 20 presented C-peptide concentrations less than or equal to 0.5 ng/mL (r=0.565, P=0.0003). The values of fecal elastase resulted inversely related to that of HbA1c (r=0.519; P=0.0001): in 19 subjects with HbA1c greater than 8%, 14 presented values of fecal elastase less than 200 μg/g stools.

Conclusions This study shows that the residual pancreatic endocrine activity and glycemic control in type 1 diabetes mellitus are related to the pancreatic exocrine function. Moreover, our results confirm the frequent finding of a sub-clinical pancreatic exocrine deficit in these subjects.

Usefulness of 18-FDG PET in the Diagnosis and Management of Nonpancreatic Periampullary Neoplasms

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Background The role of 18-fluorodeoxyglucose positron emission tomography (18-FDG PET) in the clinical management of non pancreatic periampullary tumors has not been studied so far.

Aim Aim of this study was to examine the clinical impact of 18-FDG PET in the diagnosis and follow-up of patients with periampullary neoplasms.

Materials and Methods Twenty-three patients (14 males and 9 females, mean age 65.1 years, range 41-83) underwent whole-body 18-FDG PET and abdominal computer tomography (helical CT). In all patients malignant or benign disease was confirmed pathologically after surgery. The 18-FDG PET was analyzed visually and semi quantitatively using the standard uptake value (SUV). It was considered positive when a focal uptake occurred with a SUV of at least 2.5.

Results There were 14 ampullary tumors (9 adenocarcinomas and 5 adenomas), 7 bile duct neoplasms (6 adenocarcinoma and 1 carcinoma in situ), and 2 duodenal tumors (1 adenocarcinoma and 1 leiomyoma). Eighteen patients underwent pancreaticoduodenectomy, 2 local excision, and 3 bypass surgery. 18-FDG PET showed increased focal uptake in 20 patients (87%): 11/14 (79%) of ampullary tumors, and 100% of bile duct and duodenal tumors. 18-FDG PET showed focal uptake in 11/12 patients without detectable mass at CT scan. 18-FDG PET showed also lymph node metastases in 5 patients. SUV value of 2.7 discriminated adenomas or non invasive cancers (n=6) from invasive malignancies (n=14). Follow-up including CT and 18-FDG PET was performed in 8 patients: 18-FDG PET showed recurrent disease not seen by CT in 4 patients, confirmed CT findings in 3. One patient underwent resection of the recurrence, two patients underwent palliative surgery, 4 patients did not undergo surgery. Finally a primary lung cancer was detected by 18-FDG PET and resected.

Conclusions 18-FDG PET showed high sensitivity for detecting periampullary neoplasms. The 18-FDG PET may be useful in clinical practice when no mass has been identified by traditional imaging, to differentiate benign or border-line lesions from invasive tumors, and in the follow-up to identify recurrent disease.

New Methods of Treating the Pancreatic Fistulas: The Use of Sclerosing Substances

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Background Treatment of pancreatic fistulas is usually medical, radiological, rarely surgical.
Aim To evaluate the efficacy of new method using sclerosing substance injected in pancreatic duct through CT-guided percutaneous catheter drainage before.
Methods Embolization of pancreatic fistula was carried out in three patients (2 males, 1 female; median age 41 years, range 26-49 years). In 2 cases the fistula arose after a PD, in the third case it arose after a resection of a cyst of the pancreatic body. All patients presented postoperative pancreatic pure fistula, middle daily output(15-20 cm^3/day) persisted for middle time of 8 months (range 3-11months). All cases show pancreatic duct's fistula that was demonstrated by injection of soluble contrast-material through CT guided percutaneous catheter drainage. At last, through the same catheter a total volume of Ethibloc (approximately 8 mL) was injected in pancreatic duct in one single sitting. CT scan examination was immediately performed and after 48-72 h.
Results In consequence of this treatment the output of this fistula considerably decreased in all cases respectively from 15, 20, 20 cm^3/day , to 1, 2, 4 cm^3/day after 4 days. Two cases demonstrated by means of US complete regression of the fistula at 26 and 16 months. But after 7 days by treatment, the last patient, showed the recurrence of the fistula with output of 10 cm^3/day, and after 6 months CT demonstrated the persistence of a small pancreatic pseudocyst.
Conclusion This method to treat pancreatic fistulas after pancreatic resections allows excellent results, without major complications. It may be perform in persistent pancreatic fistula of middle daily output, and, if necessary, may be repeat again.

THE FOLLOWING ABSTRACTS HAVE BEEN ACCEPTED FOR PRESENTATION AT THE POSTER SESSION AFTER THE DATE OF PUBLICATION.

Significance and Rationale for Pancreatoduodenectomy with Portal/Mesenteric Vein Resection

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Background The involvement of the porto-mesenteric trunk by pancreatic adenocarcinoma is not associated with histologic parameters suggesting a poor prognosis but it seems to be function of tumor location and it is often impossible to determine if venous invasion is desmoplastic or cancerous at preoperative imaging. Pancreatectomy with en bloc vein resection could be useful in order to obtain an R0 resection.
Aim The authors examine the rationale of pancreato-duodenectomny with portal/ mesenteric vein resection by reviewing their experience.
Methods During the last year, we performed 30 pancreatic resection for pancreatic adenocarcinoma: 15 total pancreatectomy (TP), 10 duodenopancreatectomy (DCP), 1 small bowel autotransplantation (a patients with involvement of the superior mesenteric artery) and 4 left pancreatectomy (PS). In 7

cases (4 TP, 2 DCP and 1 PS) a portal vein resection was performed, due to the presence of suspicious infiltration of portal/mesenteric vein.

Results The mortality and morbidity of the 30 pancreatic resections was 6% and 23%, respectively. The mortality of the patients with venous was 14% (1/7, CID) and the morbidity rate was 42% (1 subfrenic collection, 1 delayed gastrointestinal function recovery and 1 gastro-intestinal hemorrhage): no complication was correlated with the venous resection. The median hospital stay was 14 day. At the histological examination, only in one case the resected vein was infiltrated by pancreatic tumor; in the other cases the vein was not dissectable from the parenchyma because of lymph node metastasis (3 cases) or perineural metastasis (3 cases; 1 of these with node metastasis). In all cases except one (R1) the procedure was classified as R0 resection at the histological examination.

Conclusions In our experience, pancreatoduodenectomy combined with portal/mesenteric vein resection should be performed every time the vein was not dissectable from the pancreas, but it has to be recommended only when a margin-negative resection is expected to be achieved.

Small Bowel Autotransplantation for Pancreatic Adenocarcinoma Involving the Superior Mesenteric Artery

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Background The presence of vascular involvement due to adenocarcinoma of the head of the pancreas is still considered by some authors a contraindication for surgery. Recently an improved survival after pancreatectomy with associated resection of the superior mesenteric vein or the portal vein was demonstrated, while the involvement of the superior mesenteric artery still remains an absolute contraindication for surgery.

Aim The authors described a case of small bowel autotransplantation in a 60-year old woman affected by an adenocarcinoma of the head of the pancreas with infiltration of the superior mesenteric artery.

Methods Intraoperatively, a neoplastic involvement of the common hepatic artery was detected, thus, a revascularization of the liver by an anastomosis of the common hepatic artery with the left gastric artery, was necessary. Then, the stomach, duodenum, pancreas, spleen, small bowel, right colon, extrahepatic bile duct, cephalad superior mesenteric vein and proximal superior mesenteric artery were resected, with en-bloc dissection of the paraaortic lymph nodes. The resected organs were flushed with chilled Celsior solution, placed in an ice-cold bath and, then, the total pancreatectomy was performed. Only the small bowel was autotransplanted by anastomozing the portal vein to the superior mesenteric vein and by anastomozing the superior mesenteric artery of the small bowel with the proximal superior mesenteric artery with the interposition of a cadaveric graft. Then, the gastrointestinal continuity was completed.

Results The intervention was 12 hours long, while the cold ischemia time was about 2 hours. The patient started normal oral feeding after 4 days. In the 6th postoperative day, the patient developed a massive hemoperitoneum due to the dissection of the common hepatic artery and reintervention was necessary. Unfortunately, the patient died 10 days after the first intervention for a multi organ failure.

Conclusions Small bowel autotransplantation could represent the only therapy in patients affected by pancreatic carcinoma with involvement of the superior mesenteric artery, at least in selected cases.

Diagnostic Pitfall: Portal Cavernoma Mimicking Pancreatic Tumor

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Background Pancreatoduodenectomy is the only possibility for cure patients with pancreatic tumor. The diagnosis remains in some cases difficult although the amelioration of diagnostic imaging.

Aim The authors described a cases of portal cavernoma that was misdiagnosed as a pancreatic cystic neoplasm.

Methods A male aged 59 was admitted to our division with a diagnosis of paraduodenal neoformation. This lesion, compressing the inferior vena cava and the portal vein, seemed to be of pancreatic origin at CT scan. The patients was submitted to an echoendoscopy that described the lesion as non-homogeneous, hypoechoic, with internal sepimentation, posteriorly located to the 2nd duodenal portion, with some signs of portal hypertension, suspected splenic vein trombosis and a non-homogeneous pancreatic head, in absence of clear focal lesions. However, the histological examination of the fine needle biopsy suggested a pancreatic cystic lesion.

Results The patient underwent surgery and only after pancreatic resection was performed, the surgeon should identify the lesion as a thrombosed portal cavernoma. The intervention has consisted of a total pancreatectomy with en-bloc portal cavernoma resection. Cephalad portal vein and proximal mesenteric vein thrombectomy and a end-to-end porto-mesenteric anastomosis was performed. The operation was 7 hours long. The patients start immediately an insulin i.v. infusion that was converted to s.c. infusion on post-operation day 4th when the patient started oral feeding. The post-operation course was complicated with a subfrenic collection due to gastric perforation that necessitated reintervention. The patients was then dismissed 36 days after intervention.

Conclusions The diagnosis of pancreatic lesion could be sometimes very difficult despite the recent innovations in imaging and endoscopy. However, the patients with neoformation of the duodenum-pancreatic bloc could be examined by a team of radiologists, gastroenterologists and surgeons skilled in biliary and pancreatic pathology in order to prevent some unnecessary and somewhat dangerous procedures.