

ORAL COMMUNICATIONS

Phosphorylation of EIF4E by MNK Supports Proliferation of Pancreatic Cancer Cells

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Context Standard first-line chemotherapy has only marginal survival advantage in pancreatic cancer. Deregulation of the RAS and the PI3K/AKT/mTOR pathways is among the major causes of increased malignancy also in this type of tumor. These signalling pathways converge on the regulation of eIF4E, a central factor of cap-dependent translation. EIF4E is upregulated in many tumours and has oncogenic properties when overexpressed. Phosphorylation of eIF4E by the MNK1/2 kinases seems required for its oncogenic potential. Moreover, it is often increased in cancer cells undergoing several stresses and chemotherapeutic treatments. **Objective** We have investigated the role of eIF4E Ser209 phosphorylation in pancreatic cancer cell proliferation and survival. We concentrated on eIF4E modulation and MNK activity during stress conditions. **Methods** We used analysis of Western blot to assay changes in the phosphorylation state of proteins involved in the RAS-PI3K pathway and in the CAP-dependent translation. We performed MTS proliferation assay or cell counts to analyze the

proliferation rate of pancreatic cancer cell lines, using MNK-inhibitor in combination with rapamycin or with serum deprivation or Cisplatin. **Results** We found that the mTOR inhibitor caused strong phosphorylation of eIF4E by MNKs. Inhibition of MNK activity affected cell cycle progression and proliferation and enhanced the cytostatic effect of mTOR inhibitor in two pancreatic cancer cell lines. The blockade of the MNKs also enhances the sensitivity of pancreatic cancer cells to serum deprivation and Cisplatin. **Conclusions** Our results imply mechanistically separate controls of eIF4E: various types of stresses (mTOR/translation inhibition, genotoxic stresses) can increase phosphorylation levels of the translation factor eIF4E, in a MNK-dependent manner. This phenomenon could represent an escape pathway or a mechanism of protection of the cell. Inhibiting MNKs activity, we potentiated cytostatic effects of chemotherapeutic agents in pancreatic cancer cell lines, indicating a novel molecular target to overcome chemoresistance.

Pancreatic Specific Transcription Factors and CK19 in Pancreatic Endocrine Tumors: Clinico-Pathological Correlations and Survival Analysis

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Context The role of transcription factors (TFs) Isl-1, Pax6, Nkx2.2, Nkx6.1, MafB and Pdx-1 in pancreas development was recently described. They regulate commitment to individual cell lineages and maintain terminally differentiated phenotype. Their disruption results in impaired development of pancreatic endocrine structures. Few data are available about their expression in pancreatic endocrine tumors (PETs). PETs are classified in WHO categories as benign (WDET-B), uncertain behavior (WDET-U), well

differentiated carcinomas (WDEC) and poorly differentiated carcinomas (PDEC). No absolute histopathological criteria are available to predict clinical course. Therefore, identification of immunohistochemical markers that could predict the biological behavior would be extremely helpful in surgical management and adjuvant therapy of PET. The expression of the intermediate filament cytokeratin 19 (CK19) has been recently proposed as predictor of survival in PETs. **Objective** To evaluate in a large

series of PETs the expression of TFs (Isl-1, Pax6, Nkx2.2, Nkx6.1, MafB, Pdx-1) and CK19 and analyze their correlation with the survival and WHO categories. **Materials and Methods** CK19 and TFs immunoreactivity was evaluated in 48 WDET-B, 32 WDET-U, 41 WDEC and 10 PDEC; a TF-score was defined: low score (LS) when the tumor expressed 0-3 TFs; high score (HS) when the tumor expressed 4-6 TFs. CK19 reactivity and TF-score were correlated with WHO categories and survival. **Results** HS for TFs (4 or more) was observed in 90% of WDET-B, in 69% of WDET-U, and in 49% of WDEC; all PDEC showed LS ($P<0.05$). Nkx6.1 was the most frequently TF associated with WDET-B (79%) in contrast to WDET-U with 50% of positive cases. Low reactivity was observed for Nkx6.1 in WDEC (20%) and PDEC

(10%) ($P<0.05$). CK19 expression was higher in WDEC (83%) than in WDET-B and WDET-U tumors (56%) ($P<0.05$). Cases with HF and low CK19 showed better survival ($P<0.0005$) and less frequent relapse of disease. **Conclusions** Endocrine specific TFs are coexpressed in most WDET-B and WDET-U; a progressive loss of expression is detected in WDEC and PDEC: the TFs biological role in pancreatic endocrine specification is maintained in PET and run in parallel with WHO PET categories. Nkx6.1 shows very limited reactivity in WDEC and PDEC. These changes in TFs expression in PET are inversely correlated with CK 19 expression. The combined analysis of TFs and CK19 and the correlation with survival analysis data could offer a better prognostic index in the clinicopathologic evaluation of PET.

Prevalence of Pancreas Divisum (PD) in Patients with Different Pancreatic Diseases

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Context PD is the most common anatomic variant observed in general population. Its role in the pathogenesis of pancreatitis is controversial. **Objective** Aim of the present study is to evaluate the prevalence of PD in patients suffering from different pancreatic diseases. **Patients and Methods** Patients suffering from pancreatic diseases observed in our Department in the period 2000-2008 who underwent ERCP or RMCP with secretin stimulation (RMCPs) were retrospectively evaluated. On the basis of clinical, radiological, pathological and functional data, patients were classified as following: group 1: pancreatic hyperenzymemia (PH), group 2: acute pancreatitis (AP), group 3: recurrent pancreatitis (RP), group 4: chronic pancreatitis (CP), group 5: pancreatic adenocarcinoma (PC), group 6: IPMN. As control group 7 (C), we studied patients who underwent ERCP with a biliary indication and with accidental visualization of pancreatic ductal system or RMCPs.

Results One-thousand and 88 patients (577 males, 511 females; mean age 55 ± 17 years) were studied. Clinical characteristic of different groups and prevalence of PD are reported in the Table. The prevalence of PD was significantly different in the groups studied ($P<0.0001$). In particular, PD was more frequent in PH, RP and CP groups vs. C ($P<0.0001$, $P<0.0001$, and $P=0.01$, respectively). **Conclusions** PD is significantly associated with inflammatory diseases of the pancreas and with asymptomatic pancreatic hyperenzymemia.

| | No. of cases | Males | Age (years) | PD |
|------|--------------|-------|-------------|-------|
| PH | 72 (7%) | 60% | 48 ± 14 | 18.1% |
| AP | 85 (8%) | 55% | 53 ± 17 | 4.7% |
| RP | 170 (16%) | 41% | 46 ± 17 | 24.7% |
| CP | 279 (26%) | 67% | 51 ± 14 | 6.5% |
| PC | 106 (10%) | 51% | 65 ± 12 | 3.3% |
| IPMN | 60 (5%) | 35% | 62 ± 13 | 2.8% |
| C | 316 (29%) | 50% | 62 ± 16 | 2.2% |
| All | 1,088 (100%) | 53% | 55 ± 17 | 8.2% |

Smoking as a Co-Factor for Causation of Chronic Pancreatitis: A Meta-Analysis

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On behalf of an *ad-hoc* Committee of the "Italian Association for the Study of the Pancreas"

Objectives To assess the evidence for tobacco smoking as a risk factor for the causation of chronic pancreatitis in alcoholic patients. **Methods** We performed a meta-analysis with random effects models to estimate pooled

relative risks of chronic pancreatitis for current, former and ever smokers, in comparison to never smokers. We also performed dose-response, heterogeneity, publication bias, and sensitivity analyses. **Results** Nine

case-control studies and two cohort studies that evaluated, overall, 1,165 patients with alcoholic chronic pancreatitis satisfied the inclusion criteria. When contrasted to never smokers, the pooled risk estimates for current smokers was 2.5 (95% CI: 1.6-3.9) overall, and 2.5 (95% CI: 1.3-4.6) when data were adjusted for alcohol consumption. A dose-response effect of tobacco use on the risk was ascertained: the relative risk for subjects smoking <1 pack/day was 2.4 (95% CI: 0.9-6.6), and increased to 3.3 (95% CI: 1.4-

7.9) in those smoking ≥ 1 pack/day. The risk diminished significantly after smoking cessation, as the relative risk estimate for former smokers dropped to a value of 1.4 (95% CI: 0.9-2.1). **Conclusion** Tobacco smoking may enhance the risk of developing chronic pancreatitis in alcoholics. Recommendation for smoking cessation, besides alcohol abstinence, should be incorporated in the management of patients with alcoholic chronic pancreatitis.

Analysis of CFTR, SPINK1 AND PRSS1 Mutations in Italian Patients with Chronic Pancreatitis

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Context Defects of PRSS1, SPINK1 and CFTR are considered causative or predisposing to pancreatitis.

Objective The aim of this study was to evaluate the impact of these defects into molecular pathology of chronic pancreatitis (CP). **Methods** Two hundred and seventy three patients with CP, 16 family members and 230 controls were investigated. The subjects were screened for PRSS1 mutations in exons 2 and 3 and SPINK1 exon 3 mutations by DGGE analysis; CFTR defects were analyzed with a panel of 32 mutations and poly-T (CF-OLA) and DGGE analysis of 8 exons of the CFTR gene. The poly-TG region in intron 8 of the CFTR gene was analysed in patients with 5 poly-T by direct sequencing. Forty patients with idiopathic chronic pancreatitis were screened for duplication-triplication in the PRSS1 gene by real-time PCR. **Results** We identified 1 mutated allele in at least 1 of 3

genes in 71 of 273 patients. The frequency of the CFTR mutations was significantly higher in the CP group versus controls, mutations frequencies in SPINK1 and PRSS1 were 5.5% and 2.6%, respectively. PRSS1 and SPINK1 mutations were identified mainly in familial cases. Family studies showed that defects in the examined genes did not always segregate with disease. **Conclusion** PRSS1 and SPINK1 defects seem to be causative for pancreatitis, whereas defects in CFTR are suggested to be associated with the disease. This study suggests the very important role of genetic analysis in the etiology of chronic pancreatitis. SPINK1 and PRSS1 mutations are relatively rare in idiopathic pancreatitis without history of familial disease. CFTR mutations are frequently associated with pancreatitis even in absence of cystic fibrosis.

Surgical and Pathological Results of Resection after Downstaging for Locally Advanced Pancreatic Cancer

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Context Chemo and chemoradiation are used in unresectable pancreatic cancer for palliation. In some patients after treatment, the tumor become resectable and some complete pathologic response are reported.

Objective To evaluate pathological and surgical results of patients who underwent to a resection after chemo or chemoradiation therapy using as a control group those patients who had in the same period an upfront resection. **Patients and Methods** Between 2000 and 2008, 423 consecutive patients with pancreatic cancer

who underwent pancreatic resection were included. In the study period 42 patients, staged at first observation as having a local advanced disease, underwent to a surgical resection after neoadjuvant therapy (NT group). The remaining 381 patients had an upfront surgery (US group). Surgical and pathological results were compared. **Results** Mortality and morbidity rate were 2.3% and 33.3% in NT group and 1.1% and 28.3% in the US group, respectively. No differences were found concerning pancreatic leakage, blood

transfusion, and redo-surgery between the two groups. In NT group 9.5 % patients had a complete pathological response (pT0N0) while in 33.3% a minimal residual disease was found (pT1N0). A lower frequency of lymphnode metastases was observed in the NT vs. US group (33.4% and 86.4%, respectively; $P<0.05$). The resection margins in the NT group was

positive (R1/2) in 28.5% in comparison to the 40% of US group ($P<0.05$). **Conclusion** Surgery after neoadjuvant therapy does not increase mortality and morbidity in comparison to that observed after an upfront surgery providing major pathological response and a high R0 resection rate.

Prognostic Clinical-Pathological Factors Associated with the Recurrence after Radical Resection for Pancreatic Endocrine Carcinomas (PECs)

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Context In the literature there are no studies which specifically address the issue of tumor recurrence (TR), timing and associated factors after curative resection for PECs. **Objective** To investigate in a single institution series which prognostic factors are associated to recurrence after radical resection for well (WDEC) and poorly differentiated (PDEC) pancreatic endocrine carcinomas. **Methods** Our prospective institutional database of 364 patients suffering from endocrine pancreatic tumor from 1990 to 2007 was queried in order to identify those patients who underwent to a curative resection for PECs. Patients with MEN1 and VHL syndromes were excluded. All the cases were classified according to WHO classification and TNM staging. In all tumors proliferative index (Ki67) was estimated. Clinical and pathological factors, i.e. age, gender, symptoms, clinical signs, tumor size, tumor location, lymph node status and ratio (LNR) were analysed. The patients were followed up at least with a six months interval and last follow-up was updated at December 2008. **Results** Fifty-six patients with WDEC and PDEC were identified with an overall resectability rate of 24.7%. Median age was 58 years (range 17-78 years) and 50% (n=28) were male. Thirty-one patients (55%) underwent to a pancreaticoduodenectomy (PD) and the

remaining 25 to a left-pancreatectomy. In 3 metastatic cases a liver resection was associated. The morbidity rate was 41% (n=23) being a pancreatic leak the most frequent complication (n=17). Mortality was nil. A median of 20 (3-57) lymph nodes were resected/evaluated and nodal metastases were found in 37 patients (66%). In this latter group the LNR was >0 and ≤ 0.15 in 25 cases (68%) and >0.15 in the other 12 cases (32%). Median follow-up was 43 months (range 5-202 months). A TR occurred in 25 cases (45%) with a median disease free survival (DFS) of 19 months (range 2-158 months). The site of recurrence was the liver in 19 cases (76%), lymph nodes in 4 cases (16%) and other sites in 2 cases (8%). At univariate analysis age, Octreoscan[®] positive, Ki67 $>5\%$ and LNR >0.15 were associated with TR and DFS ($P<0.05$), but at multivariate analysis only a Ki67 $>5\%$ (HR: 3.71) and a LNR >0.15 (HR: 4.00) were significantly associated with both TR ($P<0.0009$) and DFS ($P=0.0001$). **Conclusion** A TR can be expected in about half of the patients who underwent to a curative resection for PECs. Ki67 $>5\%$ and/or LNR >0.15 are the main independent parameters associated with recurrent disease. In the future they could be used in order to identify those patients who might benefit for an adjuvant treatment.

Bone Marrow as an Alternative Site for Islet Transplantation

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Context The liver is the current site for pancreatic islet transplantation but has many drawbacks due to

immunological and non-immunological factors. **Objective** We asked whether pancreatic islets could be

engrafted in the bone marrow (BM), an easily accessible and widely distributed transplant site that may lack the limitations seen in the liver. **Methods and Results** Syngeneic islets engrafted efficiently in the BM of C57BL/6 mice rendered diabetic by streptozocin (STZ) treatment. For over a year post-transplantation these animals showed parameters of glucose metabolism that were similar to those of non-diabetic mice. Islets in BM had a higher probability to reach euglycemia than islets in liver (2.4 fold increase, $P=0.02$), showed a compact morphology with a conserved ratio between alpha and beta cells, and

affected bone structure only very marginally. Islets in BM did not compromise hematopoietic activity, even when it was strongly induced in response to a BM aplasia-inducing infection with lymphocytic choriomeningitis virus (LCMV). **Conclusion** In conclusion, BM is an attractive and safe alternative site for pancreatic islet transplantation. The results of our study open a research line with potentially significant clinical impact, not only for the treatment of diabetes but also for other diseases amenable to treatment with cellular transplantation.

Patterns of Recurrence after Resection for Pancreatic Adenocarcinoma

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Context The great majority of patients undergoing resection of pancreatic cancer will die of the disease. The analysis of recurrence pattern after resection could help to define the adequate strategy of adjuvant treatment. **Objective** To define the pattern of recurrence in resected pancreatic cancer, possibly identifying prognostic factors for recurrence site. **Methods** From 1997 to 2007, 384 patients underwent resection for ductal carcinoma; among them, only patients followed-up at our Institution were included in the study group, to reduce the bias deriving by inadequate follow-up. The study group was therefore made by 192 patients, with scheduled clinical evaluation, CA 19-9 assessment and CT scan every 3 months (or before in case of relapse suspicion). Most of them underwent adjuvant treatment (CHT 75%, RT 86%). Log-rank and Cox regression were used for statistical analysis. **Results** Median overall survival (OS) of the study group was 23.7 months, 5-year OS was 18%. One-hundred and 58 patients (82.3%) developed recurrence (range 2-73 months); local relapse was detected in overall 71 patients (37%), and distant metastases in 111 patients (57.8%); of these, 28 (14.6%) had both local and distant recurrence. Median disease-free (DF) survival was 12.7 months. Sites of distant metastases were: liver (73 patients), lung (18), peritoneum (14), extrabdominal ln (6), bone (2), skin

(2), brain (1). Lung metastases occurred significantly later than liver's ($P=0.045$). Three out of 8 actual 5-year DF survivors recurred after 5 years (1 liver, 1 lung, and 1 lung plus local). No significant difference was found in time of recurrence between local and distant metastases, (12 and 11.5 months); similarly, no difference was observed in survival after detection of local and distant recurrence (9.4 and 11.1 months, respectively). A number of factors were evaluated, searching for prognostic determinants of recurrence. At multivariate analysis, significant factors were: nodal status (HR 4.54), nodal ratio (HR 4.41), diameter (HR 1.13), and adjuvant therapy (HR 0.47). As regards site of recurrence, no factor (including margin status) significantly predicted local relapse, whereas nodal ratio (HR 6.46) and adjuvant therapy (HR 0.43) were significant determinants for distant metastases. **Conclusion** Distant metastases is the most frequent recurrence site, suggesting the adequacy of a chemotherapy-first strategy in adjuvant therapy. Local relapse affected 37% of patients and it was not related to margin status, indicating that R-factor should not be a determinant for adjuvant RT. No difference in recurrence time was detected between local and distant sites. Recurrence may occur even after a prolonged DF survival.

Blockade of Plasminogen alpha-Enolase Interaction Inhibits Pancreatic Cancer Cell Lines Invasion

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Context Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive malignancy characterized by rapid

progression, invasiveness and resistance to treatment. In our laboratory it has been demonstrated that 62% of

PDAC patients have circulating antibodies against alpha-enolase and most of them showed a longer time free of disease compared with those without antibodies. Alpha-enolase is a key enzyme of the glycolytic pathway and it is primarily localized in the cytoplasm. Many reports have indicated that alpha-enolase is also expressed on the surface of immune cells and tumor cells where it acts as a plasminogen receptor. We have observed that alpha-enolase is expressed on the surface of PDAC cells, where it may contribute to plasminogen activation into plasmin, which is a serine-protease involved in extracellular matrix degradation, thus increasing invasion of cancer cells. **Objective** To verify if enolase could have a role in invasion of pancreatic cancer cells and if we could block it with an antibody against alpha-enolase that compete with plasminogen binding. **Methods** We analyzed surface alpha-enolase expression on PDAC cell lines by cytofluorimetric analysis. To assess the CF-PAC-1 invasion potential we performed an invasion matrigel assay with transwells and to assess proliferation a MTT test. We mutated alpha-enolase with site directed mutagenesis. The alpha-enolase mutated forms were produced and tested for plasminogen binding to alpha-enolase in an ELISA assay. **Results** We found that treatment with a mouse monoclonal antibody that

recognize human alpha-enolase inhibits plasminogen-dependent migration through matrigel of a PDAC cell line (CF-PAC-1). By contrast, this antibody does not influence *in vitro* cell growth. Now we focus to understand the mechanisms by which the anti-alpha-enolase mAb exerts its effects. To do this, mutants of alpha-enolase, with one or more mutations in the putative plasminogen binding site, were produced and their ability to bind plasminogen was evaluated by an immunoenzymatic assay. The mutation in lysine 433, alone and in combination with mutation in lysine 421 and 419, strongly inhibited plasminogen binding to alpha-enolase. This prompts us to analyze the effects of mutants in transfected PDAC cells. CF-PAC-1 cells will be transfected with alpha-enolase wild-type or triple mutated (lysines 419-421-433) to evaluate *in vivo* their potential to counteract metastatization. In parallel, genetically engineered mice that develop spontaneously PDAC will be exploited to evaluate the anti-alpha-enolase monoclonal antibody potential in tumor growth inhibition. **Conclusion** Alpha-enolase is expressed on cell surface of some PDAC cell lines where is crucial for CF-PAC-1 cell line invasion. A mAb against alpha-enolase inhibits plasminogen dependent invasion through matrigel.

Main-Duct and Combined IPMNS Are the Same Clinical Entity and Distinct from Branch-Duct IPMNS

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Context Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas comprise main-duct (MD), branch-duct (BD) and combined types. **Objective** The aim of this study was to evaluate the clinico-epidemiological characteristics and prognosis of a large series of patients with IPMNs, to elucidate differences among the three types. **Methods** Three-hundreds and 89 patients who underwent pancreatic resection for IPMN were identified. **Results** One-hundred and 59 (41%) patients had BD-IPMNs, 149 (38%) combined-IPMNs, and 81 (21%) MD-IPMNs. MD- and combined-IPMNs occurred more frequently in males (56%) while BD-IPMNs in females (57%) ($P < 0.05$). All IPMNs subtypes were generally located in the proximal pancreas. Incidental diagnosis was more common in BD-IPMNs (34.5%) than in MD- (13.5%) and combined- (19%) ones ($P = 0.001$). Prevalence of adenoma was 44% in BD-, 11% in MD- and 8% in combined-IPMNs ($P = 0.0001$). The rate of invasive

cancer was 11% in BD-IPMNs but 42% and 48% in combined- and MD-IPMNs ($P = 0.0001$). Patients with combined and MD-IPMNs with invasive cancer were older than those with noninvasive tumors (suggesting tumor progression) while this age difference was not found in BD-IPMNs. 5-year DSS was 100% for patients with noninvasive BD-IPMNs and combined-IPMNs and 95% for patients with noninvasive MD-IPMNs; 5-year DSS was 56%, 51%, and 64%, for BD-IPMNs, MD-IPMNs, and combined-IPMNs with invasive cancer, respectively. **Conclusion** BD-IPMNs have a specific profile, likely representing a specific entity. Combined-IPMNs show close overlapping in regard to clinico-pathological-epidemiological characteristics with MD-IPMNs, and should be considered an extension of MD-IPMNs to the branch-ducts. These two subtypes show a more aggressive biological behavior.

Neoadjuvant Therapy for Resectable Pancreatic Adenocarcinoma: An Interim Report of a Prospective Controlled Randomized Study

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Context Surgical resection has been considered the only way to "cure" pancreatic adenocarcinoma; however about 80% of the patients develops early local recurrences or distant metastases. Thus is due to the high rate of R1 resection. **Objective** To compare neoadjuvant chemoradiation therapy plus surgery versus surgery alone in patients with resectable pancreatic adenocarcinoma in a prospective, controlled, randomized study. The primary end-point was to evaluate the R0 resection rate in the two groups (evaluated with intention-to-treat criteria); the secondary end-points was to evaluate safety and efficacy of neoadjuvant therapy, postoperative mortality, morbidity, lymph node-ratio and pTNM stage. **Methods** The selection criteria of eligible patients are based on past and present medical history, imaging findings (thoraco-abdominal multidetector CT, liver CEUS) and core biopsy. All patients with resectable pancreatic adenocarcinoma were randomized to receive either neoadjuvant therapy plus surgery (group A) or surgery alone (group B). Neoadjuvant therapy consisted of gemcitabine (1,000 mg/m²) combined with radiation therapy (45 Gy plus boost of 9 Gy). **Results** From March 2007 to June 2009 we enrolled 20 consecutive patients (11 males and 9 female, mean age 68.9±5.7 years). Sixteen patients were eligible for the study: 7 (43.7%) were randomized to receive neoadjuvant therapy plus surgery and 9 (56.3%) patients to receive surgery alone. Data were available only in 14 patients. R0 resection rate was

60% (3/5) in group A and 11.1% (1/9) in group B without statistically significant difference (P=0.095) probably due to the small number of patients evaluated. Morbidity rate during neoadjuvant therapy was 80% (4/5) but only one patient (20%) did not complete neoadjuvant treatment. After neoadjuvant therapy one case (20%) had a progression of the disease, two cases had one partial response (40%) and the remaining one a stable disease (40%), respectively. Surgical resection was performed in 4 patients of group A (80%) and in 8 (88.8%) patients of group B, because one case was found unresectable at laparotomy. Overall postoperative mortality was 1/12 (8.3%) without significantly difference in the two groups (P=1.000); overall postoperative morbidity was 5/12 (41.7%): group A, 0%; group B, 62.5% (P=0.081). For analysis of others secondary end-points we excluded two patients (16.6%) with final pathologic diagnosis of cholangiocarcinoma. Mean total number of lymph node removed with surgical specimen was similar in the two groups (A: n=32±11 vs. B: n=29±11, P=0.748). Mean number of lymph node metastasis was lesser in group A than in group B (n=2±3 vs. n=9±5, P=0.051). There was no difference in two group regarding pTNM stage (P=0.400). **Conclusion** Despite the small number of patients, preliminary data suggest that neoadjuvant chemoradiation therapy plus surgery increases the R0 resection rate, reduces the lymph nodes-ratio and allows a better postoperative course.

The Modification of a Preoperative Prognostic Factor Can Improve the Overall Survival in Patients with Resected Pancreatic Adenocarcinoma

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Context Recent evidences indicate that preoperative platelet-lymphocyte (P/L) ratio represents a significant independent prognostic index in patients with resected pancreatic adenocarcinoma: an elevated P/L ratio is associated with short survival. Interleukin-2 immunotherapy has been used to improve immune response to cancer and surgical stress, modifying lymphocyte levels. **Objective** To assess the possibility to modulate P/L ratio through pre- and post-operative administration of recombinant interleukin-2 (rIL-2) and to analyze if the induced variation of P/L ratio

influences survival in patients with resectable pancreatic adenocarcinoma. **Methods** Sixteen patients with resectable pancreatic adenocarcinoma received rIL-2 immunotherapy, consisting in a preoperative subcutaneous administration of 12 millions IU/day for 3 consecutive days and a low-dose postoperative cycle (on 30th day). This group of patients has been compared to a control group of 15 patients that underwent only radical surgery. **Results** The two groups were comparable for type of operation, tumor stage and preoperative P/L ratio (162.8 in rIL2 group

vs. 134.4 in control group). After surgery, P/L ratio was significantly reduced in rIL-2 group on 1st (90.3 vs. 290.8, $P<0.00001$), 7th (135.5 vs. 219.6, $P<0.04$) and 14th (197.2 vs. 325.7, $P<0.03$) postoperative days, compared with control group. In the following period there were no differences in the two groups for P/L ratio. Survival was significantly longer in rIL-2 group than in control group (23 vs. 13 months, $P=0.04$). **Conclusion** Preoperative rIL-2 immunotherapy can reduce P/L ratio in resected pancreatic adenocarcinoma

patients, with an effect that lasts until 14th postoperative day. Considering that P/L ratio is an independent prognostic marker, the modification of this parameter through rIL-2 immunotherapy resulted in a modification of survival. The postoperative reduction of P/L ratio in rIL-2 treated patients was in fact associated with a longer overall survival than in the control group, which underwent only radical surgical resection.

Identification of Coxsackievirus in Tissue and Serum of Patients with Idiopathic Acute Recurrent Pancreatitis

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Context While alcohol abuse and biliary disease can result in the development of pancreatitis, the factors involved in the idiopathic form of the disease are not also identified. We propose that coxsackievirus infection may account for a subset of patients with pancreatitis of unknown aetiology. Evidence to support this concept comes from serological studies and, as in case reports and animal models, from exocrine pancreatic tissue. There is recent evidence of the presence of enteroviruses in the duodenal mucosa of patients with type-1 diabetes. **Objective** The purpose of this study was to analyse if coxsackievirus is present in the duodenal mucosa of patients with idiopathic acute recurrent pancreatitis. **Methods** Serum and duodenal biopsy samples were collected from patients affected by idiopathic recurrent acute pancreatitis (IRAP) and, as controls, by acute biliary pancreatitis (ABP) and dyspepsia. We measured serum amylase, lipase, C-reactive protein (CRP), anti-HSV1, anti-HSV2, anti-CMV, and anti-coxsackievirus antibodies. The biopsy samples were used for morphological

analysis (hematoxylin and eosin) and coxsackievirus RNA determination by RT-PCR. **Results** Twenty-two consecutive patients (18 males, 82% and 4 females, 18%) entered the study. The patients' mean age was 53.8 years (range: 26-77 years). Six had ABP, 7 had IARP, and 9 had dyspepsia. The serum levels of amylase, lipase and CRP increased significantly in the ABP group ($P<0.05$) compared with patients IRAP and dyspepsia. The percentage of patients with antibodies to HSV1, HSV2, or CMV was not different in the three groups. A significantly greater number of IRAP than ABP patients had antibodies to coxsackievirus ($P<0.05$). Morphological analysis revealed normal duodenal mucosa in all study patients. All biopsies were negative for the presence of coxsackievirus RNA. **Conclusion** Coxsackievirus seems to be not involved in the pathogenesis of idiopathic acute recurrent pancreatitis. However, the presence of anti-coxsackievirus antibodies in these patients can suggest further investigational studies.

Advanced Pancreatic Cancer (APC): A Monocenter Experience in 53 Patients. Is it Possible a Second Line Treatment?

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Context To date, gemcitabine (GEM) remains the cornerstone of chemotherapy (CHT) for APC. According to the literature combination of GEM with other drugs, such as platinum compounds, seems to improve time to progression (TTP), overall survival (OS) and clinical benefit (CB), although no reaching statistical significance except for erlotinib. **Objective** To determine the impact of CHT in terms of OS and TTP. **Methods** We analyzed retrospectively a series of

53 patients affected by APC and treated with different CHT between December 2003 and August 2007. The Kaplan-Meier method was used. Among the 53 patients only 38 patients were considered for the statistic analysis. There were 23 males and 15 females (median age at diagnosis of 59.8 years; ECOG 0-2). The metastatic sites were liver and lung. Twenty-two of the 38 patients received GEMOX as first line CHT and the remaining patients received a difference

doublet gemcitabine CHT (e.g. erlotinib, capecitabine, irinotecan); twenty-one patients received a second line CHT; six patients received a third line therapy and one patient received a fourth line CHT. **Results** The median survival observed in all patients treated with different lines of CHT was 12.0 months (SD 1.0; 95% C.I.: 10.051-14.016) and the median TTP was 3.5 months (SD 0.15; 95% C.I.: 3.213-3.787). The 80% of patients maintained a good performance status (ECOG 0-1)

despite having made more lines of CHT. The main toxicities were: leuco-piastrinopenia, diarrhea (patients treated with erlotinib and capecitabine), nausea, fever and peripheral neuropathy (patients treated with OHP). **Conclusions** Our experience shows that patients affected by APC could benefit from a second-line treatment with a trend of improvement in overall survival when compared with data derived from studies of first line and preserving a good quality of life also.

Detection of IgG Antibodies against a *Helicobacter Pylori*-Derived Protein Is Typical of Sera from Patients with Autoimmune Pancreatitis

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Context Chronic autoimmune pancreatitis (AIP) is characterized by a chronic inflammatory process in which prominent lymphocyte infiltration with associated fibrosis of the pancreas causes organ dysfunction. The cause of the disease is still unknown. An autoimmune origin for AIP has been suggested but never proven and little is known about its actual pathogenesis. **Methods and Patients** In order to clarify the disease pathogenesis we screened a random peptide library with pooled IgG immunoglobulins derived from 20 patients with AIP. Among the identified peptides, one was recognized by the majority of patients' sera, but not by sera of normal donors and of patients with other autoimmune diseases. The peptide showed homology with a *Helicobacter pylori* derived protein and with UBR2, a protein ubiquitination enzyme highly expressed in pancreas, and kidney. UBR2 is present in acinar cells of the pancreas and is expressed also in the fetal tissue. Anti-peptide antibodies affinity purified from patients' sera recognize the *Helicobacter pylori* derived protein and UBR2. 20 patients affected by focal autoimmune pancreatitis (AIP), 40 by pancreatic adenocarcinoma (PC), 21 by alcoholic

chronic pancreatitis and 18 by intraductal papillary-mucinous neoplasm (IPMN), 17 by systemic sclerosis, 20 by rheumatoid arthritis and 40 healthy donors were studied (training set). To validate the results obtained, we enrolled an additional 15 patients with AIP and 70 patients with PC (validation set). **Results** In the training set, we found that 19 out of 20 (95%) patients with AIP had serum IgG antibodies against the peptide, 4 out of 40 (10%) patients with PC, whereas no reactivity was detected in the other groups. In the validation set, 14 out of 15 AIP patients (93%) and 1 out of 70 PC patients (1.4%) resulted positive. Combining the training and validation sets, 33 out of 35 AIP patients (94%) and 5 out of 110 PC patients (4.5%) were positive for antibodies, with a sensitivity of 94%, a specificity of 95%, PPV of 87% and NPV of 98%. **Conclusions** Our findings suggest that *Helicobacter pylori* infection can be linked to the pathogenesis of AIP and that UBR2 can be considered a novel autoantigen target in AIP. Most importantly, the identified peptide can discriminate AIP from other pancreatic disorders, particularly from pancreatic adenocarcinoma.

CXCR4+ but not CD133+ or ESA+/CD24+/CD44+ Phenotype Identifies a Subpopulation of Cancer Cell with Stem Cell Features in Pancreatic Cancer Primary Tumor and Cell Lines

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Context CD133+ (plus or minus CXCR4 expression) or ESA⁺/CD24⁺/CD44⁺ cells were described as putative cancer stem cells (CSC) in pancreatic cancer.

Objective The aim of this study is to evaluate the consistency of this evidence by: i) testing the ability of these markers to identify CSC in a large panel of

pancreatic cancer cell lines; and ii) correlating the frequency of these phenotypes in primary tumor with clinical outcome. **Methods** Putative CSC marker expression has been evaluated by flow cytometry in ductal pancreatic cancer cell lines (n=17) and in primary tumor of patients with pancreatic ductal adenocarcinoma (n=29). In cell lines, CD133⁺, CXCR4⁺ or ESA⁺/CD24⁺/CD44⁺ expression was correlated with *in vitro* and *in vivo* clonogenicity, *in vitro* and *in vivo* proliferation rate and *in vitro* chemoresistance. In patients, CD133⁺, CXCR4⁺, ESA⁺/CD24⁺/CD44⁺ cell frequency in primary tumor was correlated prospectively with the time to relapse and the overall survival. **Results** ESA⁺/CD24⁺/CD44⁺, CD133⁺, CXCR4⁺ expression resulted heterogeneous in cell lines: respectively from 0 to 91.3%, from 0 to 98.5%, and from 0.01% to 2.4% of all cells. CD133 expression correlated with CD24⁺/CD44⁺/ESA⁺ expression (r=0.543; P=0.024). In the inter cell lines

analysis, no correlation has been observed between CD133⁺ or ESA⁺/CD24⁺/CD44⁺ expression and clonogenicity, chemoresistance or proliferation rate. On the other hand CXCR4⁺ expression correlated to *in vitro* chemoresistance (P=0.028) and *in vivo* clonogenicity (P=0.042). ESA⁺/CD24⁺/CD44⁺, CD133⁺ and CXCR4⁺ cell subsets represent respectively 0-6.2%, 0-41% and 0.35-11.1%; these phenotypes have been correlated with overall survival and time to relapse. Only CXCR4 positivity resulted a risk factor for recurrence (0.028; hazard ratio 1.31. 95% CI: 1.03-1.66; Cox regression analysis) while no correlation has been noticed with other stem cell markers described. **Conclusion** CXCR4⁺, but not CD133⁺, and ESA⁺/CD24⁺/CD44⁺ phenotype identifies a subpopulation of cells with high clonogenicity and chemoresistance in cell lines and correlate with tumor aggressive behavior in human.

Radiofrequency Ablation in Locally Advanced Pancreatic Cancer: Preliminary Results

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Context There are no available data in literature regarding survival after radiofrequency ablation (RFA) of locally advanced pancreatic cancer (LAPC) associated to adjuvant therapy. **Objective** Aim of the study is to evaluate survival and time to progression after RFA in LAPC compared to gold standard treatment. **Methods** Sixty-eight patients with cytologically proven LAPC were enrolled between February 2007 and June 2009. Variables were compared using the chi-square and Fisher test as appropriate. Differences were considered to be statistically significant at P<0.05. **Results** Fifty-six patients were eligible for a medium term follow-up study (≥6 months). The median age was 67 years with a male/female ratio of 32/24. The tumor was located in the head in 37 patients and in the body/tail in 19 patients with median size of 40 mm in both. Eighteen patients (32%) had chemotherapy whereas 38 had RFA as first treatment. Median overall survival was 12 months (IQR 6.75-18.25 months), median follow-up after RFA was 7 months (IQR 4-13.25 months).

Median survival after chemotherapy followed by RFA was 16 months (IQR 12-23 months), which was comparable to 16-month survival after gold standard treatment for LAPC (gemcitabine plus radiotherapy) but which was significantly higher when compared to survival after RFA as first treatment (8 months, IQR 5-16, P=0,008). Among patients deceased for disease, median survival was significantly higher in those who underwent chemotherapy before RFA (7 vs. 15 months; P=0.01). Three patients underwent resective surgery after RFA followed by adjuvant therapy. Nowadays, 22 out of 56 patients (39%) are progression free, with median survival of 8.5 months (IQR 5.25-16.5 months) and median follow-up after RFA of 6.5 months (IQR 4.25-11 months). **Conclusions** The present results are strongly influenced by the lack homogeneity in our population. In selected patients RFA may have a significant role in multimodal approach to LAPC; both further follow-up and studies are needed to compare survival and time to progression in RFA plus CT-RT and CT-RT alone.

Significant Association of DNA Repair Polymorphisms with Survival in Pancreatic Cancer Patients Treated with Polychemotherapeutic Regimens

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Context Pancreatic adenocarcinoma (PDAC) has the worst prognosis of any major malignancy, and the identification of predictive factors of drug activity is crucial for maximizing therapeutic efficacy and minimizing useless treatments. The Human Genome Project led to the discovery of a number of DNA sequence variants, the majority of them being single-nucleotide polymorphisms (SNPs). These SNPs can affect the susceptibility of patients to anticancer drugs, and a pharmacogenetic approach to customize PDAC treatment according to genetic characteristics represents a modern and intriguing challenge.

Objective To evaluate whether common SNPs in genes involved in the mechanism of action/resistance of anticancer drugs were associated with the overall survival (OS) of PDAC patients treated with polychemotherapeutic regimens, including gemcitabine, cisplatin, epirubicin, docetaxel, capecitabine and 5-fluorouracil. **Methods** We studied by allelic discrimination assays 10 SNPs of 7 genes (ERCC1, XPD, XRCC1, CYP1B1, ABCB1, CDA, and RRM1) in 145 advanced PDAC patients treated in first-line with the PDGX, PEGX or FLEC regimens, in two different Italian institutions (Carrara Civic

Hospital and S. Raffaele Scientific Institute), from 2005 to 2009. Associations of genotypes with OS were evaluated by log-rank test and Cox proportional regression models. **Results** Three SNPs in the DNA repair genes were significantly associated with OS in univariable analysis. In particular, XPD-Lys751Gln and ERCC1-C118T remained significant predictors for OS in multivariate model, including also the clinical factors which resulted significant to the univariate analysis (age, stage, and PS). Patients harboring the XPD Gln751Gln genotype (n=22) had a significantly shorter OS (median 262 days, 95%CI 173-351 days vs. 446 days, 95%CI 359-453 days in Lys751Lys+LysGln patients, with a HR ranging from 1.6 to 8.0, P=0.003). This strong genotype association with OS was observed in all the patients enrolled in the study, as well as in the subgroup of gemcitabine-treated patients (n=123), epirubicin-treated patients (n=112) and docetaxel-treated patients (n=33). Further studies on the relationship between SNPs and OS in the different regimens are ongoing, enrolling patients treated with gemcitabine-alone. **Conclusions** SNPs of DNA repair genes have a potential value as prognostic markers for OS in patients with advanced PDAC.

Virtual MDCT Pancreatography of Intraductal Papillary Mucinous Neoplasm of the Pancreas

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Context The recent introduction of virtual pancreatography may help in detecting additional signs of malignancy of intraductal mucinous neoplasm of the pancreas (IPMN). **Objective** To assess feasibility and accuracy of virtual MDCT pancreatography in patients with IPMN of the pancreas. **Methods** Sixteen patients with suspected IPMN of the pancreas underwent a 64 row MDCT (General Electric, Milwaukee), before and after contrast medium administration. Post-contrastographic scans were acquired on pancreatic and venous phase, by applying a slice thickness of 1.25 and 0.6 mm and a reconstruction interval of 0.6 and 0.4 mm, respectively. Cross-sectional images were

processed with a dedicated commercially available software (NAVIGATOR-GE), to obtain a virtual endoscopic view of pancreatic ducts. On axial images and on virtual endoscopy, we evaluated: the dilation of the main pancreatic duct, the presence of communications between the main duct and branches ducts and the presence of endoluminal papillary projections. All patients underwent surgery. **Results** In all cases, high quality virtual endoscopic images were obtained. In 4 patients, we posed the suspicion of combined IPMN, in 12 cases of main duct type; histology posed the diagnosis of a combined type in 7 cases while 9 cases were considered as main duct type.

On the basis of virtual endoscopic images evaluation, we posed the suspicion of malignant degeneration in 10/16 cases; histology posed the diagnosis of a malignant form in 11 cases. **Conclusion** MDCT pancreatoscopy is a feasible, new method of images data set computer processing that may allow a

confidential diagnosis especially in mucin producing neoplasms; particularly, the technique may contribute to clinical and surgical management, especially in patients with suspected IPMN in assessing signs of malignancy.

Magnetic Resonance Imaging of Advanced Pancreatic Adenocarcinoma: Monitoring the Response to Chemotherapy with Diffusion-Weighted Sequences

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Context Chemotherapy is the only option for non-operable pancreatic adenocarcinoma to improve survival and, moreover, quality of life; however, response to treatment is difficult to assess as tumor regression cannot be measured since 2-3 months. **Objective** Sensitive to water motion, diffusion-weighted imaging (DWI) could potentially assess modifications of neoplastic tissue following administration of chemotherapy: we evaluated the role of pancreatic DWI in this field. **Methods** Standard and diffusion-weighted (b factor=600) respiratory-triggered MRI of upper abdomen was performed in 15 patients with stage III and IV pancreatic adenocarcinoma before and during administration of a multidrug gemcitabine-based regimen: examination was repeated 2 weeks after every cycle for 2 months. Tumor mean areas and apparent diffusion coefficient (ADC) values were calculated tracing peritumoral ROIs and compared during follow-up; response was objectivated using CT, PET-CT (RECIST criteria) and CA 19-9 at 2-3 months. Clinical follow-up ranged from 2 to 12 months.

Results DWI was feasible and well tolerated in all patients. During chemotherapeutic treatment, in 12/15 patients we noticed a significant increase of tumor ADC value after 1 month of therapy respect to baseline (1.74 ± 0.26 vs. 1.46 ± 0.24 mm²/s; P=0.001), probably related to drug-induced edema and necrosis, while tumor shrinkage was not appreciable in the same interval. In unresponsive patients (3/15) no significant increase of ADC was observed. Standard criteria classified tumor response late (3 months), with serum CA 19-9 expressed only by 50% of patients. **Conclusion** In pancreatic adenocarcinoma undergoing chemotherapy, quantitative DWI can accurately assess early modifications of neoplastic tissue in term of increased water diffusivity prior to reduction in tumor size or serum marker concentration (which are late events); no variations of ADC values seem to occur in patients who will not respond to therapy. Quantitative DWI is helpful to early monitor the efficacy of chemotherapy in advanced pancreatic adenocarcinoma, predicting its medium-term response.

Pancreatic Cancer Gene Therapy with Heat Inducible Diphtheria Toxin Variant CRM197 (DTA197): *In Vivo* Preliminary Results

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Context Heat shock elements (HSEs) regulate gene transcription of heat shock proteins (HSPs) in response to cellular stress. We ascertained whether an artificial sequence encompassing five tandem HSEs inserted upstream the HSPA6 promoter, controlling the expression of DTA197, is suitable for pancreatic cancer (PC) gene therapy *in vivo*. **Methods** Seventeen female nude mice were s.c. inoculated with 3 millions of transfected (eGFP to optimize heat shock or

DTA197 for tumor cell killing) or non transfected (control) PC PSN1 cells. To induce transgene expression heat shock was obtained by heating the cutaneous surface employing a device made in house. **Results** Optimal heat shock (9-fold increase of eGFP mRNA, Q-RT-PCR) was obtained by heating twice the tumor mass, 72 h interval. Heating did not significantly modify the growth pattern of control tumors, which was close to that of untreated PSN1-DTA197. DTA197

mRNA expression was quantified (Q-RT-PCR) in 4 tumor masses, 2 from a control and 2 from experimental mice. With respect to control masses, a 7.13- and 5.60-fold increase was found in the two heated masses. Tumor volume (calliper) of treated PSN1-DTA197 was delayed with respect to that in untreated PSN1-DTA197 masses (repeated measures analysis of variance: F=5.89, P=0.07). In one treated

mouse a complete disappearance (10-day follow-up after treatment) of the tumor mass was documented both by calliper and by *in vivo* bioluminescence imaging. **Conclusions** DTA197 expression under the control of the heat inducible promoter engineered by us appears to be a promising tool in arresting PC growth *in vivo*.

ARP-1 Silencing Inhibits Pancreatic Tumor Growth in Nude Mice

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Context Apolipoprotein regulatory protein 1 (ARP-1) is an orphan nuclear receptor (i.e. a receptor whose ligand have yet to be identified) belonging to the chicken ovalbumin transcription factors (COUP-TFs) family. ARP-1 regulates the transcription of the target genes binding to specific regions of their promoters as homo- or hetero-dimers acting both as a transcriptional repressor and as an activator. Interestingly, it has been recently reported that nuclear receptors (e.g. PPARg and the estrogen receptors) are implicated in the pathogenesis of tumor of various origin (such as pancreatic cancer). While the role of ARP during development is well characterized, its role in adult tissues and cancer disease is largely unknown.

Objective The aim of this study is to evaluate the expression of ARP-1 in primary human pancreatic tumors and to examine its role in the regulation of tumor growth in nude mice. **Methods** Expression levels of ARP-1 in human pancreatic tumor samples were evaluated by RQ-PCR and immunohistochemistry on frozen sections. MiaPaca-1 and PANC-1 cell lines expressing shRNA against ARP-1 in a doxycycline (Dox) inducible manner were produced. Nude mice carrying xenograft tumours were produced by injection

of MiaPaca-1 shRNA expressing cells; mice were administered with Dox and their tumor growth was assessed. **Results** RQ-PCR and immunohistochemistry on primary samples demonstrated that ARP-1 is over-expressed in 50% of primary samples with the expression localized mostly in tumorous cells. To further investigate the functional relevance of ARP-1 in pancreatic cancer we generated cell lines producing shRNA against the receptor. We evidenced that silencing of ARP-1 reduces the proliferation rate, cell motility and anchorage independent growth *in vitro*. In tubules formation experiments with H-MEC cells, tubule formation was reduced by 60% when conditioned medium obtained from ARP-1 silenced cells was used. In a nude mice xenograft model silencing of ARP-1 reduces tumor growth by 50%; this effect is mediated by the inhibition of cells proliferation and neo-angiogenesis. **Conclusions** The preclinical data reported indicate that ARP-1 expression is increased in most of the tumor analysed and it is an important regulator of the behavior of pancreatic adenocarcinoma cells lines, thus representing a possible new target for pancreatic cancer therapy.

Adjuvant PEFG (Cisplatin, Epirubicin, 5-Fluorouracil, Gemcitabine) or Gemcitabine in Pancreatic Cancer: A Randomized Phase II Trial

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Context PEFG regimen significantly improved progression-free survival and overall survival (OS) as compared with gemcitabine (G) in stage III and IV

pancreatic adenocarcinoma (PA). **Objective** We assessed the impact upon disease control of PEFG regimen and G in the adjuvant setting as well.

Methods Patients with resected PA, stage IB-III, aged 18-70 years, Karnofsky performance status (PS) >60 were randomized within 8 weeks from surgery to receive either G 1 g/m²/week Q3 every 4 weeks (Arm A), or PEFG (cisplatin and epirubicin at 40 mg/m² each on day one, gemcitabine at 600 mg/m² on days 1 and 8, and 5-FU at 200 mg/m²/day on days 1 to 28) every 4 weeks (Arm B). In both arms chemotherapy was administered for 3 months and followed by radiotherapy (54-60 Gy in 27-30 fractions) with concurrent 5-FU 250 mg/m²/day. The primary endpoint was the probability of being disease-free at 1 year (DFS1y) from surgery. The Fleming design was used to calculate the sample size. Assuming P0=35% and P1=55%, alpha=0.05 and beta=0.10, the study was to enroll 51 patients per arm. The treatment regimen had to be considered of interest with >23 patients being

DFS1y. **Results** Between August 2003 and August 2008, 102 patients were enrolled, stratified by center and resection margin and randomized (51 per arm). An intent-to-treat analysis on eligible patients was performed. Patients' characteristics were (A/B): median age 61/60 years, median PS 90/90, stage IB-IIA 25/15%; stage IIB 63/78%; stage III 12/7%; grade 3 29/46%; and R1 35/29%. To date, 50 A and 48 B patients are assessable for the primary endpoint: 23 (46%) and 31 (65%) patients were DFS1y. Main G3-4 toxicity was: neutropenia in 15/58% and thrombocytopenia in 0/11% of cycles. **Conclusions** This is the first randomized trial on single agent or combination chemotherapy as adjuvant treatment of PA. With a mature follow-up for 98% of patients, PEFG fulfilled the primary endpoint and warrants further study while G not yet.

The Usefulness of Clavien Grading System in Evaluating the Complications after Pancreatic Surgery.

A Prospective Single Center Study

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Context Morbidity rate after pancreatic resection remains high. The lack of standardization in evaluating morbidity after these procedures has severely hampered meaningful comparisons over time and among centers. Clavien *et al.* [1] have proposed a novel standardized, objective and reproducible classification of complications after pancreatic resection based on therapy-oriented severity grading system. **Objective** To assess the usefulness of Clavien grading system in routine clinical practice. **Methods** All consecutive patients with benign or malignant lesion of pancreas or periampullary region undergoing major pancreatic resection, observed in our departments from January 2006 to June 2009, were enrolled. All the patients were analyzed regarding sex, age type of surgery, postoperative mortality and morbidity rates. According to the Clavien grading system, the postoperative course was defined in five grades. **Results** Sixty-two patients (35 men and 27 women, mean age: 62.2±9.8 years) underwent major pancreatic resection: pancreaticoduodenectomy (PD) in 41 (66.2%), left pancreatectomy in 9 (14.5%) and total pancreatectomy in 12 cases (19.3%). On the basis of histology there were 29 pancreatic adenocarcinoma (46.8 %), 9 adenocarcinoma of the ampulla (14.5%), 7 cholangiocarcinoma (11.3%), 6 intraductal pancreatic mucinous

neoplasm (9.7%), 4 serous cystic neoplasm (6.5%), 4 duodenal adenocarcinoma (6.5 %), and 3 neuroendocrine tumors (4.8%). Postoperative mortality rate was 6.5% (4/62) and postoperative morbidity rate was 66.1% (41/62). Pancreatic fistula rate was 18% (9/50). Both no complications and grade I complications occurred in 22 patients (35.5%), grade II in 27 (43.5%), grade III in 5 (8.1%), and finally, both grade IV and grade V in 4 patients (6.5 %). The length of hospital stay was strongly related to Clavien grading system (P<0.001, Spearman rank correlation). In fact, the length of hospital stay was shorter in patients with both no complications or grade I (13.2±3.5 days) than in patients with grade II (17.2±6.8 days; P=0.043), III (35.2±17.6 days; P<0.001) and IV (30.0±16.8 days; P<0.001). **Conclusion** The Clavien grading system appears to be useful in evaluating the incidence and severity of different complications after major pancreatic resection and their impact on postoperative course.

Reference

1. DeOliveira ML, Winter JM, Schafer M, Cunningham SC, Cameron JL, Yeo CJ, Clavien PA. Assessment of complications after pancreatic surgery: A novel grading system applied to 633 patients undergoing pancreaticoduodenectomy. *Ann Surg* 2006; 244:931-7. [PMID 17122618]

Substance P Pathway Is Altered in Chronic Pancreatitis

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Context The pathophysiology of pain in chronic pancreatitis (CP) is still not completely 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 degradation is mediated by the endogenous extracellular metalloenzyme called neutral endopeptidase (NEP). Further studies failed to detect NEP in patient with pancreatic disorders while increased expression of SP was detected. **Objective** We aimed to investigate NEP pathway to better evaluate the SP pathway in CP patients. **Methods** SP and NEP mRNA levels were analyzed by quantitative real time polymerase chain reaction (RT-PCR) in pancreatic tissue specimens from patients undergoing pancreatic resection for CP and healthy organ donors. NEP gene mutation analysis, NEP methylation assay and miR-128a expression were also performed. **Results** Quantitative RT-PCR demonstrated increased SP

mRNA expression in CP tissues (P<0.05) compared to controls, while NEP mRNA showed no significant changes between CP and healthy controls. Screening did not reveal any mutation of interest but only the presence of seven intronic polymorphisms located downstream or upstream of several exons. MSP analysis suggests a light tendency to NEP hypermethylation for one promoter CpG islet in about half of chronic pancreatitis samples when compared with donor group, meanwhile NEP loss of function was associated to mir-128a significant over-expression in CP patients. **Conclusions** The present data show that expression of SP is increased during chronic inflammation of the pancreas and that tissue levels of NEP are unaltered. In the SP pathway, it would appear that NEP is unable to sufficiently degrade the increased amount of SP, which may in part explain the perpetuation of pancreatic inflammation, due to mir-128a over-expression.

Diagnostic and Prognostic Implications of Autoantibodies to Phosphorylated alpha-Enolase in Pancreatic Cancer

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Context Pancreatic ductal adenocarcinoma (PDAC) is the fourth cause of cancer death in the United States and Europe. Most patients die within 12 months, and only 2% survive five years after diagnosis. Biomarkers for the early detection of PDAC are lacking. The only serological marker described, CA 19-9, may also be expressed in a chronic pancreatitis and biliary obstruction. Our results revealed the presence of auto-antibodies to the glycolytic enzyme alpha-enolase (ENOA) in PDAC patients sera. **Objective** This study was set out to characterize the ENOA isoforms and auto-antibody response against ENOA in PDAC patients. **Methods** ENOA isoforms from pancreatic cell lines were identified by two-dimensional electrophoresis Western blot (2-DE WB) and mass spectrometry, and used as targets to screen the IgG reactivity of 120 PDAC patients, 40 healthy subjects, 50 non-PDAC tumor patients, 46 chronic pancreatitis,

and 12 autoimmune disease patients. Statistical analysis was performed to correlate the auto-antibody response with clinical-pathological variables of PDAC patients. **Results** Sixty-two percent of PDAC patient produced circulating auto-antibodies to two phosphorylated ENOA isoforms 1 and 2 (ENOA1,2). Auto-antibodies to ENOA1,2 were frequent in patients with normal CA 19-9 levels and the combination of these two markers resulted in >97% diagnostic accuracy in differentiating PDAC patients from control subjects. ENOA1,2+ patients appeared to have a more favorable clinical course with significantly longer progression-free survival. **Conclusions** ENOA phosphorylation is associated with PDAC and induces specific auto-antibody production in PDAC patients. Detection of auto-antibodies against ENOA1,2 may have diagnostic and prognostic value in PDAC.

POSTER SESSION

Simultaneous Occurrence of Somatostatin-Staining Endocrine Tumors and Adenocarcinoma of the Ampulla of Vater in a Patient with Von Recklinghausen's Disease and Multiple GISTs: A Case Report

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Context Patients with Von Recklinghausen's disease (VRD) have a tendency to develop periampullary tumors, most commonly somatostatin-staining endocrine tumors (SOM-NETs) and gastrointestinal stromal tumors (GISTs). However adenocarcinoma of the ampulla in VRD is an extremely rare condition, with few cases reported in literature. **Case report** A 57-year-old male patient affected by VRD presented with painless jaundice and magnetic resonance imaging (MRI) evidence of periampullary neoplasm. An ERCP was started, but the exam was interrupted in duodenum for the presence of an impassable stenosis. Thus the patient was sent to Department of Surgery to undergo Whipple pancreaticoduodenectomy. Pathological

examination showed multiple GISTs and two adjacent tumors of the ampulla of Vater: a moderately-differentiated adenocarcinoma and a well-differentiated endocrine carcinoma with strong immunohistochemical expression of somatostatin. The postoperative course was uneventful and at 18 months follow-up the patient was asymptomatic with no sign of tumor recurrence at MRI. **Conclusion** To the best of our knowledge, this is the first report of simultaneous occurrence of adenocarcinoma and SOM-NET of the ampulla of Vater with multiple GISTs in a patient with VRD. This case suggests performing an accurate examination of the papilla of Vater in VRD patients, because of the different prognosis for various tumors that can occur.

Resectable Pancreatic Cancer: Who Really Benefit from Resection?

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Context The 1-year disease-related mortality (DRM) after resection for pancreatic cancer is around 30%. In this subgroup, recurrence is very early and survival is similar to that observed in patients with advanced disease undergoing antitumoural therapies alone. **Objective** This study examined potential preoperative parameters that would help to avoid unnecessary surgery. **Patients and Methods** Among the patients resected at our Institution from 1997 to 2006, 228 patients underwent pancreatic resection for ductal carcinoma. Using a survival cut-off of 12 months (i.e., early death (ED)), a logistic regression analysis was done in order to identify perioperative predictors of ED. **Results** Among 228 resected patients,

postoperative mortality occurred in 4 (1.8%) cases that were excluded from the analysis. In the remaining 224 patients, 43 (19.2%) died for disease within 12 months from surgery (ED) and the remaining 181 (80.8%) had a longer survival. Multivariate analysis selected duration of preoperative symptoms >40 days, CA 19-9 >200 U/mL, a pathological grading G3-G4 and a R2 resection as independent predictors of ED. **Conclusion** Duration of symptoms, CA 19-9 serum level and pathological grading can be preoperatively used in order to identify patients not suitable for an upfront surgery, even if deemed resectable by high-quality imaging.

Functional and Metabolic Recovery after Pancreaticoduodenectomy: A Long Way Home

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Context Despite newest approaches in the optimization of perioperative care for elective surgical patients, few

data exist on medium period rehabilitation after major pancreatic surgery in terms of nutritional profile and

muscular functions. **Objective** To evaluate the impact of pancreaticoduodenectomy (PD) on micronutrients plasmatic levels and functional/nutritional recovery in patients undergoing surgical procedure. **Methods** We observed 28 consecutive patients undergoing PD for malignancy. In all patients C and E vitamins, selenium and zinc plasmatic levels were registered baseline and on postoperative day (POD) 1, 3, 7 and 30. Moreover, body weight and muscular strength were measured. According to recent concept of early postoperative oral intake, patients were allowed to assume oral solid food intake from POD 3, when tolerated. Muscular strength was measured in kg by a hand-grip dynamometer (lower normal level 40 kg). Postoperative food intake, postoperative mobilization, length of hospital stay and postoperative complications were also registered. **Results** Twelve of 28 patients (43%) had a preoperative weight loss (WL). Mean preoperative WL was 7.7 kg (11.1%), with a BMI near the normal range (mean 25 kg/m²). Mean first oral postoperative food intake occurred after 3.7 days. C and E vitamins,

selenium and zinc plasmatic levels significantly dropped after surgery. In particular C vitamin, zinc and selenium levels assessed strongly below normal lower levels. One month after surgery the patients showed a 4.3 kg average decrease in body weight (P=0.05 *versus* preoperative). No difference in weight loss was observed in complicated patients compared to patients with an uneventful course. Mean preoperative muscular strength was strongly lower than normal values in all patients (mean handgrip 36.5 kg). A further decrease was found on POD 1 (mean 30.5 kg), POD 3 (mean 32 kg), POD 7 (mean 34.5 kg) and POD 30 (mean 34 kg). Most of patients were able to stand in bed from postoperative day 1. **Conclusions** The vast majority of patients undergoing pancreaticoduodenectomy, regardless of their nutritional status at the time of surgery, have postoperative significant weight loss and micronutrients consumption, even they start eating food few days after the operation. This nutritional evidence is associated to the poor functional outcome found in hand grip strength values.

Preoperative Oral Administration of High Concentration Mixtures in Patients Undergoing Pancreaticoduodenectomy for Malignancy: A Safe Procedure?

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Context Fasting after midnight has become standard in elective surgery, even if recent trials do not support this practice, suggesting a 2 h and 6 h preoperative fast for clear liquids and solids, respectively. Safety of composite fluids remains still controversial. **Objective** To evaluate the safety and tolerability of a high concentration mixture (booster) of antioxidants administrated close to induction in patients undergoing pancreaticoduodenectomy (PD). **Methods** From December 2007 to May 2008 we performed a double-blind randomized placebo-controlled trial on 36 patients undergoing PD for malignancy. Patients received either a booster of 300 mL of antioxidants (glutamine, vitamin C, vitamin E, selenium, zinc, beta-carotene and green tea extract) or a placebo. The substrates were administrated at 3 p.m. and 9 p.m. the day before surgery and 3 hours before surgery. Gastric residual volume, respiratory parameters and tolerability to the product were registered for every patient. Gastric residual volume was evaluated by placement of nasogastric tube at induction time. Tolerability was

evaluated by VAS questionnaires delivered to all patients after every product intake and in postoperative day 1 (POD 1). Pulmonary function was evaluated by blood gas concentrations measurement. Patients with GERD or other gastric impairments were excluded from the observation. **Results** Product was well tolerated in both group and no statistical differences in VAS questionnaires were registered. Pulmonary function decreased in both groups on POD 1 and 3 and recovered on POD 7 with no differences in the two groups. Neither pulmonary complications nor gastric impairment related to product intake were registered. Median gastric residual volume was 0 mL in treated group (mean 45.6 mL) and 20 mL in the placebo group (mean 43.05 mL) (P NS). **Conclusions** In our experience, perioperative administration of fluids close to surgical procedure is a safe procedure. Moreover, this evidence seems to be valid also for composite mixtures. These data could allow surgeons to treat patients with functional substrates potentially able to improve postoperative outcome.

Unusual Paraneoplastic Syndrome in Neuroendocrine Tumor (NET) of the Pancreas

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Context NETs represent a small group of pancreatic neoplasia (10%). The diagnosis of NETs is difficult if the tumor is small and not functioning. CT scan and MRI have a good sensitivity if the tumor is >2 cm, otherwise sensitivity and specificity are lower than 50%. Myasthenia gravis (MG) is a neuromuscular junction disorder mainly caused by antibodies against acetylcholine receptor (AChR). The common onset is with eyelid ptosis, muscular weakness and fatigability. Sometimes MG occurs along with neoplasm (thymoma in the most frequent) as a paraneoplastic disease; less frequently is associated with extrathymic malignancies. No reports in literature are available about pancreatic malignant disease and MG. We report a case of a woman with MG Ab negative with a NET in the head of the pancreas. **Case Report** A 32-year-old woman with previous thyroidectomy for multinodular goitre, was referred to neurologist for weakness, symmetric eyelid ptosis and progressive loss of strength suitable for MG. Neck CT revealed a fatty infiltration of thymus. She had a positive Tensilon test. The patient started pyridostigmine with partial clinical response but after 3 months a worsening of symptoms occurred. This unusual course and negative Ab led the neurologist to further investigations. The patient underwent a PET scan which revealed a "captatio" in the pancreatic head. She was referred to our Endoscopy Unit for EUS+FNAB. EUS revealed a hypoechoic lesion in the pancreatic head of 9.3x8 mm with regular

borders. Body and tail were unremarkable. An FNA of the lesion was performed. The patient underwent then ERCP with sfinterotomy and PD cannulation. A pancreatic juice aspiration was performed with CEA, cromogranine and CA 19.9 dosage. Cromogranine, CEA, CA 19.9 and NSE in blood sample and pancreatic juice were normal. 5-HIAA and vanilmandelic acid in urine were negative. Cytopathologist confirmed a well-differentiated NET. The patient was discharged after two weeks and surgeons planned an enucleation of the lesion. Before surgery we performed EUS with insertion of Visicoil into the lesion to help its localization with intraoperative US during surgery. She was discharged after two weeks with a small pancreatic fistula which healed spontaneously in 2 weeks and now she is well. She does not discontinued pyridostigmine due to recurrence of symptoms. **Conclusion** MG is a neurological disease associated frequently with positivity of AChR. Sometimes MG is a paraneoplastic syndrome associated with thymus and extrathymus cancer. Although complete removal of primary tumor, neurological symptoms usually do not disappear after surgery and recurrence is quite frequent. No reports are available in literature about neurological disorder associated with pancreatic neoplasm. We described a case of NET of the pancreas diagnosed with EUS, associated with paraneoplastic MG.

Non-Functioning Pancreatic Endocrine Tumors: Any Correlation of Tumor Size with Malignancy?

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Context In most endocrine gastrointestinal tumor, such as stomach, appendix and rectum tumor size (TS) correlates with the presence of both nodal and liver metastases guiding the type of surgery. For sporadic non functioning pancreatic endocrine tumor (NFPETs) the presence of a dimensional therapeutic-driving cut-off is still debated. **Objective** To assess whether TS is associated with a malignant potential in sporadic NFPETs. **Methods** From the institutional prospective database (1990 to 2007), 137 patients who underwent to a pancreatic resection of the primary tumor for well-differentiated NFPET were selected. Pathological criteria of malignancy at diagnosis and/or recurrence of the disease were correlated with TS using 2 different

cut-off (<2 and ≥2 cm and ≤1 and >1 cm). **Results** According to the WHO classification 42.2% were well differentiated endocrine carcinoma and 57.8% well differentiated endocrine tumor (33.6% benign and 24.2% uncertain behaviour). The median TS of the primary lesion was 3 cm (IQR: 1.5-4.5 cm) with an 11% and 36.8% of the lesions ≤1 and <2 cm in size, respectively. A TS ≥2 cm significantly correlates with malignancy with a sensitivity of 84%, specificity of 54% and negative predict value (NPV) of 80% (P<0.0001). A lower specificity value (19%) with a higher sensitivity (98%) and NPV (93%) is obtained with >1 cm cut-off (P<0.0001). TS ≥2 cm showed a correlation with most of the pathological parameters

evaluated: liver metastases (sensitivity: 89.5%, specificity: 41%; P=0.011; NPV 93%), nodal involvement (sensitivity: 85.3%, specificity: 41%; P=0.002; NPV 84%), macroscopic vascular invasion (sensitivity: 93%, specificity 45%; P<0.000; NPV 96%), angioinvasion (sensitivity: 89%, specificity 55%; P=0.001; NPV 87%), Ki67 >2% (sensitivity: 83%, specificity: 46%; P=0.001; NPV 83%). With >1 cm cut-off lower specificity and higher sensitivity and NPV were obtained: liver metastases (sensitivity: 95%, specificity: 12%; P NS; NPV 93%), nodal involvement (sensitivity: 100%, specificity: 12%; P=0.04; NPV 100%), macroscopic vascular invasion (sensitivity: 100%, specificity: 14%; P=0.04; NPV 100%),

angioinvasion (sensitivity: 100%, specificity: 19%; P=0.004; NPV 100%), Ki67 >2% (sensitivity: 98%, specificity: 15%; P=0.03; NPV 93%). However, TS size did not correlate with disease specific survival (DSS) (P=0.088), but tumors ≥ 2 cm had a significantly poorer disease free survival (DFS) (P=0.013). **Conclusions** In NFPET primary tumor size correlates with both malignancy and DFS, representing, in the absence of macroscopic signs of malignancy, a good parameter in order to define the extension of surgery. One cm cut-off statistically better distinguishes patients whose tumor is not a carcinoma, however a 2 cm cut-off is clinically more useful.

Circulating Tumor Cells in Resectable Pancreatic Cancer: A New Prognostic Marker?

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Context Pancreatic adenocarcinoma has a really poor prognosis, even in resected patients, with a median overall survival of 24 months. About 20% of patients have a relapse (local or distant) within 6 months from surgery, with a median disease free survival (DFS) of 13.5 months. Many markers were investigated to find a correlation to this unpredictable trend, but no markers are actually available before surgery. **Objective** To investigate the presence of circulating tumor cells (CTCs) in patients undergoing pancreatic resection for malignancy, in peripheral and portal circulation. **Methods** We enrolled 10 patients (from February to April 2009) undergoing pancreaticoduodenectomy or distal pancreatectomy for malignancy. Ten mL blood samples were collected intraoperatively both from systemic and portal circulation (PC) at the same time. Blood samples were analyzed for CTCs with J&J Veridex CellSearch[®] within 72 hours from collection. **Results** We found CTCs in 5 patients: 1 patient had 5

cells in PC and 2 cells in systemic circulation (SC); 1 patient had 4 cells in PC and 1 cell in SC; 1 patient had 1 cell both in PC and SC; 2 patients had 1 cell only in PC. No correlations were found between presence or number of CTCs and tumor size, grading, stage and preoperative serum levels of CA 19-9. All enrolled patients are now undergoing a strict follow-up to understand the supposed clinical correlation between the presence of CTCs and the risk of early postoperative malignancy relapse. **Conclusion** These preliminary results show that 50% of patients undergoing pancreatic resection for malignancy have CTCs in peripheral or portal circulation. These results still have to be confirmed by evaluation of a larger patient population data and the concerning follow-up. CTCs could represent a new preoperative marker of systemic disease in patients with resectable pancreatic cancer, allowing a better patients' selection before surgery.

Pancreatic and Extrapancreatic Lesions in Patients with Intrapapillary Mucinous Tumors of the Pancreas: A Single Center Experience

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Objective To evaluate the frequency of pancreatic and extrapancreatic neoplasia in patients having intraductal papillary mucinous neoplasias and to evaluate whether pancreatic or extrapancreatic tumors are synchronous or metachronous to IPMNs. **Patients** One hundred and forty-two patients with IPMN diagnosed using the

Sendai criteria were enrolled; there were 56 males and 86 females, mean age 69.5 years, range 37-98 years. Six patients (4.2%) had IPMN Type I, 103 (72.5%) IPMN Type II and 33 (23.2%) had IPMN Type III. **Methods** All patients were studied using the following imaging techniques: ultrasonography (US), multi-

detector computed tomography (MDCT) and cholangio-Wirsung magnetic resonance (CWMR). **Results** The tumor was localized in the head in 43 patients (30.3%), in the body in 13 (9.2%), in the tail in 10 (7.0%), in the head-body in 17 (12.0%), in the body-tail in 15 (10.6%) and it was diffuse throughout the gland in 44 (31.0%). Twenty patients (14.1%) had associated pancreatic or extrapancreatic diseases. In particular, 4 patients were operated on for adenocarcinoma of the pancreas (2.8%), 7 had chronic pancreatitis (4.9%), 1 had a pancreatic lipoma (0.7%), 2 were operated on for a non-functioning pancreatic endocrine tumor (1.4%), 1 had previously been operated on for lung cancer (0.7%), 3 had previously been operated on for colon carcinoma (2.1%) 1 patient had been operated on twice for lung and renal carcinoma, and 1 for a peritoneal metastasis from an

unknown tumor (0.7%). In evaluating the distribution of pancreatic or extrapancreatic diseases according to the type of IPMN, the distribution of the various pancreatic or extrapancreatic diseases was not significantly different among types I, II and III of IPMNs ($P=0.776$). Furthermore, the age of the patients without extrapancreatic or pancreatic diseases (69.6 ± 10.8 years) was similar to those of patients having extrapancreatic or pancreatic diseases (69.2 ± 9.1 years) ($P=0.732$). Finally, the gender of patients without extrapancreatic or pancreatic diseases was not statistically different (males: 46, 37.7%; females: 76, 62.3%) from those having extrapancreatic or pancreatic diseases (males: 10, 50.0%; females: 10, 50.0%) ($P=0.330$). **Conclusions** The majority of pancreatic and extrapancreatic cancers occurs before the diagnosis of IPMNs and are not related to the type of IPMN.

Transarterial Chemoembolization (TACE) of Liver Metastasis from Pancreatic Well Differentiated Endocrine Carcinoma

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Objective To evaluate the efficacy of hepatic transarterial chemoembolization (TACE) to control the growth of liver metastasis from pancreatic well differentiated endocrine carcinoma (WDEC), the safety of the procedure and long-term survival. **Material and Methods** From 2004 to 2009 at our Institute 635 sessions of TACE were performed; 44 of them (6.9%) were performed in 11 patients (mean of 4 sessions per patient) for the treatment of liver metastasis from pancreatic WDEC, out of 37 patients with metastatic WDEC (29.7%) The indication for TACE was the presence of multifocal metastases, with diameter less than 5 cm, without extrahepatic disease. The study group was composed by 5 females and 6 men with a mean age of 57.4 years (range 40-72 years). Four patients presented liver metastasis at the time of diagnosis of pancreatic neoplasm, whereas 7 developed metastasis during the follow-up (mean 37 months, median 22 months; range 5-77 months). Ten patients presented bilobar liver metastasis and one patient was

affected by unilobar disease; 10 patients were affected by non-functioning carcinoma whereas 1 patient was affected by malignant insulinoma. The TACE was performed with doxorubicin emulsified in lipiodol followed by gelatine sponge particles embolization. Imaging follow-up was performed with unenhanced and contrast-enhanced CT scan at 1, 3, 6 months and every 6 months after TACE. The mean follow up was 34.1 months (range 12-72 months). **Results** two patients developed hepatic abscesses (6.8% of total sessions) after TACE; one was treated by percutaneous drainage and one by conservative therapy. During the follow-up, 7 of 11 patients (63.3%) had stable disease, 2 patients showed a partial response and 2 patients exhibited a progressive disease. Two patients underwent surgical hepatic resection at 6 and 52 months after TACE, respectively. All patients are alive. **Conclusions** TACE may be considered as an effective and safe treatment which can provide a long term palliation for liver metastasis from pancreatic WDEC.

Multidetector CT Assessing Neuroendocrine Pancreatic Neoplasm Nature: Correlation between MDCT and Histological Findings

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Context Neuroendocrine pancreatic neoplasms are rare tumors, which therapeutic approach mainly depends on

their clinical and morphological presentation. MDCT study of neuroendocrine pancreatic neoplasm can

assess lesions' nature and may thus suggest a possible therapeutic approach. **Objective** To evaluate the role of multidetector CT in assessing the nature of neuroendocrine pancreatic neoplasms. **Methods** We analysed 55 lesions in 36 patients (3 patients had, respectively, 15, 5 and 2 lesions). CT was performed before and after 120 mL iodine contrast medium intravenous administration (5 mL/min) in early arterial (15"), pancreatic (30"), venous (70") and delayed (180") phases. Three different post-contrastographic patterns were identified: pattern A, including lesions with "early arterial" or "pancreatic" enhancement (15"/30") and rapid wash-out; pattern B, including lesions with early wash-in and no wash-out and lesions with enhancement only in the "delayed" phase. CT findings were compared with pathological results after surgery. **Results** At histopathology, 24 lesions resulted

to be benign, 20 malignant and 9 borderline. At CT, 29/55 lesions showed pattern A (average dimension-a.d 13 mm); at histopathology 23 out of 29 resulted to be benign (diameter <2 cm in all cases), 1 malignant (12 mm) and 5 borderline (all <2 cm). Pattern B included 26/55 lesions (a.d. 41 mm); at histopathology 20 out of 26 resulted to be malignant (≥ 2 cm in all cases, a.d 39 mm), 4 borderline (a.d. 18 mm) and 2 benign (15 mm and 20 mm, respectively). Pattern A showed a positive predictive value (PPV) of 79% in predicting neuroendocrine pancreatic lesions benignity, while pattern B showed a PPV of 77% in predicting malignancy. **Conclusion** Multidetector CT may suggest the nature of neuroendocrine pancreatic neoplasms on the basis of their enhancement pattern. Our series confirm that lesions with diameter greater than 2 cm should be suspected to be malignant.

A Retrospective Cohort Study on External Drainage of the Pancreatic Duct for High-Risk Pancreatic Anastomosis

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Context External drainage of the pancreatic duct has been suggested to reduce pancreatic fistula (PF) rate after pancreaticoduodenectomy (PD). **Objective** To compare the outcome of patients undergoing PD with high-risk pancreas treated with or without external stenting. **Methods** Retrospective evaluation of prospectively collected data. Between 2000 and 2008, 598 patients underwent PD; 186 of them (32.7%) had high-risk pancreatic remnant (duct ≤ 3 mm, soft texture) and were evaluated in the present study. Nine-three patients were treated by external drainage of the pancreatic duct (5-8 Fr. silicon catheter), whereas 93 patients had no stent. The choice of external drainage was made according to surgeon preference. Primary end-points were incidence and severity of PF (ISGPF definition). **Results** Mean duct diameter was 2.12 mm

in the stent group and 2.49 mm in no-stent group ($P < 0.01$). PF rate was higher in the stent group ($P < 0.01$): incidence of PF in stent group was 59.1% (grade A 35 patients, 63.6%; grade B 11 patients, 20%; grade C 9 patients, 16.3%), in no-stent group it was 38.7% (grade A 19 patients, 52.7%; grade B 5 patients, 13.9%; grade C 12 patients, 33.3%). In the multivariate analysis external stent and young age were significant predictors of PF. Mortality was 4.3% and 5.3%. After 7 days from operation only 33.3% of patients with external stent had a daily pancreatic drainage > 100 mL. **Conclusions** Despite the possible selection bias regarding the use of stent in higher-risk patients, external drainage of pancreatic duct seems detrimental in high-risk anastomosis. This could be explained by the frequent obstructed flow of the external stent.

Biliary Strictures following Pancreaticoduodenectomy: A Single-Institution Experience after 755 Consecutive Patients

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Context The incidence and course of strictures of the biliary-enteric anastomosis after pancreaticoduodenectomy (PD) have been poorly investigated, due to few long-survivors and to the paucity of studies focusing on late complications after hospital discharge. **Objective** To investigate the incidence, management and outcome of postoperative biliary strictures after PD. **Methods** Between November 1996 and October 2006, 755

consecutive patients (527 for malignancies and 228 for benign diseases) underwent PD in our institution. We performed a retrospective analysis of a prospectively collected database, considering a follow-up period of two years, to determine the incidence and outcome of biliary strictures following PD. **Results** Sixteen of the 755 patients (2.1%) who underwent PD developed postoperative jaundice or cholangitis, secondary to a

stricture of the biliary-enteric anastomosis. The median time to stricture development was 16.5 months (range: 4-76 months). No difference was observed in the incidence of biliary stenosis for benign (n=5; 2.1%) or malignant disease (n=11; 2.1%), nor in the median time to stricture formation. By univariate analysis biliary strictures were associated with prior cholecystectomy (odds ratio, OR=3.82; P=0.01). Preoperative percutaneous biliary stenting and postoperative biliary fistula were associated with the formation of biliary stenosis, even if not statistically significant. Preoperative endoscopic biliary drainage appeared to be a protective factor against stricture, but not

statistically significant. Recurrent disease was found in 4 patients with malignant disease and one patient had a biliary stenosis due to recurrence in the perihilar nodes. All the strictures were managed conservatively with percutaneous biliary balloon dilatation and stenting; 4 patients had multiple biliary dilatations (mean 1.4; range 1-4). None of the patients required redo biliary-enteric anastomosis. **Conclusion** Postoperative biliary stricture after PD is an infrequent and usually benign complication. The only significant univariate predictor of stricture formation was previous cholecystectomy. Strictures can be managed successfully, with percutaneous biliary dilatation and temporary stenting.

Two Layer Open Pancreaticogastrostomy: A Prospective Initial Experience in a Low Volume Center

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Context Management of pancreatic stump following pancreaticoduodenectomy (PD) is still a source of concern. Pancreaticogastrostomy (PG) seems actually to be preferred in the presence of soft residual parenchyma. **Objective** To describe a technical modification of PG evaluated on an initial study group of 15 patients. **Methods** From March 2008 to April 2009 prospective data were collected on 15 patients who had PG for the pancreatic stump as part of a PD. All the procedures were performed by the same surgeon. The pancreatic stump was largely mobilized. A button suture between gastric serous and the anterior pancreatic capsule was first performed using monofilament 4 zero, followed by posterior and anterior gastrotomy and invagination of the pancreatic stump into the gastric lumen. A second row of sutures was then completed between the gastric mucosa and the rim of the pancreatic stump. A nasogastric tube was then positioned avoiding direct contact with the anastomosis, followed by closure of the anterior gastrotomy. Finally the anastomosis was reinforced posteriorly by an interrupted suture between the gastric serous and the glandular capsule. All patients

underwent immunonutrition for one week before surgery. **Results** This group of patients consisted of 9 men and 6 women with an average age of 68 years. In 5 of the patients the pylorus was preserved. No grade B or C fistula were observed, whereas, 4 grade A fistula, according to the classification of the ISGPF, have been observed. Mortality was 0%. One patient developed a pancreatitis with a minimal leak of the gastrojejunal anastomosis. There were 3 cases of delayed gastric emptying. The mean hospitalization time was 12.1 days. Histological examination led to the diagnosis of 9 ductal adenocarcinomas, 3 carcinomas of the papilla, 1 duodenal carcinoma, 1 chronic pancreatitis and 1 duodenal polyposis (Spigelmann stage IV). **Conclusion** PG seems to be a safe procedure with a very low morbidity also in a low volume center. In our opinion this two-layer technique with the aid of the anterior gastrotomy facilitates the performance of the anastomosis which can be also easily controlled. Our major complication occurred in presence of an extrasoft parenchyma that remains the principal concern of this intervention.

Managing Unsuspected Tumor Invasion of the Superior Mesenteric-Portal Vein During Surgery for Pancreatic Head Cancer: A Case Report

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Context In some cases synchronous superior mesenteric-portal vein resection can be performed during pancreatic resection for cancer. The

reconstruction technique is usually primary anastomosis. Rarely an autologous vein graft needed and usually they are the internal jugular vein, the long

saphenous vein or the superficial femoral vein. **Case Report** A 68-year-old man was admitted to our institute for obstructive jaundice. Laboratory tests showed: total bilirubin 16.57 mg/dL (reference range: 0.2-1.1 mg/dL); direct bilirubin 13.02 mg/dL (reference range: 0-0.3); gamma-GT 792 U/L (reference range: 8-61 U/L); ALP 876 U/L (reference range: 98-280 U/L); GOT 102 U/L (reference range: 0-38 U/L); GPT 214 U/L (reference range: 0-41 U/L); CA 19-9 5,821 U/L (reference range: 0-37 U/L). Ultrasonography (US) showed a hypoechoic mass of the pancreatic head, 3 cm in diameter. Moreover a spiral, multislices computed tomography (CT) scan showed grade 1 involvement of the superior mesenteric-portal vein (SMPV). A US-guided core biopsy allowed diagnosis of adenocarcinoma. At laparotomy, US revealed a >180° vein infiltration of the SMPV of about 3 cm in length. A pylorus-preserving total pancreatectomy with SMPV resection, extending for about 4 cm in length,

was performed. The reconstruction of the SMPV was performed utilizing an autograft of splenic vein. Histological examination of the margin of the splenic vein was tumor-free. Portal vein occlusion time was 30 minutes. Blood loss was 1,650 mL and operating time was 465 minutes. The histologic examination of the specimen showed a pT3, N1, MX, well-differentiated adenocarcinoma. The resected portal vein segment was 4 cm long and involvement of the vessel wall was reached the intima. The resection margins were negative (R0). The postoperative course was uneventful and today the patient is alive, well and disease free at 8 months after surgery. **Conclusions** The reconstruction of the superior mesenteric-portal vein with a splenic vein autograft is performed in selected cases. It allows a reduction of operating time, it is a less invasive approach than reconstruction using an internal jugular vein autograft and it can be an oncologically correct approach.

“Binding” Pancreaticojejunostomy after Pancreaticoduodenectomy: Preliminary Results of a New Technique to Treat the Pancreatic Stump

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Context Postoperative pancreatic fistula (POPF) is the most common complication and the major cause of morbidity and mortality after pancreaticoduodenectomy (PD). The reported rates of POPF range from 2% to 20%. To prevent anastomotic leakage different techniques of treating the pancreatic stump have been described. **Objective** We prospectively evaluated the efficacy of a new anastomosis procedure in preventing POPF after PD called “binding pancreaticojejunostomy” and originally described by Peng. **Methods** All consecutive patients with benign or malignant lesions of pancreatic head or periampullary region undergoing PD were enrolled. The binding pancreaticojejunostomy was performed as follows: the distal cut end of jejunum was everted for 3 cm, the exposed mucosa destroyed by electric coagulation and, after Tissucol[®] application, the sero-muscular sheath of jejunum was bound to the invaginated pancreatic stump. Pre-intra and postoperative data were collected for every patient. POPF was defined according to the International Study Group on Pancreatic Fistula (ISGPF). The primary end-point of the study was to evaluate the incidence of pancreatic fistula. As secondary end-points, we compared the operative time, the amount of blood transfusion units, postoperative mortality and morbidity, the appearance of pancreatic fistula and length of hospitalization of these patients

(group A) with those who underwent Wirsung-jejunoanastomosis (group B) and those in whom pancreatic stump was carried out with stapler or suture (group C). **Results** From January to June 2009, nine patients were enrolled (4 men, 5 women, mean age 67.7±8.7 years). There were 7 pancreatic adenocarcinomas, 1 neuroendocrine tumor and 1 patient with IPMN. The mean operative time was 347±51 minutes. Two patients (22.2%) needed of blood transfusion. Four cases (44.4%) had a Wirsung duct diameter greater than 3 mm; 5 (55.6%) less than 3 mm. Postoperative mortality and morbidity rate were 11.1% (1/9) and 44.4% (4/9), respectively. The length of hospital stay was 15±9 days. A grade A POPF was detected in one patients (11.1%) in which Wirsung duct was dilated (>3 mm). When compared group A with group B (n=9), there were no statistically significant differences except for operative time, that was shorter in group A (P=0.019). When compared group A with group C (n=5), there were two statistically significant differences: POPF rate was more frequent in group C (80%, 4/5) (P=0.023); the length of hospital stay was shorter in group A (P=0.034). **Conclusion** Binding pancreaticojejunostomy is a safe and reliable anastomotic procedure, which can be use in alternative to Wirsung-jejunoanastomosis.

En-Bloc Vascular Resection for “Locally Advanced” Pancreatic Cancer

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Context Locally advanced pancreatic cancer often requires pancreatectomy with en bloc main peripancreatic vessels resection to achieve a radical operation. **Methods** Since November 1987 until December 2008, 206 (19%) patients out of a total of 1,060 pancreatic resections received a resection of peripancreatic vessels (PRPV) en bloc with pancreatectomy. There were 73 (46%) males and 87 (54%) females, with a mean age of 64.4 years (range: 37-84 years). One hundred and sixty patients (78%) had a final histologic diagnosis of pancreatic ductal adenocarcinoma. One hundred and eighteen patients (74%) received an isolated venous resection (IVR), 15 patients (9%) an isolated arterial resection (IAR) and 27 (17%) an artero-venous resection (AVR). Overall 185 vascular segments were resected in 160 patients. **Results** Perioperative mortality and morbidity occurred to 8 (5%) and 59 patients (37%), respectively. IVR, IAR and AVR mortality and morbidity rates were 4.2% (5/118) and 35.6% (42/118), 0 (0/15) and 40% (6/15), 11.1% (3/27) and 29.6% (8/27), respectively (P NS). Final pathologic exam confirmed vascular infiltration

in 99 patients (99/160; 62%). One-, 3- and 5-year actuarial survival rates were 63.8%, 18% and 8.2%, respectively. Survival at 1-, 3- and 5-years was 62.1%, 15.5% and 13.3% in IVR, 65.8%, 40.5% and 0 in IAR, and 59.5%, 19.1% and 0 in AVR group, respectively (P NS). Overall survival, at the same time points, in cases with no infiltration or even in the absence of involvement of tunica intima was 77.2%, 19.2% and 7.3%, respectively, which is statistically favourable as regard as patients with tumor invasion reaching the tunica intima (50.4%, 9.2% and 9.2%, respectively) (P=0.0004). **Conclusions** PRPV can be performed safely. Even in the group of ductal adenocarcinomas, we registered cases of prolonged survival; these results might be further improved by modern medical therapies. Actual vascular infiltration reaching the tunica intima, a clue difficult, if not impossible, to define preoperatively or even during surgery before crossing the point of no return, is a prognostic marker of higher tumor aggressiveness and correlates with significantly poorer outcomes.

Robotic Pancreatectomies

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Context As compared to laparoscopy the Da Vinci® Surgical System (DSS) carries a number of potential advantages, which may improve surgeon’s ability to face with complex operations. Pancreatic resections might be one of the fields of development of the DSS. **Objective** To report our initial experience with the DSS in right-sided and left-sided pancreatic resections. **Methods** Between April 2008 and June 2009, 17 patients were selected for possible robotic pancreatic resections. There were 4 males and 13 females, with a mean age of 61.6 years and a mean body mass index of 25.4 kg/m². Patients with a preoperative diagnosis of possible pancreatic cancer were not considered for minimally invasive surgery. Patients deemed suitable for a minimally invasive procedure were hence operated on with the DSS when candidate to pancreaticoduodenectomy (PD) or when a distal pancreatectomy (DP) was thought to be more technically demanding with the respect to cases usually treated laparoscopically. **Results** Five patients underwent PD, 10 DP, 1 total pancreatectomy and 1 enucleation. No procedure was converted to

conventional laparoscopy or open surgery. Mean operative time was 420 minutes. In each procedure blood loss was so minimal as to be difficult to measure. There was no perioperative mortality. Perioperative complications occurred in 9 patients (52.9%), including 7 pancreatic fistulas (43.7%), one intra-abdominal fluid collection (5.8%) and one (5.8%) myocardial ischemia. All complications resolved with a conservative treatment. Postoperative mean hospital stay was 14 days. Considering only patients with an uneventful post-operative course, the mean hospital stay was 10 days. Final pathology diagnosis was: neuroendocrine tumor in 3 cases, IPMN in 3, mucinous cystadenoma in 3, serous cystadenoma in 2, chronic pancreatitis in 2, and bile duct cancer, ampullary cancer, ductal adenocarcinoma and pancreatic cyst in one. **Conclusions** Our initial experience confirms that pancreatic resections, including PD, can be performed laparoscopically by using the DSS. The actual benefits of the use of the DSS in the surgical treatment of well selected patients with pancreatic disease can be evaluated in a prospective randomized study only.

Resection of Intraductal Papillary Mucinous Neoplasms (IPMNs) of the Pancreas: The Role of Intraoperative Ultrasonography (IOUS)

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Context IPMNs are neoplasms of the pancreatic duct epithelium increasingly identified in the last two decades, have malignant potential, with a broad histologic spectrum ranging from dysplasia to invasive carcinoma, and can be multifocal. Segmental pancreatic resection are increasingly considered to be adequate for lesions with low malignant potential.

Objective The aim of the study was to define the role of IOUS in candidates to pancreatic resection for IPMNs. **Methods** Ten patients with IPMNs were included in the study; 6 were males and 4 were females; mean±SD age was 71±7 years (range: 61-84 years). All underwent pre-operative CT-scan and MRCP for staging. Three patients had invasive carcinoma and IPMNs, 2 had multifocal and 5 had unifocal IPMNs, respectively. IOUS was performed after division of the gastrocolic ligament and exposure of the anterior aspect of the pancreas to explore the parenchyma, the tumor and the peripancreatic vessels, and then before pancreatic division to define resection margins. Resection margins were submitted for intraoperative frozen section analysis in all cases.

Results IOUS was useful to define the resection margin in patients with invasive carcinoma: in one patient with an invasive carcinoma of the tail and multiple IPMNs, the IOUS showed a 20 mm tumor of the isthmus which was included in the resected specimen and resulted to contain focal in-situ carcinoma. In patients with multifocal tumours, IOUS was useful to define the resection margins of the dominant IPMN. In patients with unifocal tumor, IOUS was useful to obtain negative resection margins: 2 patients underwent DCP, 1 underwent distal pancreatectomy without splenic preservation for a concomitant splenic lymphoma, 2 underwent IOUS-guided resection of the tail with splenic preservation. Resection margins were negative at intraoperative frozen section analysis in all cases. **Conclusion** IOUS is of clinical utility in selected patients with IPMNs undergoing pancreatic surgery. IOUS should be routinely used in planning and guiding the surgeon, especially in patients with multifocal neoplasms and in candidates to segmental conservative pancreatic resection.

A Fast-Track Programme in Pancreatic Surgery: Prospective Single Center Experience

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Context The concept of fast track surgery is well accepted in colorectal surgery with accelerated post-operative recovery. Still conflict exists if these concepts can be applied to major surgical procedure such as pancreatic surgery. **Objective** We aimed to evaluate the impact of fast track protocol in patients undergoing mayor pancreatic surgery. **Methods** Between February 2005 and February 2009, 212 consecutive patients underwent pancreatic procedures. The study group consisted of 101 consecutive patients underwent pancreatic resections. **Results** Overall morbidity rate (percentage of patients with at least one complication) was 34.1%. The most complications were managed by non surgical means. Leak of the

pancreatic anastomosis occurred in 5 out of 70 patients who received a pancreaticojejunostomy. Six patients required operative revision because of complications. Postoperative haemorrhage (PPH) occurred in 7 patients (6.9%), wound infection in 7 (6.9%) cases, and biliary leak in 4 cases (3.9%). In-hospital mortality occurred in 3 patients (2.9%). On average, patients were discharged at the postoperative day 10 (range 7-69 days). The 30-day readmission rate was 4.9%. **Conclusion** Fast tack protocol programmes are feasible, easy, and applicable also to major surgical procedure such as pancreaticoduodenectomy without affecting patient safety.

Is CD133 a Marker of Cancer Stem Cells in Ductal Pancreatic Cancer?

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Context CD133 has been identified as a putative stem cell marker in many normal and malignant tissues.

Objective The aim of the study is to understand if CD133 is a marker of cancer stem cells in ductal pancreatic cancer. **Methods** CD133 expression has been evaluated: i) by immunohistochemistry in non neoplastic pancreatic tissue (n=8) and in ductal adenocarcinoma (n=6), and ii) by flow cytometry in primary duct cells obtained from pancreas of heart beating donors (n=12) and in ductal adenocarcinoma pancreatic cell lines (n=17). Pancreatic cancer cell lines were characterized for proliferation rate, *in vitro* and *in vivo* clonogenicity, chemoresistance to gemcitabine and expression of stem cells markers other than CD133 (i.e. CD24/CD44/ESA triple positivity, CD166, C-Kit, CD73). Moreover, we evaluated by quantitative real-time PCR the expression of epithelial/mesenchymal transcriptional factors (cytokeratin 19, HNF1beta, sox17, nestin, snail1, vimentin) and transcriptional factors involved in pancreas development. **Results** In non neoplastic pancreatic tissue, CD133 was evident on the apical but not the basolateral side of all epithelial cells lining pancreatic ducts and CD133+ cells resulted positive also for the duct cell marker CK19. No CD133 staining was detected in endocrine

cells in the islets of Langerhans, acinar exocrine cells, and connective tissue. In primary cell cultures of the non endocrine cell fraction obtained after islets isolation, CD133 stained all small epithelial ductal components and costained with epithelial markers like CK19, EpCAM and CA 19.9. In ductal adenocarcinoma CD133 immunoreactivity was evident in all tumoral epithelial cells. In cell lines CD133 expression is heterogeneous: high (n=4; 60-96%), intermediate (n=2; 31-40%) and low (n=11; 0.9-8%). The CD133 expression did not fully overlap the expression of other stem cell markers (CD24⁺/CD44⁺/ESA⁺). In an inter-lines analysis proliferation rate, clonogenicity *in vitro* and *in vivo* and chemoresistance did not significantly segregate with CD133 positivity. On the other hand, CD133 correlated with expression of transcriptional factor involved in pancreas development and epithelial differentiation (i.e. Krt19, PDX1, HNF1beta, sox17). Finally CD133+ and CD133- cells showed similar sensitivity to chemotherapeutic agent gemcitabine in a intra-lines analysis. **Conclusion** *In vivo* CD133 is largely expressed on normal and neoplastic duct cells. *In vitro* CD133 does not identify a subpopulation of cancer cells with high clonogenicity and chemoresistance.

Quality of Life in Patients with Neuroendocrine Tumors of the Pancreas

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Context Pancreatic neuroendocrine tumors (PNETs) have generally slow growing and patients may have prolonged survival. **Objective** To assess the quality of life (QoL) of PNET patients. **Patients** Fifty-one consecutive patients (21 males, 30 females, mean±SD age 61.0±10.3 years) with proven PNETs were studied. **Methods** SF-12 questionnaire able to explore the physical (PCS) and mental (MCS) aspects of daily life was used. To explore the psychological aspects of the disease, four questionnaires were also used (GHQ-12 for non-psychotic psychiatric disorders, STAY Y-1 and Y-2 for anxiety, BDI-II for depressive symptoms). Forty-four sex- and age-matched Italian normative subjects were included to evaluate for SF-12, STAY Y-1 and STAY Y-2. **Results** Seven patients refused to

participate to the study and they were clinically similar to the 44 participants who accepted to complete the questionnaires. PNET patients had values of PCS score (44.7±11.0) no significantly different from the norms (46.1±9.9, P=0.610), whereas MCS score was significantly lower in patients (42.3±13.0) as compared to the norms (48.2±9.8, P=0.036). The STAY scores were similar in patients and norms. GHQ-12 identified 11 patients (25.0%) having non-psychotic psychiatric disorders while BDI-II identified 8 patients (18.2%) with moderate and 9 (20.5%) with mild depression. **Conclusions** The PNET patients have a good physical but an impaired mental component of their QoL. About 40% of them may have mild to moderate depressive symptoms.

Pancreatic Cancer Alters Human CD4+ T Lymphocyte Function: A Piece of the Immunevasion Puzzle

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Context Tumors might evade immunesurveillance by impairing CD4+ T cells function. **Objective** We compared the effects of pancreatic cancer (PC) and other gastrointestinal cancer (GIC) cells on: i) CD4+ T cells proliferation, migration and differentiation, and ii) expansion of CD4+ memory (CD45RO), naïve (CD45RA), activated (CD69) and regulatory (CD25) subsets. **Methods** CD4+ T cells, from 29 blood donors, were cultured for 4 days in control or pancreatic (BxPC3, Capan1, MiaPaCa2), colorectal (HT29), gastric (AGS) or hepatocellular (HepG2) cancer cell conditioned media (CM). To assess migration, a transwell system with or without hSDFalpha was used; migrating cells were estimated by a luminescent assay. Cell proliferation, with or without allogenic PBMC, was evaluated after 72 h (³H-thymidine incorporation). Before and after 4 culture days we evaluated

IFNgamma production (ELISA) and CD45RA, CD45RO, CD69 and CD25 membrane expression (FACS) in control and conditioned CD4+ T cells. **Results** PC cells, differently from other GIC cells, inhibit CD4+ T cell proliferation both in the presence and absence of PBMC (P<0.001). Under hSDFalpha chemotaxis only PC cell CM significantly reduced lymphocyte migration with respect to control (P<0.001). All PC CM significantly induced CD4+ T cell IFNgamma production (P<0.05) with respect to control or other GIC CM (P NS). Control or tumor CM did not modify CD45RA, CD45RO or CD25 subsets. CD69 positive cells were significantly expanded by PC (P<0.001) but not by other GIC cell CM. **Conclusions** These *in vitro* findings support the hypothesis that PC might evade immunesurveillance by altering CD4+ T lymphocytes.

Endocrine (beta-Cell) Functional Index and beta-Cell Mass in a Murine Diabetic Model: Which Is the Best?

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Context The beta-cell mass is an important parameter in the pathophysiology of experimental diabetes, but in many cases its measurement is difficult and often inaccurate. **Objective** To find a new accurate neuroendocrine functional index (NFI) using a morphometric analysis (MA) and to compare NFI with beta cell mass (BCM) values in a murine model of type-2 diabetes. **Methods** Total neuroendocrine surface (TNS), total beta cell surface (TBCS) and islet number (IN) were determined by an MA program (Analysis b, Olympus) on paraffined pancreas tissue sections stained with hematoxylin (blue) and conjugated anti-insulin antibody (brown) (Histomouse kit, Zymed) from five groups of mice: controls (C), diabetics (D), diabetics treated with a new antioxidant agent (IAC, Medestea): low dose (T1), middle dose (T2) and high IAC dose (T3) (n=4 for each group). By using this program, it was possible to calculate all surfaces (μm^2) on the basis of the colour (blue or brown). Statistical analysis was performed by GraphPad program (n=4;

paired Student's t test, 95% CI, and ANOVA test; P<0.05). For each group, we also calculated beta-cell mass (BCM) in the usual way (i.e., ratio between beta cell area and islet area multiplied by total pancreas weight) and we measured plasma glucose levels (G) and total pancreatic insulin content (IC). **Results** MA revealed that T2 and T3 mice had significantly higher values than D mice in terms of IN, TNS and TBCS. No statistical differences were found when C vs. T2, C vs. T3, and T2 vs. T3 were compared. Mean number of islets/ mm^2 (MIN) was as follows: C=1.067, D=0.353, T1=0.496, T2=0.662 and T3=0.808. We calculated EFI as MINxTBCS product. In the different mice groups, EFI was: C=1.014, D=0.192, T1=0.288, T2=0.553 and T3=0.654. We obtained a best correlation analysis matching EFI instead of BCM: (EFI vs. MIN, P=0.0006; EFI vs. G, P=0.0496; EFI vs. IC, P=0.0285; BCM vs. MIN, P=0.0155; BCM vs. G, P=0.0123; BCM vs. IC, P=0.1871). **Conclusion** By using MA in this murine model, we found that NFI values showed a

“better” statistic correlation than BCM in 2 out of 3 parameters and a significant correlation with all parameters analysed. We intend to introduce this new

index for endocrine functional analysis in this and other diabetic models.

PMP22 Gene Duplication in Pancreatic Ductal Adenocarcinoma

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Context The peripheral myelin protein 22 (PMP22) gene is usually expressed in nervous systems. Both PMP22 mRNA and protein have been demonstrated in pancreatic ductal adenocarcinoma (PDAC) tissues. DNA amplification of 17p11.2-12 region related to Charcot-Marie-Tooth 1A syndrome, (CMT1A) is associated with a duplication of PMP22 gene. Some authors observed this genetic condition in other tumors such as osteosarcoma. **Objective** To evaluate the presence of CMT1A-like genomic condition associated with a duplication of PMP22 gene in PDAC patients. **Methods** We analyzed 13 PDAC frozen tissues and 3 primary pancreatic tumor cell cultures (PPTCCs). We used as positive controls 3 patients affected by CMT1A neuropathy and we used 3 normal subjects (genetically unaffected) as negative controls. DNA extraction was performed in all 21 cases by standard procedure. The

duplication of 17p11.2-12 region related to CMT1A syndrome was evaluated by PCR reaction and digestion by two endonucleases (EcoRI and NsiI). **Results** The positive cases (CMT1A patients) showed a 1.7 kbp specific DNA fragment. This alteration is not present in healthy subjects used as negative control. The specific DNA fragment associated with a duplication CMT1A-like was observed in 38% (5/13) PDAC patients and in 66% (2/3) of our PPTCCs. Additionally all amplified PDAC samples (7/7) showed a 2.1 kbp fragment. **Conclusion** The same genetic alteration present autosomic dominant CMT1A syndrome was observed in a group of PDAC patients. This condition has been found in other tumors: osteosarcoma, glioma and glioblastoma. Further studies need to clarify the origin of CMT1A duplication in PDAC patients.

Selective Effect of Ukrain in Primary Pancreatic Tumor Cell Cultures

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Context Current therapy for PDAC is surgery followed by adjuvant radiotherapy and chemotherapy for early-stage and palliative chemotherapy for advanced disease. Gemcitabine is the standard drug in both adjuvant and palliative treatment. A new drug, NSC-631570 (ukrain), used for the palliative cure of unresectable PDAC, showed a greater median survival in combination with gemcitabine with respect to gemcitabine alone (10.4 months vs. 5.2 months; P<0.001). Furthermore, ukrain showed to have a selective citotoxic effects only in cancer cell lines derived from different tumors, but not in normal cell lines. **Objective** The goal is to study the citotoxic effects of ukrain in primary pancreatic cancer cell lines

(PPTCCs) and short term culture of fibroblast derived from the PDAC (F-PDAC). **Methods** In this study we tested the ukrain effects in 4 PPTCCs and 2 F-PDAC. Cytotoxicity was assessed by the CellTiter 96 kit (Promega, Madison, MA, USA) based on the cellular metabolism of the tetrazolium compound XTT, which is reduced by living cells to yield a soluble formazan product in the presence of the electron coupling agent phenazine methosulfate. To evaluate variations of ukrain concentration in the medium we used the fluorescence property of ukrain using the AlphaDigiDoc software by UV light excitation (ULADC test). **Results** *In vitro* citotoxic effects of ukrain in PPTCCs were higher compared to those observed in F-

PDAC (20% alive cells vs. 80% alive cells, 10 μ M (Ukrain); $P < 0.05$). Indeed the ULA-DC test revealed that the PPTCCs cells consumed more drug than F-PDAC (paired Student's test, $p < 0.001$, $n = 4$).

Conclusion These data showed a selective effect in PPTCCs and this may be related to a different transport system or related to a higher metabolism of the drug in pancreatic cancer cells.

Early and Late Complications in Laparoscopic Spleen Preserving Distal Pancreatectomy with or without Splenic Vessels Sacrifice: A Case Control Study

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Context During distal pancreatectomy it is possible to preserve the spleen with the sacrifice of the splenic vessels (SVS) or with their preservation (SVP). Early and late complications of SVS are not well known yet.

Objective The aim of this study is to review our experience with laparoscopic spleen preserving distal pancreatectomy. **Methods** We designed a 1:2 case control study in which all 7 patients who underwent SPDP with SVS from 2002 to 2007 were enrolled as study group (group 1). Fourteen patients undergone SVP operation in the same period were enrolled and matched to the study group in age and histotypes. They represent the control group (group 2). All patients had blood test and underwent MDCT scan or MRI of the abdomen. Follow-up period ended on June 2009.

Results Among 7 patients in group 1, one underwent splenectomy for splenic infarction on 3rd post-operative day; one patient with an uneventful postoperative course died for lung cancer during the follow-up. As

regard the 5 patients still alive, 3 have gastric varices associated to thrombocytopenia in 2 of them. All patients are asymptomatic. In group 2, 1 had splenectomy in the post-operative course for infected collection. Among 13 evaluable patients, three developed asymptomatic gastric varices with thrombocytopenia in two of them. All these three patients had had a complicated post-operative course related to 1 abdominal collection and 2 pancreatic fistulas grade B. **Conclusion** In our experience, laparoscopic spleen preserving distal pancreatectomy is a safe and feasible operation but spleen preservation *per se* represents a condition leading to specific early and late complications. SVS spleen preserving distal pancreatectomy doubled the complication rate in the long term follow-up so that this technique should not be applied as routine procedure. However, gastric varices following SPDP seem to be an indolent condition with very low risk for bleeding.

Clinical and Radiological Findings of Patients Suffering from Chronic Pancreatitis (CP) Associated with Cystic Dystrophy of the Duodenal Wall (CDDW) compared to alcoholic CP (ACP)

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Context CDDW is a newly recognized form of CP. However, some authors suggest that it may represent only a particular form of ACP. Furthermore, the clinical and radiological aspects of CDDW are described only in few reports. **Objective** Aim of the present study was to evaluate the clinical and radiological aspects of patients suffering CDDW compared with those with ACP. **Patients and Methods** Clinical and radiological data of 82 patients suffering from CDDW (77 males and 5 females, mean

age at the onset of the disease 42 ± 9 years), present in database of our Department since 1995, were retrospectively evaluated. The diagnosis of CDDW was made on surgical specimens in 64/82 patients (78%). In the remaining 14 patients the diagnosis was based on imaging (EUS, CT and MR). As control population we studied 50 patients suffering from ACP (defined as daily alcohol intake ≥ 80 g) (45 males, 5 females, mean age at the onset of the disease 43 ± 11 years). **Results** Among 82 patients with CDDW, in 32 (41%) a solid-

type disease was diagnosed and in 48 (59%) of cystic-type. The disease was localized only in the head of the pancreas in 22 patients (27%) with normal pancreas proper and in the head plus body-tail of the pancreas in 60 patients (73%). The Table reports the differences between CDDW and ACP. No differences were observed in the regards of alcohol and smoking habits. **Conclusions** CDDW and ACP differ in some clinical and radiological aspects. CDDW seems to represent a distinct clinical entity from ACP.

| | CDDW | ACP | P value |
|--------------------------------------|------|------|---------|
| Number of patients | 82 | 50 | – |
| Acute pancreatitis at clinical onset | 45% | 84% | <0.001 |
| Necrosis at CT | 3.5% | 22% | 0.002 |
| Pain | 100% | 100% | NS |
| Vomiting | 40% | 12% | 0.001 |
| Jaundice | 16% | 2% | 0.017 |
| Diabetes | 17% | 29% | NS |
| Steatorrea | 16% | 48% | <0.001 |
| Pancreatic calcifications | 61% | 80% | 0.033 |
| Calcifications at clinical onset | 9.8% | 28% | 0.008 |
| Surgery | 83% | 48% | <0.001 |

Non-Neoplastic Mimickers of Invasive Pancreatic Carcinoma Associated to Intraductal Papillary Mucinous Neoplasm

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Context Intraductal papillary mucinous tumor (IPMN) is a pancreatic tumor characterized by intraductal proliferation of mucinous cells that leads to cystic dilatation of the involved ducts due to the hypersecreted mucus. The usual clinical presentation shows recurrent episodes of acute pancreatitis due to temporary obstruction of the main pancreatic duct. About half of the patients with IPMN have recurrent attacks of acute pancreatitis and develop pancreatic failure with weight loss, diabetes and/or steatorrhea and obstructive chronic pancreatitis (OCP), leading to ductal stenosis upstream, to islets aggregations and to replacement of the acinar cells with fibrotic tissue. This process in the long-standing gets accompanied by intralobular fibrosis; attacks of recurrent acute pancreatitis often hesitate in the formation of necrotizing abscesses. After these modifications, the pancreatic structure is characterized by the presence of nodular areas which can mimate a carcinoma at radiological analysis (US, TC, NMR). It is known that up to 5% of the masses preoperatively diagnosed as carcinomas prove to be actually non-neoplastic on pathologic examination after pancreatectomy is performed; chronic inflammatory lesions are the leading cause of this phenomenon (pseudotumoral

pancreatitis). **Case Report** We present three cases of IPMN in which OCP associated with features of recurrent acute pancreatitis, realized nodular areas of fibrosis and necrotizing abscesses, clinically resembling an invasive carcinoma. Total pancreatectomy was performed. In all cases progression from low-grade to high-grade dysplasia and finally to invasive carcinoma was observed. **Conclusion** A variety of etiologically and clinicopathologically distinct entities, such as OCP associated to IPMN, may form “pseudotumors” in the pancreas that mimate carcinoma and may come to the attention of surgical pathologists with the preoperative diagnosis of invasive pancreatic cancer. Therefore, about 5% of clinically diagnosed “carcinomas” prove to be “pseudotumors” after microscopic examination. The knowledge of the clinical, radiologic, and pathologic findings is crucial in making the correct preoperative diagnosis. But pathologic examination remains critical in the evaluation of such cases. We cannot overrate the role of gross examination and dissection in these cases, in order both to find out small neoplastic lesions, and to determine the precise location of the process and its characteristics.

Role of Adjuvant Chemoradiotherapy (CRT) and Chemoytherapy alone in Pancreatic Cancer: Experience in 25 Patients

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Context To date, the role of adjuvant chemoradiotherapy (CRT) in pancreatic cancer is still controversial. We analyzed the impact of adjuvant

CRT and chemotherapy alone on time to progression (TTP) and one- and two-year survival rates in operated R1 and R0 pancreatic patients. **Methods** We analyzed

retrospectively a series of 25 patients with resected pancreatic adenocarcinoma who underwent R0 (n=13) or R1 (n=12) surgery, between 2003 and 2008. The staging, according to AJCC criteria was: IA in 1 case (n=1, R0), IIA in 6 cases (n=2, R0; n=4 R1), IIB in 15 cases (n=8 R0; n=7 R1), III in 3 cases (n=2 R0; n=1 R1). This series included 18 males and 7 females (median age at diagnosis 63 years; ECOG 0-2). After surgery, among the 25 patients considered, 13 received adjuvant gemcitabine (GEM) alone (1,000 mg/m² days 1, 8, 15, every 28) for 6 months and 12 patients received GEM with the same schedule followed by CRT. All patients who underwent R0 resection were treated with CT alone while R1 patients received CRT.

Results The overall median TTP was 7.31 months (range 1.93-13.8 months) and overall one- and two-year survival rates were 56 % and 24 %, respectively. The analysis for the R1 and R0 patients is reported in the Table. **Conclusions** In our experience, according to the literature, there is no improvement in OS and TTP with radiotherapy combined to chemotherapy in R1 patients. So, should we treat these patients as locally advanced pancreatic patients?

| Patients | TTP (months) | Survival rate (%) | |
|-------------------|--------------|-------------------|--------|
| | | 1-year | 2-year |
| R0 plus R1 | 7.31 | 56.00 | 24.00 |
| R0 | 7.77 | 69.23 | 30.76 |
| R1 | 6.37 | 41.66 | 17.66 |

Chronic Pancreatitis Associated with Serous Cystic Tumors of the Pancreas: A New Issue to Be Explored

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Context Serous cystic tumors (SCTs) of the pancreas are benign lesions often incidentally diagnosed. Their association with chronic pancreatitis (CP) has not been investigated so far, and it is unclear whether this aspect may be relevant for their management. **Objective** In the present study we estimated the prevalence of secondary chronic pancreatitis in patients undergone resection for SCTs and evaluated its association with: i) tumor size, ii) postoperative complications, and iii) long-term pancreatic exocrine and endocrine function. **Methods** Pancreatic resection margins of 65 consecutive patients operated for SCTs at our Institution were analyzed by an experienced pathologist. CP was classified in four stages (focal, mild, moderate, and severe) according to the degree of fibrosis, acinar atrophy and main pancreatic duct diameter. Clinical data, morbidity and mortality were retrieved from our electronic database. Furthermore, quality of life was evaluated by EORTC QLQ-C30 questionnaire and by an institutional questionnaire focused on exocrine and endocrine pancreatic function. **Results** CP was found in 11 out of 65 (17%) patients resected for SCTs of the pancreas and classified as focal in 2 cases (18.2%), mild in 2 cases (18.2%), moderate in 3 cases (22.3%), and severe in 4 cases (36.3%). It was mainly associated with lesions located

in the head/uncinate process: 8 (72.7%) versus 3 lesions (27.3%) in the body/tail. Median age of patients with CP was significantly higher in comparison with patients without CP (59 years versus 49 years, P=0.05). Also, tumor size was significantly greater in CP group (median diameter 5.1 cm versus 3.7 cm, P=0.026). No significant difference in main pancreatic duct diameter was found. There were no postoperative deaths. The rate of postoperative complications, and in particular of pancreatic fistula, was not significantly different in the two groups. Median follow-up was 55 months (range 14-187 months). There were no differences in terms of quality of life (EORTC QLQ-C30). However, the rate of both exocrine and endocrine insufficiency was significantly higher in patients with CP (steatorrhea 20% versus 11.1%, P=0.05; postoperative diabetes 10% versus 4.6%, P=0.02). **Conclusions** SCTs of the pancreas are frequently associated with CP, especially when maximum tumor diameter is >5 cm. Once signs of CP have developed, long-term impairment of exocrine and endocrine functions following pancreatic surgery is significantly higher. Accordingly, direct/indirect evidence of CP at presentation or during follow-up may represent an additional parameter for recommending surgical resection.

Systemic Gemcitabine and Capecitabine plus Intra-Arterial Epirubicin and Cisplatin as Second-Line Chemotherapy in Gemcitabine-Failure Pancreatic Cancer

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Context Approximately half of the patients with advanced pancreatic carcinoma (APC) failing previous gemcitabine-based treatment are still in a good performance status and, in daily clinical practice, are frequently submitted to second-line chemotherapy. However, limited investigation on second-line treatment has been performed and no standard chemotherapy is established when patients have become refractory to gemcitabine. **Objective** In patients failing first-line treatment with gemcitabine, we evaluated activity and toxicity of a new combined approach: epirubicin and cisplatin given intra-arterially through the celiac axis plus systemic gemcitabine and capecitabine. **Methods** Based on our previous phase I study, patients with APC progressed after gemcitabine were treated with EC-GEMCAP: on day 1 intra-arterial epirubicin 35 mg/m² and cisplatin 42 mg/m², on day 2 systemic gemcitabine at 1,000 mg/m² and on days 2-15 capecitabine at 650 mg/m² twice a day. Cycles were repeated every 28 days. **Results** Twenty-six patients were enrolled onto the study. There were 18 males and 8 females, with a median age of 56 years (range 35-75

years); 69% had an ECOG PS of 0. Eight patients (30%) had undergone surgery and received prior adjuvant chemotherapy. Twelve patients had stage IVa disease, 11 had stage IVb and 3 had loco-regional relapse. No patient had extra-abdominal disease. Grade 3 and 4 neutropenia were observed in 15% and 11% of patients, respectively. Eleven percent experienced a grade 3 and 8% a grade 4 thrombocytopenia. Grade 3 anemia occurred in 4%. The other toxicity was: grade 2 mucositis in 11%, grade 1 diarrhea in 4%, grade 2 nausea and vomiting in 11%, and mild hand-foot syndrome in 8%. We observed 8 PR (30%) and 10 SD (38%). Median PFS was 5.2 months (range 1-20+ months), and median OS was 8.5 months (range 1-22 months). Eight patients are progressed-free and 11 patients are still alive. **Conclusions** EC-GEMCAP as second line chemotherapy in patients with gemcitabine-failure APC seems to be well tolerated. It has demonstrated a good activity and could be considered in patients with good PS, failing first-line chemotherapy.

Endoscopic Ultrasonography (EUS) Impact on Diagnostic and Therapeutic Management in Pancreatic Diseases (PD)

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Context EUS has been shown to be a highly effective test for PD imaging with an accuracy better than other transcutaneous imaging techniques. EUS accuracy for diagnosis and staging PD has been shown to have a pivotal influence on patient management. **Objective** To evaluate the EUS impact of EUS on diagnostic and therapeutic management in patients with PD. **Methods** We studied EUS impact in a series of 48 consecutive patients (22 M, 26 F; mean age: 67.6 years, range 41-85 years) in which EUS results could be controlled (by follow-up, surgery or ERCP). All patients underwent to radial or linear scanning EUS (Olympus UE-160 AL; Pentax FG 36 UX, echoendoscopes) for suspected PD (42 patients) or for staging of a pancreatic tumor (6 patients) on the basis of a previous diagnostic work-up (consisting with US+CT in 26 patients, US in 12 patients, CT+ERCP in 6 patients, CT+PTC in 2 patients and upper GI endoscopy in 2 patients). EUS

impact was judged on the basis of diagnosis change and/or of patient management change. **Results** Ten out of the 26 patients studied by US+CT had pancreatic tumor diagnosis confirmed or demonstrated by EUS. Sixteen out of the 26 patients with suspected pancreatic tumor at US+CT proved to have at EUS: chronic pancreatitis (8 patients), choledocholithiasis (4 patients), and normal pancreatic tissue (4 patients). Eight out of the 12 patients with suspected pancreatic tumor at US showed at EUS: pancreatic tumor (2 patients), ampullary carcinoma (2 patients), insulinoma (2 patients), and normal pancreatic tissue (2 patients). Four out of the 12 patients with US diagnosis of chronic pancreatitis showed a normal pancreas at EUS. In six patients showing at ERCP+CT a distal biliary stenosis, EUS diagnosed a pancreatic head tumor in 4 patients, and a cholangiocarcinoma and an ampullary carcinoma in 1 patient, respectively. Upper GI

endoscopy suspected duodenal stenosis from pancreatic cancer in 2 patients but EUS findings were normal. The CT+PTC diagnoses of ampullary carcinoma were changed in pancreatic head tumor by EUS. All EUS diagnoses proved to be true by following tests/follow-up. EUS results implied: a change of diagnosis in 36/48 (75%) patients; a change in patient management in

26/48 (54%) patients. **Conclusion** Our data confirm that the impact of EUS on diagnosis and management of patients with PD is substantial. Therefore, after abdominal non invasive US, EUS could be performed as a first line diagnostic test in PD also in view of FNA capabilities.

COX-2 Gene CpG Islands Methylation Status and SNP-765G>C as Potential Biomarkers of Prognosis in Pancreatic Adenocarcinoma

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Context Inflammatory and mitogen stimuli trigger the expression of the inducible form of cyclooxygenases, the COX-2, whose over-expression is associated with apoptosis inhibition, metastatic potential increase and neo-angiogenesis. The up-regulation of COX-2 has been described in various tumors including pancreatic adenocarcinoma where it correlates with a poor prognosis. The regulation of the enzyme expression can be modified: i) by the presence of a SNP in position -765G>C in the promoter region, where the transition eliminates a binding site for the stimulatory protein 1 (Sp1), a transcriptional activator; and ii) by a specific methylation status of the CpG islands of the gene. Therefore, the interaction between genetic and epigenetic factors could spread more light on the possible mechanisms which cause the deregulation of the enzyme expression in the pancreatic cancer.

Objective To verify the methylation status of COX-2 gene and the frequency of the polymorphism -765 G>C in a group of subjects with pancreatic adenocarcinoma.

Methods The polymorphism in position -765 G>C was studied in a cohort study (60 subjects with pancreatic carcinoma vs. 100 controls) using a restriction fragment length polymorphism-PCR (RFLP-PCR) technique, while the methylation status was studied

with a methylation-specific-PCR (MSP) technique; in this last case neoplastic and peritumoral cells were isolated by laser micro-dissection on paraffin embedded tissues. We verified the expression of the protein by immunohistochemistry (IHC) in 16 tumor samples using a monoclonal antibody anti-COX-2.

Results The frequency of the -765 G>C polymorphism did not show any statistically significant difference between cases and controls, even if the SNP, evaluated on DNA extracted from the tumor tissue analysed for the methylation status, showed an allelic frequency associated to an elevated production of COX-2 (genotype GG). The study about the methylation status showed that the CpG islands are not methylated in tumor cells, while the peri-tumoral cells are methylated in a high percentage; moreover, at IHC we found a high expression of COX-2 in the tumor cells. **Conclusion** Our preliminary data let us hypothesize a relationship between SNP, methylation status and tissue expression of COX-2. A confirm of these data could identify the methylation status as a risk factor for the development of the tumor to be used in the early diagnosis and, in association with SNP, as a potential prognostic biomarker.

The Chemokine Receptor CX3CR1 Is Involved in the Neural Tropism and Malignant Behavior of Ductal Pancreatic Adenocarcinoma

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Context Tumor perineural dissemination is a hallmark of human pancreatic ductal adenocarcinoma (PDAC) and represents a major source of local tumor recurrence

after surgery. **Objective** In this study we address the question whether the chemokine receptor CX3CR1 (whose unique ligand, the transmembrane chemokine

CX3CL1, is expressed by neurons and nerve fibers) is involved in the neurotropism of PDAC cells to local peripheral nerves. **Methods** Neoplastic cells were obtained from PDAC cell lines and surgical specimens. Functional activity of CX3CR1 was analysed by chemotaxis and adhesion assays. Expression of integrins and focal adhesion kinase (FAK) was assessed by confocal microscopy and CX3CR1 expression in surgical specimens by immunohistochemistry. **Results** Tumor cells express the chemokine receptor CX3CR1, absent in normal pancreatic ducts. CX3CR1+ tumor cells migrated in response to human recombinant CX3CL1 and specifically adhered to CX3CL1-expressing cells of neural origin, via mechanisms involving activation of G proteins, beta1 integrins and FAK.

Immunohistochemistry of CX3CR1 in PDAC specimens revealed that 90% of the samples were positive with a heterogeneous pattern of expression. High receptor score was significantly associated with tumor perineural infiltration evaluated histologically (P=0.026). Regression analyses showed that high CX3CR1 expression and perineural invasion were strongly associated with local and earlier tumor recurrence (P=0.007). **Conclusions** This study shows that the CX3CR1 receptor may be involved in PDAC tumor neurotropism and it is a relevant and independent risk factor to predict an early local tumor relapse in resected patients. We are now presently investigating whether mutations in *K-ras*, an early genetic lesion in pancreatic adenocarcinoma can play a role in the upregulation of CX3CR1.

Water, Fire and Burning Ashes: May Aquaporin Kinetic and Gene Expression Help Figuring out further Understanding of Acute Oedematous Pancreatitis?

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Context In some cases of edematous form of acute pancreatitis (AP) the clinical course seems to follow pathophysiological mechanisms to be fully predicted and unfolded as yet. In virtually all cases, marked edema of the parenchyma is observed and such changes are displayed by the classical experimental cerulein-induced AP. Aquaporins (AQPs) are widely distributed in mammals and represent a family of membrane proteins controlling water channel, regulating cellular permeability and transport in health as well as in disease. To the best of our knowledge, there is a paucity of data regarding AQP status in acute pancreatitis. **Objective** The aim of the present investigation was to study and to monitor AQP localization and functional genomic expression in early cerulein-induced AP in view of getting further insights into their possible role in phenotypic expression of the disease. **Methods** Male Wistar rats weighing 200-230 g and aged 8 months were housed in individual cages in an environmental-controlled vivarium. Under phenobarbital anaesthesia 10 µg/kg/h of cerulein was infused for 3 h to induce AP and sacrifices were made at 3 h and 72 h afterwards. Pancreases were excised and examined for histology. In particular, the expression of AQP1 and AQP8 was examined by specific RT-PCR (AQP1: 5'-CTGGGTGGGACCATT

CATTG-3' and 5'TGCGGTCTGTAAAGTCGC TG-3'; AQP8: 5'-GCCTAATGAGCAGTCCCACAA-3' and 5'-TGGATCTCACTGGCTGGGCCAGCTC-3'). **Results** Control pancreases showed AQP1 and AQP8 localized in pancreatic ductal cells together with capillary endothelia and in acinar cells, respectively. During early phase (3 h) of AP, AQP1 expression significantly decreased in all sites and further worsened later on (72 h) despite overall histological improvement of AP. The same pattern was observed with AQP8 at 3 h but this level remained stable at 72 h observation. On the other hand, immunoblot showed unchanged band densitometry for protein level of AQP1 but decreased for AQP8 (at 3 h and 72 h). At immunohistochemistry AQP1 disappeared in ductal cells (looking normal at histology) but strongly increased in capillary endothelia. AQP8 disappeared in the apical membrane of acinar cells at 3 h but less than 50% was detected at 72 h. **Conclusion** The gene expression/protein level discrepancy noted for AQP1 and AQP8 are likely due to different turnover and half-life. On the other hand, "normal" histology may still hide significant prolonged epigenomic abnormalities which warrant further studies aimed in view of possible implication for the clinical course of AP.

Serum and Urine Trypsinogen Activation Peptide in Assessing Post-ERCP Pancreatic Damage

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Context Trypsinogen activation peptide (TAP) is a small peptide capable of activating trypsinogen into trypsin which, in turn, is able to activate all other proteolytic enzymes secreted by the pancreatic gland. TAP therefore reflects the amount of activation trypsinogen, not taking into account how much trypsin is active or linked to specific inhibitors. TAP is released into the peritoneal cavity and circulates after which the peptide is rapidly metabolized in the kidney and excreted in the urine. It seems logical that the greater the quantity of trypsinogen activated, the more the pancreas is damaged. We have previously reported that in patients undergoing therapeutic ERCP, the serum TAP concentrations determined before and 6 hours after the execution of the endoscopy did not differ and this phenomenon may be due to the fact that the half-life of TAP is about 8 minutes; thus, it is possible that the 6-hour interval is too long to detect any alteration of serum TAP. **Objective** To evaluate serum and urine TAP concentration hourly after ERCP and to establish its role in the early diagnosis of post-procedural acute pancreatitis (AP); exploring whether the administration of gabexate mesylate (GM) could prevent the activation of trypsinogen by blocking trypsin activation. Serum trypsinogen was also assayed

in the same serum samples. **Patients and Methods** Seventy-five patients were enrolled in the study and 81.3% of them received GM. Post-procedural mild AP developed in 13 patients (17.3%) (19.7% of patients who received GM and 7.1% of those who did not; P=0.440). **Results.** In the 65 patients who completed the study, 2-hour post-ERCP serum TAP concentrations were elevated (P=0.034 vs. pre-ERCP) whereas these concentrations significantly declined at 4 hours (P=0.006). Urine TAP showed a similar behavior. Mean serum trypsinogen concentrations were slightly below the upper reference limit before ERCP and then significantly increased thereafter. Serum and urine TAP levels, as well as serum trypsinogen concentration, showed no significant differences between patients who developed AP and those who did not. Within the group of the patients who received gabexate mesylate, serum TAP concentrations were significantly lower at 1 and 2 hours after ERCP in the patients who developed AP (P=0.033 and P=0.041, respectively). **Conclusions** Serum and urine concentrations of TAP are detectable very early in patients who undergo ERCP examination, i.e. within the first 6 hours. TAP determination is of limited value in assessing pancreatic damage.

Role of CCL2/MCP-1 in Islet Transplantation

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Context High levels of donor-derived CCL2/MCP-1 have been associated with poor islet allograft outcome in patients with type 1 diabetes. **Objective** The aim of our work was to determine whether CCL2/MCP-1 secreted by the islet has independent pro-inflammatory effects that influence engraftment and graft acceptance. **Research Design and Methods** A mouse model of syngeneic intraportal islet marginal mass transplantation in which CCL2^{-/-} mice were used alternatively as islet donors or recipients was established to determine whether donor and/or recipient CCL2/MCP-1 affected islet function post

transplant. In man, we analyzed the relationship of islet CCL2/MCP-1 and/or post islet transplant inflammation (CRP concentration) to islet function post transplant in 30 patients with type 1 diabetes who received a single islet infusion obtained from single donor. **Results** Both in mouse and human CCL2/MCP-1 is significantly positively associated with other cytokines/chemokines, in particular with the highly released "pro inflammatory" IL-6 and CXCL8/IL-8 or CXCL1/KC. Transplantation of CCL2^{-/-} islet into syngenic recipients did not improve the transplant function. Transplantation of islet into CCL2^{-/-} syngenic

recipients led to a significant improvement of transplant function and partial abrogation of local hepatic inflammation. When evaluated in human islet, CCL2/MCP-1 release was strongly related to the immediate local inflammatory response in the liver and impacted short-term human islet function dependently by the induced inflammatory response and independently by the immunosuppressive therapy.

Conclusions The data showed that islet CCL2/MCP-1 release is a sign of “inflamed” islets without having a direct role in graft failure. On the other hands, a causal effect for developing detrimental pro-inflammatory conditions after transplant was proved for recipient CCL2/MCP-1. Strategies to selectively decrease recipient, but not donor, CCL2/MCP-1 release may increase the success of islet transplantation.

Rapamycin Does not Adversely Affect Intrahepatic Islet Engraftment in Mice and Improves Early Islet Engraftment in Human

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Objective In this study we examined the effect of rapamycin (RAPA), a key component of the immunosuppressive regimen in clinical islet transplantation, on islet engraftment and function *in vivo*. **Methods and Results** Diabetic C57BL/6 or BALB/C recipient mice were transplanted with 350 syngeneic islets through the portal vein (PV-Tx; C57BL/6, n=60; BALB/C, n=22) and treated with once-daily oral RAPA (1 mg/kg) or vehicle. No differences in post-transplant blood glucose concentrations and glucose tolerance were observed between RAPA- and vehicle-treated mice. The impact of RAPA on human islet engraftment was assessed in 10 patients with type 1 diabetes treated with 0.1 mg/kg/day rapamycin before islet transplantation.

Compared to non pre-treated islet transplant recipients (n=12), RAPA pre-treated patients had increased blood RAPA concentrations (P=0.006) and fasting C-peptide concentrations (P=0.005) in the two weeks post-transplant. RAPA pre-treatment was associated with a reduction in chemokines CCL2 and CCL3 concentrations pre-transplant (P<0.01), and a dampened chemokine response (P=0.005) post-transplant. Concordantly, *in vitro* RAPA inhibited the secretion of CCL2 and CCL3 by monocytes. **Conclusion** Rapamycin does not adversely affect intrahepatic islet engraftment in the mouse, and potentially improves islet engraftment in humans by an anti-inflammatory mechanism.

Total Pancreatectomy with Islet Autotransplantation after Pancreaticoduodenectomy with Complications: Two Case Reports

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Context Pancreaticoduodenectomy is the treatment of choice for patients with resectable disease of the pancreatic head or periampullary region. The leakage of the pancreaticoenterostomy remains the major cause of death or complications, especially in cases with soft pancreas and pancreatic duct diameter ≤ 3 mm. When a re-laparotomy is indicated, completion of pancreatectomy is a surgical option, but it is unfrequently performed, owing to the fears of brittle postoperative diabetes. We report our experience of two cases of completion of pancreatectomy, after pancreaticoduodenectomy, with islet autotransplantation. **Case Reports** Case 1. A 60-year-old male underwent pancreaticoduodenectomy for adeno-

carcinoma; a biliary-pancreatic leakage was observed in the first postoperative day and he was initially treated conservatively by the placement of a percutaneous biliary drainage. Later, when the patient developed a septic state, he underwent reoperation: completion of pancreatectomy with intraoperative islet autotransplantation was performed. The following postoperative stay was regular; antibiotic therapy was administered based on a pancreatic specimen’s positive cultural exam. The patient’s daily insuline requirements are only 4 insulin units after 6 months. Case 2. A 48-year-old male underwent a pancreaticoduodenectomy for a well differentiated neuroendocrine carcinoma of the ampulla, complicated by a low output

pancreatic fistula. Three weeks after surgery, when the patient was already discharged without drainage, a gastrointestinal bleeding occurred so he underwent a reoperation: bleeding from a pseudoaneurysm originating from the ligated gastroduodenal artery was found and hemostasis performed but the flogistic state of the residual pancreas did not allow to fashion a new pancreatic anastomosis, so completion of

pancreatectomy was performed; the islet equivalents were isolated and infused in the liver after 24 hours through transhepatic portal vein catheterization. The following postoperative stay was regular. After 5 months the patient is insulin independent. **Conclusions** Total pancreatectomy with islet autotransplantation is safe and can be performed successfully for complications after pancreaticoduodenectomy.

Ukrain (NSC 631570) in the Treatment of Pancreatic Cancer

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Context Ukrain (NSC 631570) is a promising agent for the therapy of pancreas cancer. In the tests with pancreas cancer cell lines Jurkat, MiaPaCa2, AsPC1, BxPC3 und THP-1, ukrain had a strong inhibiting effect on these cell lines. The mitotic analysis revealed mitotic arrest of cancer cells in the prophase and/or metaphase. **Survey of Clinical Studies** First clinical studies confirmed the efficacy of ukrain in the treatment of pancreas cancer. A total of 28 pancreas cancer patients with pancreatic adenocarcinoma were treated with ukrain in an open study. All the patients presented with advanced and/or metastatic disease that made curable radical surgery impossible. Ukrain was administered at a dose of 20 mg three times a week for the first three months and then at a dose of 20 mg once a week for 4 months (total dose: 320 mg). Partial remission was achieved in 24 cases (85.7%) while four patients (14.3%) did not respond to treatment. The mean survival of the patients treated with ukrain was 26.1 months. Two randomized trials have been performed so far to study the effectiveness of ukrain in the treatment of patients with unresectable pancreatic cancer. A total of 42 patients with pancreas cancer received, after palliative surgery, either NSC 631570 combined with vitamin C or vitamin C alone. Median

survival was more than twice as long in the group treated with NSC 631570 than in the control group (18.8 vs. 6.4 months); 5 of 21 patients survived 3 years, 1 patient is still alive after 5 years. In another controlled clinical trial, a total of 3x30 patients with histologically proven unresectable adenocarcinoma of the pancreas were treated either with gemcitabine (arm A), NSC 631570 (arm B), or a combination of NSC 631570 plus gemcitabine (arm C). Median survival was significantly longer in the groups B and C compared with the group A (5.2 months, 7.9 months, and 10.4 months in groups A, B, and C, respectively; $P < 0.01$); the 12-month survival rate was 13%, 29%, and 32% in groups A, B, and C, respectively. In arm A, nausea seemed to be more frequent than in arm B and C, whereas in arm B and arm C fever was observed more frequently. In arm C hematological toxicities WHO II occurred significantly more frequently than in arm A and arm B. Increases in liver enzymes occurred in all three arms in the same frequency and were related to stent occlusion or disease progression of hepatic metastases. **Conclusion** Further clinical trials should reveal the best combination therapy modalities for ukrain.

Diffusion-Weighted Magnetic Resonance Imaging (DWI) of Pancreatic Focal Qualitative and Quantitative Assessment

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Context Non-invasive differential diagnosis of pancreatic focal lesions still represents a challenge. High contrast resolution of MRI can be improved using DWI, a supplemental tool to measure water diffusivity which can vary in tumors respect to normal glandular tissue. **Objective** We set up a high b value DWI sequence on 42 patients with pancreatic focal lesions already detected with CT and endoscopic ultrasound, to assess its diagnostic performance. **Methods** Diffusion-weighted respiratory-triggered and free-breathing

(DWIBS) MRI of upper abdomen using a b factor of 600 was performed in 42 patients with a total of 48 lesions: 31 adenocarcinomas, 5 neuroendocrine carcinomas, 7 various cystic lesions, and 5 pancreatitis (including 4 autoimmune). Qualitative assessment was performed on diffusion-weighted images, while quantitative assessment was obtained tracing peritumoral ROIs on apparent diffusion coefficient (ADC) maps. **Results** Qualitative DWI was feasible and well tolerated in all patients using respiratory

triggering, with all solid lesions (ranging from 5 mm to 10 cm) clearly visible as hyperintense on b=600 images. Also DWIBS correctly depicted all lesions with good quality PET-like images, excepted for typical false positives due to hyperintensity of intestinal fluid, lymph nodes and spleen. With quantitative DWI only slight differences in mean ADC values between different solid masses were seen (adenocarcinoma: 1.52 mm²/s; neuroendocrine: 1.43 mm²/s; pancreatitis: 1.22 mm²/s; P NS); cystic lesions showed a significantly higher mean ADC than solid (3.45 mm²/s), as expected. **Conclusion** Qualitative

DWI has a high diagnostic sensitivity in pancreatic focal disease, regardless its nature, and may improve visibility of very small lesions, because it enhances visibility of most pancreatic focal lesions compared to morphological MR sequences. Quantitative DWI seems not to offer significant additive value in lesion characterization due to inconspicuous differences in ADC values, especially between solid tumors and pancreatitis; in cystic lesions different ADC values may reflect different fluid composition (serous vs. mucinous).

The Pancreatic Cancer Derived S100A8 N-Terminal Peptide Augments Intracellular Ca²⁺ Oscillations and Insulin Release

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Context S100A8 N-terminal peptide (NT-S100A8) was isolated by us from pancreatic cancer (PC) tissue.

Objective We verified whether NT-S100A8 alters: i) PC cell growth and invasion; and ii) insulin release and intracellular Ca²⁺ ([Ca²⁺]_i) oscillations of insulin secreting cells. **Methods** BxPC3, Capan1, MiaPaCa2, Panc1 (human PC cell lines), beta-TC-6 (mouse insulinoma cell line). PC cell growth (trypan blue) and invasion (matrigel) were assessed in the absence (control) or presence of 50, 200 and 500 nM NT-S100A8. In control and NT-S100A8 stimulated beta-TC-6 culture medium, insulin (RIA) and Ca²⁺ (gas analyzer) were measured at 2, 3, 5, 10, 15, 30 and 60 minutes. [Ca²⁺]_i oscillations of control, 50 and 500 nM NT-S100A8 stimulated beta-TC-6 was monitored (Fluo-4, epifluorescence microscopy) for three minutes. **Results** Five-hundred nM NT-S100A8 stimulated BxPC3 cell growth only (F=3.7, P<0.05). NT-S100A8 dose dependently enhanced Capan1 (chi-

squared=16.9, P<0.01), reduced MiaPaCa2 (chi-squared=24.7, P<0.001) and Panc1 (chi-squared=16.0, P<0.05) invasion. Five-hundred nM NT-S100A8 induced a rapid (2 minutes) and persistent (further 3 minutes) insulin release (F=3.01, P<0.05). The same dosage enhanced beta-TC-6 [Ca²⁺]_i oscillations both after one (F=6.05, P<0.01) or two minutes (F=7.42, P<0.01). The mean difference±SE between the number of [Ca²⁺]_i spikes recorded one minute after and one minute preceding NT-S100A8 stimulation were: -0.24±0.6, 1.16±0.6, and 3.4±0.6 spikes/min for control, 50, and 500 nM stimulated cells. In the medium [Ca²⁺]_i significantly decreased with respect to control cells (F=6.3, P<0.01). **Conclusions** i) NT-S100A8 exerts a mild effect on PC cell growth, while it both enhances or reduces PC cell invasion, responses being cell line specific; ii) NT-S100A8 enhances [Ca²⁺]_i oscillations and insulin release, probably by inducing Ca²⁺ influx from the extracellular space.

Resume of Work after Distal Pancreatectomy: Laparoscopic Approach Is Better. A Single Institution Comparative Study in 116 Patients

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Context An increasing number of patients with pancreatic neoplasms can now be managed by laparoscopic distal pancreatectomy. **Objective** Aim of this study was to compare perioperative and long-term outcomes of laparoscopic distal pancreatectomy (LDP)

with open distal pancreatectomy (ODP). **Methods** Between 2000 and 2006, all patients with benign neoplasms of the pancreatic body/tail were addressed to LDP or ODP according to the choice of two experienced pancreatic surgeons (CB and PP). All the

procedures were performed at the Pancreatic Unit of Verona. The laparoscopic resections were executed by two surgeons (GLM and GB). All perioperative data were prospectively collected and patients were followed up. Multivariate analysis was performed using binary logistic regression. **Results** Seventy-three (62.9%) patients underwent ODP and 43 (37.1%) LDP. Overall mortality was nil. In the comparison there were no differences between ODP and LDP group in median operative time (180 vs. 180 minutes), overall complications (45.2% vs. 48.2%), pancreatic fistula rates (13.7% vs. 27.9%), fluid collections (16.4% vs. 18.6%), re-explorations (9.6% vs. 9.3%), length of hospital stay (9 vs. 8 days), postoperative diabetes

(30% vs. 22.5%) and incisional hernia (17.4% vs. 5%) . LDP patients had a higher incidence of spleen-preserving procedures (44.2% vs. 11%; $P<0.0001$), a shorter median time to resume work (3 vs. 6 weeks; $P<0.0001$) and postoperative exocrine insufficiency (0% vs. 10.3%; $P<0.05$). By multivariate analysis, LDP was an independent factor for shorter resume to work (odds ratio 0.05; 95% confidence interval 0.01-0.25). **Conclusions** Overall morbidity and pancreatic fistula rates are similar for LDP and ODP. LDP is associated with a shorter time to resume work and this should be considered in the cost effectiveness analyses in future clinical trials.

Hypofractionated Radiotherapy with Tomotherapy Concomitant to Chemotherapy in Pancreatic Adenocarcinoma. Early Results of a Phase I Study

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Context Even after the most active chemoradiation regimens, R0 or R1 resections of initially unresectable pancreatic adenocarcinoma (PA) are infrequent. The use of higher radiation dose is limited by the radio-sensitivity of surrounding organs such as duodenum. It was decided to administer a standard dose to the tumor and higher doses to a tumor sub-volume (TSV) infiltrating the vessels. **Objective** To evaluate the feasibility of hypofractionated radiotherapy with simultaneous integrated boost (SIB) at escalating doses to a TSV infiltrating vessels, concomitant to chemotherapy. **Methods** Twenty-nine patients with PA were treated after 4-6 cycles of chemotherapy. Median age: 60 years; stage III: 23 patients; stage IV or local relapse: 6 patients. Two targets were defined: the tumor and a TSV 1 cm around the infiltrated vessels. Radiation therapy was delivered with tomotherapy. Sixteen patients were enrolled in the phase I study: the tumor received a fixed dose of 44.25 Gy, whereas the TSV received an escalating dose with SIB (48 Gy: 4 patients; 50 Gy: 6 patients; 52 Gy: 3 patients; 55 Gy: 3 patients) in 15 fractions (SIB group). During the

planned observational periods of 3 months between successive dose levels, 13 additional patients were treated off-study with 44.25 Gy in 15 fractions only to the tumor (no SIB group). Concomitant 5-FU, 250 mg/m²/day c.i., was delivered in 6 patients; 23 patients received capecitabine, 1,250 mg/m²/day. **Results** Toxicity. 28/29 evaluable patients. G1-G2: diarrhea 21%, N/V 46%, abdominal pain 25%, anorexia 14%, neutropenia 7%. Two patients (7%) had G3 toxicity: gastric ulcer (1 patient at 48 Gy) and gastro-duodenitis (1 patient at 55 Gy). Responses. SIB group: 15/16 evaluable patients, PR 27%, SD 53%, PD 20%. No SIB group: 13/13 evaluable patients, CR 7%, PR 31%, SD 31%, PD 31%. Median TTP, median TTLP and median survival for all patients were 11.6, 14.9 and 18.2 months, respectively. **Conclusions** The phase I study is ongoing. Once the maximum tolerated dose is reached, the efficacy of higher dose on TSV will be tested in a phase II study. A dose of 44.25 Gy in 15 fractions to the tumor, concomitant to 5-FU c.i. or capecitabine, is feasible and seems to provide a promising response rate.

Planning Design of Locally Advanced Pancreatic Carcinoma (LAPC) Using Four Dimensional Computed Tomography (4DCT) Technique and Tomotherapy (TT)

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Context The impact of organ motion has to be taken into account in the definition of the target in external

radiotherapy. 4DCT is a new technique to assess organ motion due to respiration. Daily image-guidance with

TT permits to adjust patient positioning in order to take set-up and motion uncertainties into account at each fraction; furthermore it performs an highly conformational dose distribution. **Objective** To study the impact of 4DCT imaging on conventional 3 dimensional-conformal RT (3DCRT) planning and to compare 3DCRT with TT plans in LAPC. **Methods and Materials** Contrast-enhanced 4DCT scans were performed in 15 patients. Four series of images corresponding to two extreme and two intermediate respiratory phases were generated for each patient. 4DCT based planning target volumes PTVs (4DPTVs) were created by the union of gross tumor volumes (GTVs) contoured on the four series of images plus a margin of 0.5 cm. Standard PTVs (STPTVs) were derived from a GTV contoured on an intermediate phase plus a standard margin of 1-1.5 cm. Two 3DCRT plans, one on 4DPTV, the other on STPTV, and a TT plan on 4DPTV were optimized to deliver 60

Gy in 30 fractions. 4DPTVs vs. STPTVs 3D-CRT plans, and TT vs. 3DCRT plans (on 4DPTVs) were compared. **Results** 4DPTVs resulted smaller than STPTVs in all patients with an average volume reduction of 37%. The overlaps between PTV and stomach/duodenum were reduced by an average of 61% and 42%, respectively, when comparing 4DPTV vs. STPTV. Consequently, 3DCRT plans on 4DPTV better spared healthy organs: the fraction of duodenum and stomach receiving more than 50 Gy decreased on average by about 8 cm³ and 18 cm³, respectively. TT allowed a further sparing compared with 3DCRT when considering 4DPTV: in the intermediate-high dose region (20-55 Gy) the mean sparing was about 8 cm³ for both organs. **Conclusions** The use of 4DCT technique decreases the unnecessary irradiation of healthy tissues next to the pancreas. TT allows a further sparing of stomach and duodenum both at intermediate and high dose levels.

Pancreatic Metastases from Melanoma: Outcomes of Five Consecutive Pancreaticoduodenectomies in a Single Institution

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Context Patients with metastases from melanoma usually present widespread systemic disease at the time of diagnosis contraindicating surgery. However, in case of limited disease amenable to resection surgery may be indicated. Pancreas is a rare metastatic site and in literature only 12 cases of pancreatic resection for isolated metastases from melanoma have been reported to date. **Objective** The aim of this study was to report the outcomes of five consecutive cases of metastatic melanoma to the pancreas that underwent pancreatic resection in a single institution. **Methods** We retrospectively identified patients from the San Raffaele Scientific Institute Pancreatic Surgery database who underwent pancreatic resection for pancreatic metastases from melanoma between August 2005 and February 2009. **Results** Five patients were identified, three males and two females, with a median age of 48 years. Two patients had a history of skin melanoma previously subjected to surgery (both with lymph node involvement), one had a history of choroidal melanoma. The median time from resection of the primary lesion was 30 months. Two patients had no history of melanoma. All but one patient were symptomatic at presentation; three of them presented with jaundice, two with abdominal pain, one with

nausea and asthenia. All patients had a pancreatic lesion identified by CT scan; preoperative cytological diagnosis was obtained in two cases by EUS-guided FNAB, in the other three cases preoperative diagnosis of pancreatic neoplasm was formulated. In four patients the lesion was located in the head of the pancreas, and in one it originated from the duodenum infiltrating pancreatic head. All patients underwent pancreaticoduodenectomy. In two cases an associated procedure was necessary (in one case liver metastasectomy and subcutaneous lesion removal, in another patient removal of two subcutaneous lesions). All patients were apparently disease-free at the end of surgery. Three patients developed postoperative complications: two patients experienced pancreatic leakages, one a biliary fistula. No postoperative mortality was observed. Three of the five patients died for early progression at 3, 5, and 12 months after surgery (two liver metastases and one local relapse). The other 2 patients are disease free at 6 and 7 months after surgery. **Conclusions** Patients with pancreatic metastases from melanoma have a poor prognosis, however, owing to the limited results of systemic therapy, resection should be considered as a reasonable option in selected cases.

Follow-up of Patients with Acute Recurrent Pancreatitis and not Dilated Pancreatic Ducts by Repeated EUS

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Context EUS is nowadays considered the imaging reference procedure in the diagnosis and follow-up of chronic pancreatitis (CP) due to its capability to detect both ductal and parenchyma changes, often not detectable by other procedures. For these reasons, in patients with suspected CP, as those with acute recurrent pancreatitis (ARP) without apparent lesions, EUS can be proposed for detecting and monitoring CP signs. **Objective** To investigate signs of chronic pancreatitis by repeated EUSs in patients with ARP and not dilated pancreatic ducts. **Patients and Methods** All patients between 2006 and 2009 with almost two episodes of acute pancreatitis (ARP) without chronic pancreatitis or pancreatic malignancies by an abdominal US, CT and/or MR and submitted to almost two EUSs were included in the study. EUSs were performed using linear echoendoscopes and were repeated with a delay time of one year. For diagnosing CP the following EUS abnormalities were evaluated: main pancreatic duct irregularity, main pancreatic duct dilation, visible side branches, hyperechoic duct walls,

cysts, stones (ductal abnormalities); hyperechoic foci, hyperechoic strands, hypoechoic lobules, atrophy (parenchymal abnormalities). CP was defined when a total of ≥ 4 EUS pancreatic abnormalities were detected. **Results** Twenty-one ARP patients, 8 women and 13 men with a mean age of 52.9 years (range: 27-79 years) were evaluated during a mean time between the first and last EUS of 23.3 months (range: 10-38 months). The mean number of EUS performed in each patient was 2.6 (range: 2-4). The diagnosis of CP was made in 3/21 patients (14.3%) by the first EUS, in 3 of the remaining 18 patients (16.7%) by the second EUS. By this second EUS section 2/18 had IPMT and were excluded from the study. Comparing the second with the first section the number of patients with ≥ 3 EUS abnormalities increased from 16.6% (3/18) to 56.25% (9/16) ($P=0.03$). No changes in the number of EUS abnormalities were observed at the third and fourth section. **Conclusion** The medium-term follow-up of patients with acute recurrent pancreatitis by repeated EUS is useful to identify early signs of CP.

Serum Leptin, but no Adiponectin and RAGE, Is Able to Distinguish between Chronic Benign and Malignant Pancreatic Diseases

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Context Serum leptin and adiponectin determinations have been proposed as markers for distinguishing pancreatic cancer and chronic pancreatitis; however, no studies exist in patients with autoimmune pancreatitis and in those with intraductal papillary-mucinous tumors of the pancreas (IPMT). No data are for the serum levels of receptor for advanced glycation end products (RAGE) available in patients with chronic pancreatic diseases. **Objective** To evaluate the circulating concentrations of leptin, adiponectin, and RAGE in patients with chronic pancreatic diseases. **Patients** Seventy-five subjects (47 males, 28 females, mean age 67.0 ± 13.2 years; range: 37-97 years) were studied: 6 patients (8.0%) had autoimmune pancreatitis, 23 patients (30.7%) had chronic pancreatitis, 34 (45.3%) had pancreatic cancer, and the remaining 12 (16.0%) had IPMT. **Methods** Leptin, adiponectin and RAGE were determined on serum using commercial kits (R&D Systems, Minneapolis,

MN, USA). The leptin concentrations were normalized to the lower and upper reference limits because of the different gender reference ranges. **Results** Normalized leptin concentrations were significantly lower in chronic pancreatitis patients (0.53 ± 1.28 ; $P=0.008$) and in those with pancreatic cancer (0.12 ± 0.33 ; $P<0.001$) as compared to the overall population (0.58 ± 1.23) whereas autoimmune pancreatitis patients had significantly higher concentrations of this protein (2.18 ± 2.56 ; $P=0.004$) as compared to the overall population. Adiponectin and RAGE concentrations were similar among the four groups of patients studied. Among the clinical variables, pain alone was significantly related to the normalized leptin concentrations (patients with pain 0.18 ± 0.54 ; patients without pain 1.07 ± 1.64 ; $P=0.001$). **Conclusions** Serum leptin seems to be a good marker for differentiating autoimmune pancreatitis patients from those with chronic pancreatitis and pancreatic cancer.

Risk Factors, Clinical Features and Outcome of Early Onset Pancreatic Cancer Subjects Compared to Older Patients

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Context The median onset age of pancreatic adenocarcinoma (PADC) is >60 years but 5-10% of patients are diagnosed <50 years, and defined as early onset pancreatic cancer (EOPC). Risk factors, clinical presentation and outcome of EOPC have not been investigated specifically, nor compared to those of older PDAC patients, but a role for smoking and genetic syndromes have been hypothesized. **Objective** To analyze the prevalence of EOPC and its risk factors, features, clinical presentation and outcome compared with PDAC patients aged >50 years. **Methods** Prospective cohort (May 2006 to May 2009) of PDAC patients. All were administered a questionnaire about familial, medical and environmental risk factors and disease presentation. We also analyzed histological features, tumor stage, and survival. The differences between EOPC (<50 years at diagnosis) and older PDAC patients (controls) were assessed through appropriate statistics. **Results** Amongst 88 PDAC patients, 9 were EOPC (10.2%). There were no significant differences for sex distribution, BMI before diagnosis (median 27 kg/m² in both), alcohol intake nor for family history (FH) of any cancer. One EOPC (11.1%) patient and 4 controls (5%) had PDAC 1st degree FH. There were no cases of genetic syndromes associated with PDAC in EOPC cases. EOPC group

had a higher rate of smokers (77.7% vs. 54.4%) and heavy (pack/year 20) smokers (55.5% vs. 32.9%) than the controls, albeit without a significant difference. None of the EOPC and 36/79 controls (18 in the 12 months before diagnosis) reported diabetes. EOPC patients had a more advanced disease at diagnosis with distant metastases in 7 (66.6%) vs. 30 (37.9%) of controls (P=0.05). Tumor was in the head in 66.6% of EOPC vs. 86% of controls in which, accordingly, jaundice was more frequent (44.3% vs. 11.1%). Two EOPC (22.2%) vs. 30 controls (37.9%) received surgery with radical intent. Survival was similar at 6 (77.7% EOPC vs. 50.7%), 12 (37%, vs. 24.1%) and 24 months (0 vs. 6.9%). **Conclusion** Our results confirm that 10% of PDAC are EOPC, and suggest that smoking may be a risk factor for EOPC, while we did not find a high prevalence of genetic syndromes for which a screening could have been indicated. Importantly, some 2/3 of EOPC present with metastatic disease at diagnosis, and with different symptoms also possibly supporting the case for a different biology. The study is ongoing to confirm these hypotheses in a wider population and investigate whether any peculiar features of EOPC may help in identifying subjects to be screened for minimal or pre-invasive tumors.

Robotic Cyst-Jejunostomy (and Cholecystectomy) for the Treatment of Pancreatic Pseudocysts: A Case Report

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Context Pancreatic pseudocysts represent one of the most frequent complications in patients with a history of acute pancreatitis. The interventional treatments for pancreatic pseudocysts are reserved to symptomatic patients, with high volume and/or complicated lesions and when a very quick growth is observed. Mostly of the cases are treated by endoscopic approach or by traditional "open" surgery. In the last years the improvement of laparoscopic era, first, and then the development of more sophisticated minimally invasive techniques, created the basis for a new era in pancreatic surgery. Recently with the Da Vinci Surgical System[®] more complicated operations, in which a reconstructive

phase is necessary, are easier approached by minimally invasive techniques. **Case Report** We describe a case of a 68-year-old male patient affected by pancreatic pseudocyst with a personal history of two episodes of biliary acute pancreatitis. The first episode of mild acute pancreatitis occurred on February 2009, when the patient was treated with a conservative therapy until the following month when another episode occurred and the patient was cured in the same way. A CT scan demonstrated a pseudocyst localized at the pancreatic body 18 cm in diameter. An MRCP showed gallbladder stones but was negative for gallstones in the biliary tree. Due to size and symptoms (pain) of the patient, a

surgical drainage was decided. We performed an Roux-an-Y cyst-jejunostomy and colecystectomy by totally robotic approach with 5 trocars incisions. The intraoperative blood loss was negligible. The operative time was 6 h. The cyst-jejunostomy and the jejunojejunostomy were totally done by robotic approach. No drainage was used. No complications occurred during surgery. The post-operative course was uneventful except for presence of fever from the second to the sixth post-operative day, in absence of

abdominal fluid collections, as demonstrated by ultrasound controls and without a significant leukocytosis. Fever was treated with paracetamol. The patient was discharged on the 8th post-operative day. One month after surgery the patient was in good conditions and painless. **Conclusion** This is a report of another possible application of robotic surgery in pancreatology. However, the advantages of this kind of approach would be demonstrated by prospective studies.

Intraductal Papillary Mucinous Neoplasm: A Pathological Study of “Minimal Invasion”

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Context Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a disease entity characterized by intraductal growth of mucinous cells, abundant mucin production, and subsequent cystic dilatation of pancreatic ducts. IPMN displays a spectrum of histological findings and has got the potential for malignant transformation developing from adenoma to invasive carcinoma. Noninvasive IPMNs were classified as “adenoma”, “borderline”, or “carcinoma” depending on the degree of dysplasia within the lesion. Carcinomas are also classified as “noninvasive” or “invasive” and it is reported that noninvasive IPMN shows a favourable postoperative outcome in comparison with invasive ones. Recently, the Japan Pancreatic Society classified intraductal papillary mucinos carcinoma (IPMC) into minimally invasive IPMC (MI-IPMC) and invasive carcinoma originating in IPMC (IC-IPMC), the latter being more advanced with a worse surgical outcome. However, the pathological definition of “minimally invasion” has not been made clear and only Nara *et al.* [1] in the English literature tried to define criteria of minimal invasion. According to Nara, IPMN is characterized by prominent mucous secretion into the lumen that sometimes spills out forming a mucous lake around the pancreatic duct, due to rupture of the dilated duct

occupied by mucin (mucous rupture). This is diagnosed as minimal invasion if mucous lakes are not associated with mucinous carcinoma showing evident infiltrative growth findings. **Objective and Methods** We evaluated all cases of IPMN diagnosed in our department applying the Nara’s criteria and using seriated sections of the most representative areas in order to verify their reproducibility. **Results** Five cases of IPMN with mild or severe dysplasia characterized by periductal mucous lake with or without few floating dysplastic cells were observed. These mucous lakes are not a clear expression of minimally invasion but rather of ductal rupture due to high pressure caused by the hypersecreted mucin following by inflammatory and/or fibrous reaction. As well as similar aspects of mucinous neoplasms of other sites (ovary, breast, etc.) we think that some of these mucous lakes are better defined as pseudo-infiltration rather than real, although minimal, invasion. **Conclusion** Despite this definition histological validation and diagnosis of MI-IPMC remains up to now a challenge to the pathologists.

Reference

1. Nara S, Shimada K, Kosuge T, Kanai Y, Hiraoka N. Minimally invasive intraductal papillary-mucinous carcinoma of the pancreas: clinicopathologic study of 104 intraductal papillary-mucinous neoplasms. *Am J Surg Pathol* 2008; 32:243-55. [PMID 18223327]

PES-003, a New Pro-Drug for Pancreatic Cancer Therapy

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Context Pancreatic cancer continues to be a leading cause of cancer death in the Western world. Depending

on the extent of the tumor at the time of diagnosis, the prognosis is generally regarded as poor, with a median

survival of 6 months. Gemcitabine is the current standard of care for metastatic and non resectable cancers. New promising drugs have failed in phase II/III trials in demonstrating efficacy compared to gemcitabine alone, prompting the need of the identification of new chemotherapy agents. The suicide gene therapy with adenovirus carrying the viral thymidine kinase gene and the aciclovir analogue ganciclovir has been extensively applied in *in vitro* studies against various type of tumours and among them pancreatic cancer. The main advantage of this putative therapy is the specificity for the cancer cells given by virus tropism and the lower toxicity, compared to gemcitabine, due to the use of a pro-drug to be activated inside the infected cells; however, this approach is undermined by the risk linked to the use of the same virus on which the strategy is based upon. Interestingly, 90% of pancreatic tumors show telomerase activity and telomerase expression correlates with the tumor staging. We decided to exploit this property, maintaining the specificity for cancer cells, creating a thymidine analogue pro-drug,

PES-003, that after being metabolised by telomerase release an activated form of aciclovir. **Objective** The aim of this study is to evaluate the efficacy of pancreatic cancer treatment with PES-003 *in vitro* and *in vivo*. **Methods** Cell viability and proliferation of pancreatic cancer cells treated with PES-003 were evaluated by WST1 and Br-dU assay. Presence of PES and its metabolites inside the cells were evaluated by mass spectrometry analysis. *In vivo* efficacy of PES-003 was evaluated in nude mice carrying xenograft tumors of various cell lines. **Results** The pro-drug is actively metabolised inside the cells; furthermore treated cells showed a reduction in proliferation and viability correlated with cell telomerase activity. Xenograft tumors treated with PES-003 show a reduced growth with a T/C index ranging from 0.5 to 0.7 depending on the cell line; immunohistochemistry analysis demonstrated that this effect is mainly due to increased apoptotic levels. **Conclusions** The data presented indicate that PES-003 is active against human pancreatic cancer cell lines *in vitro* and *in vivo*, mainly by inducing proliferation arrest and apoptosis.

Successful Percutaneous Drainage of Post-Acute Pancreatitis Pseudocyst

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Context Severe acute pancreatitis (AP) is a common cause of pseudocysts. Treatment is indicated when they become symptomatic, in phase of growth or complicated. **Case Report** We report a case of severe AP complicated by a large pseudocyst treated with percutaneous drainage. A 41-year-old man was admitted in our hospital do to an attack of severe AP. Aetiology was hyperlipidaemia (BMI: 42 kg/m² and serum triglyceride level >600 mg/dL). Contrast-enhanced CT showed a large necrosis of the pancreatic body and tail with peripancreatic fluid collections. Treatment of pancreatitis in ICU consisted of oxygen, nasogastric tube, CVC infusion of fluid, gabexate mesilate, somatostatin, meropenem, PPI, albumin, LMW heparin, and analgesics. In the second week the patient had recurrent hyperpyrexia. *Staphylococcus haemolyticus* was cultured from the removed CVC. A treatment with vancomycin was started with complete remission of the fever. After 2 weeks, a localized retrogastric fluid collection of 10 cm diameter became evident and was submitted to US-guided FN aspiration of 120 mL of brown liquid with cultural examination negative for bacterial. After one month, the patient was

discharged without pain and fever, but with an enlarged peripancreatic fluid collection (18 cm diameter), treated with octreotide. The patient was readmitted due to abdominal pain and vomit. Blood tests were normal, except for hemoglobin (11.1 g/dL) and GGT (126 U/L). Abdominal CT demonstrated a peripancreatic fluid collection of 18 cm diameter. Study of the pancreatic duct by RMCP was not possible due to the presence of metallic foreign body. The patient underwent US-guided external drainage by 8 Fr catheter with aspiration of 800 mL of brown liquid. The procedure was well tolerated without any complication. The drainage was maintained for 3 weeks and than removed since there was no fluid collected in the bag. At present the patient had an asymptomatic, uncomplicated pseudocyst of 5 cm diameter. The reasons for percutaneous drainage option were severe obesity and competence in US-guided invasive procedures in our US unit. **Conclusions** The prognosis of severe necrotizing AP due to hypertriglyceridaemia is poor. This is a case in which simple standard treatment associated with external drainage was very successful.

A Rare Case of Malignant Insulinoma

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Context Neuroendocrine tumors of the pancreas (pNET) are rare tumors and they can be functioning or non-functioning. The most common functioning pNETs are insulinomas and these tumors are usually they are benign. We report a case of large, malignant insulinoma. **Case Report** A 60-year-old man was admitted to our institute for the presence of the classical Whipple's triad: recent onset (about 1 month) of neuroglucopenic and adrenergic symptoms (overnight frequent episodes of sweating, palpitations and dizziness); blood glucose levels less than 50 mg/dL (reference range: 60-110 mg/dL) and relief of symptoms obtained with administration of oral glucose. Both basal insulin and C-peptide serum levels were 35 µU/mL (reference range: 2-25 µU/mL) and 4.9 ng/mL (reference range: 1.1-4.4 ng/mL), respectively. A CT scan showed a large pancreatic body-tail solid mass of about 15 cm in diameter, with central necrotic area with calcifications and enlarged peripancreatic lymph nodes. Surgical approach was planned and a distal splenopancreatectomy was performed. Pathological

examination of the specimen showed a solid mass of 15 cm in diameter, with a firm consistency and diffuse calcifications, that mainly replaced the pancreatic parenchyma with massive invasion of the fat tissue. The mitotic rate was less than 10 mitosis per 10 high-power fields; there were 8 metastasis on 38 examined peripancreatic nodes. Surgical margins were tumor free and Ki-67 was 5.4%. Tumor cells displayed diffuse positivity for synaptophysin, only focal positivity for chromogranin and heterogeneous positivity for insulin. A final diagnosis of well differentiated pancreatic endocrine carcinoma, histological grade 2 (G2), pT3N1M0, was performed. The postoperative course was uneventful and the patient is alive, well, disease-free with a good control of blood glucose level at 3 months after surgery. **Conclusion** The occurrence of large insulinoma is rare in clinical practice and this case confirms previous studies indicating that the malignant potential of these tumors increase with the size.

Preliminary Results on the Role of Contrast Enhanced Ultrasonography for Cystic Lesions of the Pancreas: Analysis of 26 Patients

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Context Cystic pancreatic lesions show different morphological characteristics and have a different biologic behaviour. Sometime it is possible to recognized morphologic features predictive of malignancy. Even if the multidetector computed tomography (CT) and magnetic resonance cholangiopancreatography (CWMR) are the gold standards for imaging diagnosis of pancreatic cystic lesions, contrast enhanced ultrasonography (CEUS) represents an easy, simple and reproducible emergent imaging modality. **Objective** We evaluated the diagnostic value of CEUS in assessing the morphological features of pancreatic cystic lesions. **Methods** All consecutive patients with pancreatic cystic lesions admitted to our departments, from December 2008 to May 2009, were enrolled. CEUS was performed with a Iu22 ultrasound apparatus with a

1-5 MHz convex probe, using harmonic microbubble-specific imaging with low acoustic ultrasound pressure (Power Modulation[®]). The images were evaluated dynamically, and the time was calculated simultaneously as soon as the contrast agent was injected. Site, size and number of the lesion, presence of septa, solid component and presence of main pancreatic duct dilatation were recorded; when multiple cysts were present, the largest cyst was considered. Surgical treatment was carried out in all symptomatic patients and in the asymptomatic patients according to the international consensus guidelines [1]. **Results** Twenty-six patients were enrolled into the study. They were 18 (69.2%) females and 8 (30.8%) males with a median age of 71.2 years (range 36-88 years). The cystic lesion were usually single (22 cases, 84.6%), rarely multiple (4 cases, 15.4%); the cysts

were localized in the pancreatic head in 15 cases (57.7%), and in the body-tail in 11 cases (42.3%). The cystic median size was 2.6 cm (range 0.6-8 cm). Septa were present in 10 cases (38.5%), solid component in 7 cases (26.9%), and a dilated Wirsung duct was detected in 7 cases (26.9%). There were 3 (11.5%) symptomatic cystic lesions and 23 (88.5%) asymptomatic cystic lesions. Only 5 out of 23 cases (21.7%) with asymptomatic cysts were operated on and histology confirmed the malignant potential in all the cases (100%) (3 intraductal papillary mucinous neoplasms

type I-III, and 2 mucinous cystic neoplasms). **Conclusion** CEUS is a safe and simple imaging technique that allows to detect the morphological characteristics of the cystic pancreatic lesions especially of those patients who need of surgical treatment for their potential malignant behavior.

Reference

1. Tanaka M, Chari S, Adsay V, Fernandez-del Castillo C, Falconi M, Shimizu M, et al. International consensus guidelines for the management of Intraductal Papillary Mucinous Neoplasms and Mucinous Cystic Neoplasms of the pancreas. *Pancreatology* 2006; 6:17-32. [PMID 16327281]

Natural History of Pancreatic Cancer: A Case Report

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Context Natural history of pancreatic cancer is often unknown. Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is considered a premalignant lesion characterized by papillary proliferations of mucin-producing epithelial cells with excessive mucus production and cystic dilatation of pancreatic ducts. This case suggests the development of a pancreatic carcinoma from a non-invasive IPMN. **Case Report** A 66-year-old male was admitted to our hospital for the presence of persistent nausea and vomiting, and weight loss of 20 kg in the last year. Laboratory revealed abnormally high blood glucose levels (143 mg/dL; reference range: 60-110 mg/dL), alkaline phosphatases (418 U/L; reference range: 98-280 U/L) and GGT (93 U/L; reference range: 8-61 U/L). Serum levels of CA 19-9 and CEA were respectively 151 U/mL (reference range: 0-37 U/mL) and 9.7 ng/mL (reference range: 0-6.5 ng/mL). Ultrasonography revealed a hypoechoic mass of pancreatic head and a cyst of the body of pancreas, main duct dilatation and partial thrombosis of the mesenteric-portal confluence. Moreover, a spiral computed tomography (CT) scan showed a diffuse lymph nodes involvement and intrabdominal effusion. Endoscopic ultrasonography confirmed the hypoechoic mass and the multiple cysts on the head and the body of the pancreas. Cytology examination of the mass

allowed diagnosis of adenocarcinoma. A total pylorus-preserving pancreaticoduodenectomy, with a 5 cm superior mesenteric-portal vein resection and reconstruction with a homograft, was performed. Pathological examination of the resected specimen showed a ductal well-differentiated, biliopancreatic type invasive adenocarcinoma of pancreas of 2.5 cm in the pancreatic head; an IPMN type III with high-grade dysplasia/carcinoma in situ was also found in the body-tail of the pancreas associated to IPMN with low-grade dysplasia and IPMN with moderate dysplasia. Inflammatory thrombosis was found in the portal vein. There was a lymph node micrometastasis in the splenic hilus (pT3N1M0) and surgical margins were tumor-free. **Conclusion** This case reported is very interesting because of the coexistence of all morphologic features of the natural history of pancreatic carcinogenesis in an IPMN of biliopancreatic type. In fact, all steps of progression from low-grade dysplasia to high-grade dysplasia (IPMN) and finally to invasive biliopancreatic adenocarcinoma has been observed. This is an example that sometimes the natural history of the pancreatic cancer could be recognized and the progression towards pancreatic cancer should be avoided.

The Adenosquamous Pancreatic Cancer.

A Review of Literature and Report of 6 Cases

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Context Adenocarcinoma of the pancreas represents the most frequent pancreatic tumoural histotypes. Within the rare forms of exocrine pancreatic neoplasms pure squamous subtype (also known as

"epidermoidal") ranges from 0.5% to 3.5% while the adenosquamous represents the 0.9-4.4%. **Case Report** Six cases of adenosquamous pancreatic cancer were retrieved from our database between 2003 to 2009 (the

0.81% of pancreatic neoplasms resected for malignancies). For each one we described characteristics of presentation, laboratory and instrumental investigations, surgical approach, histological features and long-term outcome reporting possible adjuvant therapies (when available). Mean age of presentation was 63.5 years, 4 patients were male (2:1), tumor was always localized to the pancreatic head with no evidence of local invasion or metastatic lesions at diagnosis. Principal symptoms of presentation were jaundice (4/6), upper abdominal pain, weight loss (2/6) and anorexia (2/6). CA 19-9 was elevated in 3 patients with concomitant jaundice. Since three months before diagnosis one patient had clinical signs of recurrent pancreatitis. All six patients underwent to Longmire-Traverso duodeno-pancreatectomy: two R0, three R1 and one R2 resections (all N1-M0). One male patient (R1-r) developed stump pancreatitis with hemoperitoneum in perioperative period and died after an early reoperation for sepsis. One female patient (R2-r) died for

myocardial infarction 20 days after the operation and after a regular discharge without surgical complications. The remaining four patients received adjuvant therapy (gemcitabine alone or with oxaliplatin): one male patient died for local recurrence after 13 months but three patients are still alive with a Karnofsky-status of 80-90%. Within this group, one male patient (R0-r) actually presents a "free" disease period of 37 months, two (R1-r and R0-r; 1 male and 1 female) developed hepatic metastases but are still alive at 12 and 13 months, respectively. **Conclusion** Prognosis of adenosquamous pancreatic cancer remains unfortunately very poor, apparently worse than ductal pancreatic cancer. According to the reviewing literature and our experience, surgical resection of the primary associated with adjuvant multidisciplinary treatment seems to offer the best results for this kind of tumor but the lack of large and homogeneous sample does not offer a clinical evidence of the best therapeutic approach at the moment.

A Randomized Phase II Trial of Two Different Four-Drug Combinations in Advanced Pancreatic Adenocarcinoma: Cisplatin, Gemcitabine, Capecitabine, Epirubicin or Docetaxel

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Context The combination of cisplatin (P), epirubicin (E), 5-fluorouracil (F) and gemcitabine (G) (PEFG regimen) yielded a progression-free at 6 months from treatment start (PFS6) of about 50% and an 1-year overall survival (OS) around 40% in patients with advanced pancreatic adenocarcinoma (PA). **Objective** The current trial was aimed to assess whether the replacement of E with docetaxel (D) may improve PFS6. **Methods** Chemo-naïve patients with stage III or metastatic PA, KPS>50 received P (30 mg/m² day 1), G (800 mg/m² day 1) and capecitabine (1,250 mg/m²/day, days 1 to 14) and were randomized to receive either D at 25-30 mg/m² day 1 (arm A: PDXG regimen) or E at 30 mg/m² day 1 (arm B: PEXG regimen). Cycles were repeated every 14 days for a maximum of 6 months. The Fleming design was used to calculate the sample size on the probability of being PFS6 (primary endpoint). Assuming P0=40% and P1=60%, alpha=0.05 and beta=0.10, the study was to enroll 52 patients per arm. The regimen had to be considered of interest with > 26 patients being PFS6. **Results** Between July 2005 and September 2008, 105 patients were enrolled at a single institution, stratified

by stage and randomized (53 arm A). Patients' characteristics were (A/B): median age 61/59 years, KPS >70 92/88%, metastatic disease 66/65%; CA 19-9 greater than the upper limit of laboratory reference (URL) 87/90%. All patients are assessable for the primary endpoint: PFS6 was 59/56%. Median and 1-year OS was 10.7% and 41% in arm A and 10.7% and 43% in arm B. A partial response was observed in 60/37% of patients (P=0.01). A major biochemical response (reduction >89%) was observed in 44/33% and a minor biochemical response (reduction between 50% and 89%) in 42/33% of patients (P=0.03). Main per cycle G3-4 toxicity was: neutropenia 4/13% (P=0.0005), thrombocytopenia 2/4%, anemia 4/4%, fatigue 6/4%. **Conclusions** PEXG yielded similar results when compared to prior series treated by PEFG, suggesting that capecitabine may replace F. The inclusion of D instead of E yielded more objective and biochemical responses and less G3-4 neutropenia but did not improve PFS and OS. The present trial confirms the relevant impact on outcome of advanced PA of four-drug regimens.

Total Pancreatectomy: Indications, Results and Quality of Life

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Context Presently it is possible to reconsider total pancreatectomy (TP) as a viable option in the treatment of pancreatic disease. Moreover, the clinical need for TP is increasing. **Objective** The aims of this study were to identify the indications to perform a total pancreatectomy and to evaluate the outcome and quality of life of the patient who underwent to this operation. **Methods** A retrospective analysis of a prospective database, regarding all the patients who underwent total pancreatectomy from January 2005 to June 2008, was carried out. Perioperative and outcome data were analyzed in two different groups: ductal adenocarcinoma (group 1) and non-ductal adenocarcinoma (group 2). The quality of life was evaluated by using the EORTC QLQ-C30 questionnaire. **Results** Twenty (16.9%) total pancreatectomies out of 118 pancreatic resections were performed. Seven (35.0%) patients were affected by ductal adenocarcinoma (group 1) and the remaining 13 (65.0%) by pancreatic diseases different from ductal adenocarcinoma (group 2): 8 (61.5%) intraductal pancreatic mucinous neoplasms, 2 (15.4%) well

differentiated neuroendocrine carcinomas, 2 (15.4%) pancreatic metastases from renal cell cancer and, finally, 1 (7.7%) chronic pancreatitis. Eleven patients (55%) underwent primary elective total pancreatectomy; nine (45%) had a completion pancreatectomy previous pancreaticoduodenectomy. Primary elective total pancreatectomy was significantly more frequent in group 2 than in group 1. Early and long-term postoperative results were good without significant difference between the two groups except for the disease free survival that was significantly better in group 2. The follow-up examinations showed a good control of the apancreatic diabetes and of the exocrine insufficiency without differences between the two groups. **Conclusion** Currently, total pancreatectomy is a safe procedure that allows good early and late results with a good quality of life. Its indications are increasing because of the more frequent diagnose of pancreatic disease that involved the whole gland as well as intraductal pancreatic mucinous neoplasm, neuroendocrine tumors and pancreatic metastases from renal cell cancer.

Is Enucleoresection a Viable Option for Endocrine Pancreatic Tumors less than 4 cm in Diameter?

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Context Pancreatic endocrine tumors (PETs) are usually benign or low grade malignant. Thus, they should be treated with pancreatic resection that preserve the pancreatic parenchyma as much as possible. **Objective** The aim of the study was to evaluate the postoperative and long-term results of enucleo-resection in PETs. **Methods** Data were collected prospectively on 46 patients with PETs underwent surgery, with a diameter less than 4 cm observed from 1980 to 2009. Enucleoresection was performed when the tumor did not involve the main pancreatic duct (group A); typical resection was carried out in the other cases (group B). All the patients were analyzed regarding sex, age, comorbidities, symptoms, hormonal status, site and size of the tumor, and WHO classification. The two groups were compared regarding postoperative mortality, morbidity, pancreatic fistula, reoperations, disease-free survival and disease-specific survival. **Results** Of the 46

patients operated, 15(32.6%) were included in group A, and 31 (67.4%) in group B (25 left pancreatectomies and 6 pancreaticoduodenectomies). Characteristics of the two groups were similar except for the WHO classification in which there was a higher rate of well-differentiated carcinoma in group B than in group A (38.7% versus 6.7%; P=0.009). Regarding postoperative mortality, morbidity and reoperations there were no statistically significant differences between the two groups. Pancreatic fistula rate was higher in group A (33%) as compared to group B (12.9%), even if this difference was not statistically significant (P=0.127). Disease specific survival and disease free survival were similar in two groups. In particular, recurrence rate was absent in both groups. **Conclusion** Enucleoresection should be reserved to a selected group of patients (i.e. those with endocrine pancreatic tumors size less than 4 cm in diameter and far from the main pancreatic duct).

Is there a Correct Management of Pancreatic Cystic Lesions? A Single Centre Experience

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Context Over the past two decades, many authors have recommended that all cystic lesions of the pancreas have to be resected; due to amount of new knowledges this treatment strategy seems to be revised. **Objective** The aim of this study was to define the optimal management of the pancreatic cystic lesions. **Methods** Data were collected prospectively on 141 patients with pancreatic cystic lesions observed from 1990 to 2009. All the patients were analyzed regarding sex, age, presence of symptoms, site, number and size of the cysts, presence of septa, solid component, Wirsung duct dilation, and previous pancreatic diseases. They were divided in operative and nonoperative groups. The analyses were performed on an intention-to-treat basis by whether the initial decision was to surgical treat or observe the patients. **Results** Of the 141 patients included into the study, the initial management was operative in 89 (63.1%) and nonoperative in 52 (36.9%) patients. Regarding sex, number of lesions, Wirsung duct dilation, presence of septa and solid component there were no statistically significant differences between the two groups. Age was lower in

operative group than in nonoperative (57±16 years *versus* 72±11 years; P<0.001); symptoms were present in 69.3% of the cases of the operative group, while in the nonoperative group all patients were asymptomatic (P<0.001). The cysts were smaller in nonoperative group than in the operative one (2.5±1.8 cm *versus* 5.4±3.5 cm; P<0.001); the site of the lesions in nonoperative group was more frequent in the head of the pancreas (24 cases, 46.2%) whereas in the operative group the cysts were more frequently localized in body-tail (60 cases, 69.8%) (P<0.001). In the operative group there were 12.2% of patients with previous pancreatic diseases while in nonoperative group there were no patients (P=0.015). Of the 52 nonoperative patients, only 2 (3.8%) undergoing surgery because the increase of the cystic lesions. **Conclusion** We suggest that elderly patients with small asymptomatic cysts of the pancreas may be safely followed. Surgical treatment is indicated in young patients with large, symptomatic cystic lesions, usually located in the pancreatic body-tail.

Incidental Pancreatic Cystic Lesions. A Single Centre Experience

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Context Incidental pancreatic cystic lesions are defined as asymptomatic lesions diagnosed on abdominal imaging performed for other indications. These lesions seem to be increased in the last decade. **Objective** To establish the type of management and to evaluate the optimal clinical follow-up for the incidental cystic pancreatic lesions. **Methods** Data were collected prospectively on 60 patients with incidental pancreatic cystic lesions observed from 2002 to 2009. All the patients were analyzed regarding sex, age, site, number and size of the cysts, presence of septa, solid component and Wirsung duct dilation. Patients with a suspicion of serous cystic tumor, serum CA 19-9 determination and transabdominal ultrasound were carried-out every 6 months. Patients with a suspicion of an intraductal papillary mucinous neoplasm (IPMN) the type of follow-up and the

indications to surgery were evaluated according to the international consensus guidelines [1]. **Results** Of the 60 patients observed, the initial diagnosis was IPMN in 42 cases (70%) (type I, n=4; type II, n=27, type III, n=11); serous cystic tumors in 14 cases (23.3%) and others tumors in 4 cases (6.7%). Surgical approach was suggested in 13 patients (21.7%): 10 IPMN (type I, n=4; type II, n=4; type III, n=2), 1 serous cystic tumor, 1 mucinous cystic tumor and 1 endocrine cystic tumor. Of these 13 patients, 8 (61.5%) underwent surgery and the initial diagnosis was histologically confirmed in all. Of the remaining 52 patients, a follow-up was made (median follow-up: 29 months; range 12-88 months). Only 2 of these 52 patients (3.8%) underwent surgery during the follow-up period (after six and twenty months from the initial visit) due to an increase in size of the cystic lesion. **Conclusion** Surgery is not a

frequent indication in patients with incidental cystic pancreatic lesions and it is carried out only in selected cases. The follow-up criteria suggested by the international consensus guidelines [1] are a viable option for surgical approach.

Reference

1. Tanaka M, Chari S, Adsay V, Fernandez-del Castillo C, Falconi M, Shimizu M, et al. International consensus guidelines for the management of Intraductal Papillary Mucinous Neoplasms and Mucinous Cystic Neoplasms of the pancreas. *Pancreatology* 2006; 6:17-32. [PMID 16327281]

Are there Predictive Malignant Factors in Pancreatic Cystic Tumors? A Single Centre Experience

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Context Several factors are considered predictive of malignancy in pancreatic cystic tumors and they are very important to establish whether a pancreatic cystic tumors should be operated. **Objective** To evaluate the possible presence of predictive malignant factors in patients affected by pancreatic cystic tumors. **Methods** Data were collected prospectively on 91 patients with pancreatic cystic tumors undergoing surgery in the period 1990-2009. They were divided in two groups: benign/borderline tumors and malignant tumors and they were compared regarding sex, age, presence of symptoms, site, number and size of the cystic tumor, presence of septa, solid component and Wirsung duct dilation. **Results** Of the 91 patients undergoing surgery, 60 (65.9%) were benign/borderline (23 serous cystic tumors, 14 mucinous cystic tumors, 14 intraductal papillary mucinous tumors, 4 solid and cystic papillary tumors, 3 cystic lymphangiomas, 1 cystic endocrine tumors, 1 teratoma) and 31 (34.1%)

were malignant (19 mucinous cystoadenocarcinoma, 9 intraductal papillary mucinous carcinoma, 2 cystic papillary tumors and 1 endocrine cystic tumor). Regarding age, sex, number of lesions, site and size of the tumors, Wirsung duct dilation, presence of septa and solid component there were no statistically significant different between the two groups. However, the presence of septa was more frequent in benign/borderline tumors than malignant (47.5% *versus* 26.7%). Presence of symptoms was the only predictive malignant factor; in fact, symptoms (mainly abdominal pain and jaundice) were present in 83.9% of the malignant tumors respect in 59.3% of the benign/borderline tumors with OR=3.27 (95% C.I.: 1.06-10.09; P=0.039). **Conclusion** According to our experience, we suggest that the presence of symptoms increases the risk of malignancy of pancreatic cystic tumors and it represents the most important factor to indicate the surgical treatment.

Learning Curve for Laparoscopic Pancreatic Surgery: Data from a Four-Month Experience

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Context In recent years laparoscopic surgery (LPS) for pancreatic disease has made significant strides. However, this approach has been considered to be mainly investigational, so only limited series concerning LPS have been published. **Objective** The purpose of this study is to report our first four-month experience on LPS pancreatic resection. **Methods** From March 2009 to June 2009, 34 patients candidate to elective pancreatic resection in our institution were considered for LPS. Exclusion criteria for LPS were: suspected neoplastic infiltration (portal/mesenteric vein n=7 or adjacent organs n=2), organ dysfunction (n=7), BMI >35 kg/m² (n=1), and refuse to participate (n=3).

In patients undergoing laparoscopic pancreaticoduodenectomy (PD) only pancreatic resection was planned to be performed laparoscopically, while reconstruction was performed through a mini-laparotomy. The following variables were recorded: conversion rate, duration of surgery, operative blood loss, postoperative morbidity, and length of hospital stay (LOS). All patients received an early-recovery after-surgery-protocol. **Results** Laparoscopic distal pancreatectomy was attempted in 9 out of 17 patients (53%). Four out of 9 patients had cancer. In 5 patients a spleen-preserving procedure was carried-out. In 6 cases conversion to hand-assisted (n=2) or open (n=4)

procedure was necessary. Mean operative time was 271±59 min and median blood loss was 150 mL (range 50-1,800 mL). The median LOS was 6 days (range 4-20 days). One patient was reoperated for drainage of an abdominal fluid collection. Two patients experienced postoperative pancreatic fistula with output higher than 100 mL and both were managed conservatively. Postoperative mortality was 0%. Laparoscopic PD was attempted in 5 out of 17 patients (29%). All 5 patients had cancer. In 2 cases conversion to open procedure was necessary for bleeding. Mean operative laparoscopic time was 285±45 min and total operative

time was 458±52 min. Median blood loss was 350 mL (range 300-1,200 mL). The median LOS was 18 days (range 10-22 days). No patient was reoperated. Two patients experienced postoperative pancreatic fistula with output higher than 100 mL and both were managed conservatively. Postoperative mortality was 0%. **Conclusion** In our preliminary experience, LPS showed limited indication and high conversion rate in patients undergoing pancreatic resection. No mortality and morbidity rate comparable to open approach have been observed. Improving surgical skill should reduce conversion rate rather than increase LPS indication.

Incidence and Risk Factors for Secondary Cancers in Patients with Sporadic Pancreatic Endocrine Tumors

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Context Pancreatic endocrine tumors (PETs) represent a subset of pancreatic neoplasm with an increasing incidence and a prevalence of 10% of all pancreatic cancers. The incidence of secondary cancers in PETs has not been investigated specifically. **Objective** To evaluate the incidence of other primary cancers (secondary cancers: SC) in patients with PETs, and possible risk factors for their occurrence. **Methods** Cohort of consecutive patients with sporadic PETs followed-up at the 2 units. SC was defined as a different tumor that was not considered to be a metastasis of PET, diagnosed either before, synchronously, or after PET diagnosis. The rate of SC was compared with expected cases in the National Registries. Data on sex, age at diagnosis of PET, medical therapy and potential risk factor (smoking, alcohol, BMI, family history of cancer) were recorded. **Results** One-hundred and 71 PET patients were enrolled (87 M and 84 F; median age at diagnosis 53 years; median follow-up of 38 months). Twenty-two SCs in 20 patients were identified (8 M and 12 F; 11.69%) either before (15 cases, 8.71%), simultaneously with PET (3 cases, 1.75%) or during

follow-up (4 cases, 2.33%). The 5 patients who developed SCs after PET did not receive genotoxic agents (PRRT or chemotherapy). The main sites of SCs were thyroid (4 cases, 2.3%; 3 F, 3.5%), nervous system (5 cases, 2.93%; 3 M, 44%), breast (2 cases, 2.3%) and urinary bladder (3 cases, 1.75%; 2 M, 2.2%). There were no deaths related to SCs. The rate of thyroid cancers for women with PET exceeded the expected lifetime incidence in Italy (SIR 3.3). No differences between patients with or without SCs in terms of functioning status or WHO stage. As compared to patients with PETs without SCs, those with a SC were more frequently smokers (50% vs. 39%) and heavy smokers (>20 pack-year) (25% vs. 19.8%) although this difference was not significant. Cancer family history, BMI, alcohol intake and medical history were similar. **Conclusions** We identified an incidence of 11.69% of secondary cancers in PETs patients. Most SCs were diagnosed before PET and were localized in other "neuro/endocrine" organs possibly suggesting genetic susceptibility, although MEN-1 patients were excluded. Smoking may contribute to the increased risk of SCs.

Preoperative Administration of Antioxidants in Pancreatic Surgery: Double-Blind Rndomised Clinical Trial

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Context Oxidative stress due to ischemia/reperfusion injury increases systemic inflammation and impairs

immune defenses. Much interest has been recently developed for the administration of antioxidant

substrates in surgical patients. **Objective** To evaluate the impact of an oral nutritional supplement (booster) enriched with glutamine and antioxidants on postoperative oxidative stress. **Methods** We performed a double-blind placebo-controlled randomized clinical trial, involving 36 patients undergoing pancreaticoduodenectomy for cancer. Patients were randomized to receive either the booster or the placebo, identical in appearance and taste. The booster contained 50 g carbohydrates, 15 g glutamine, 750 mg vitamin C, 250 mg vitamin E, 150 µg selenium, 10 mg zinc, 5 mg beta-carotene, and 1 g green tea extract. Both drinks were administered three times prior to elective surgery, twice the day before surgery (at 3 and 9 p.m.), and once three hours before surgery. In all patients, total endogenous antioxidant capacity (TEAC) and plasma levels of vitamin C, vitamin E, selenium, zinc, F2-isoprostanes and C-reactive protein (CRP) were measured at baseline and on postoperative day +1, +3 and +7 (POD 1, 3, 7). **Results** The booster was

well-tolerated without any respiratory induced complications. Vitamin C and E plasma levels were significantly higher on POD 1 in booster group (BG) compared to placebo (P<0.001 and P=0.04, respectively). Postoperative plasma levels of selenium and zinc were higher in the BG on POD 1 (P=0.07 and P=0.05, respectively). The reduction of TEAC from baseline between groups was lower in the BG compared to placebo for each time point after surgery (P=0.01 on POD 1 and P<0.001 on POD 7), whereas F2-isoprostanes were similar in both groups. No difference was found in CRP plasma levels on POD 1, 3 and 7. **Conclusions** The present study shows that booster administration was safe, increased antioxidants substrates, improved antioxidant defences shortly after surgery, but did not reduce oxidative stress products and systemic inflammation. In patients undergoing major pancreatic resection antioxidants supplementation should be prolonged postoperatively.

Secretomes of Pancreatic Cancer vs. Normal Cell Lines Analysed and Compared by Aglobal Proteomic/Bioinformatic Approach

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Context The cancer secretome represents a rich repository where to mine potentially useful information for both cancer biology and clinical oncology. In fact, proteins abnormally released by malignant cells can influence tumor growth, invasion and metastasis. **Objective** We set up a proteomic/bioinformatic workflow to globally characterize and compare the secretome of pancreatic adenocarcinoma cell lines. **Methods** Four human pancreatic ductal carcinoma cell lines (PT45, Panc1, MiaPaCa2, and Asp1) and the normal pancreatic ductal epithelial cell line HPDE6 were grown in 5% FBS medium, washed, and incubated in FBS-free medium for 24 h. Proteins in the conditioned medium were concentrated by ultrafiltration, fractionated into 24 gel bands by electrophoresis (1DE), and in-gel digested. Digests were analysed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The MS/MS data were analyzed by Mascot. After results filtering and validation, identified proteins were listed with the quantitative index (emPAI) provided by Mascot. Pathway and functional analysis was done with

MetaCore and other bioinformatics tools. **Results** We reproducibly identified 300-500 proteins per cell line (overall, 790 unique proteins). The subset of proteins (134) common to HPDE6 and all the 4 cancer cell lines were mostly comparably expressed. All cell lines secreted unique proteins. The 85 proteins exclusively secreted by HPDE6, and the 10 proteins absent in HPDE6 but common to all cancer cell lines, may represent functionally interesting sets to investigate with targeted approaches those processes that are consistently under- or over-represented in pancreatic cancer cells. A comparative protein enrichment analysis by MetaCore of dysregulated proteins (>4-fold change, cancer vs. normal) showed that the top-ranked networks were related to processes relevant for cancer progression and spread, e.g. cell-cell adhesion, cell-matrix adhesion, extracellular matrix remodelling, inflammation. **Conclusions** This proteomic workflow based on high accuracy/resolution mass spectrometry allows the comparison of multiple secretomes for the identification of potential biomarkers and therapeutic targets.

Mesenchymal Cells Appearing in Pancreatic Tissue Culture are Bone Marrow Derived Stem Cells with the Capacity to Improve Transplanted Islet Function

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Context Adherent fibroblast-like cells have been reported to appear in cultures of human endocrine or exocrine pancreatic tissue during attempts to differentiate human beta cells from pancreatic precursors. It has been widely proposed that these cells derive from an epithelial to mesenchymal transition (EMT) of human pancreatic beta cells. Despite this, a thorough characterization of these mesenchymal cells has not yet been carried out, and there is no conclusive data that they derive from beta cells instead of other cell types intrinsic to islet preparations. **Methods and Results** We demonstrated that the human mesenchymal cells outgrowing from cultured human pancreatic endocrine or exocrine tissue are pancreatic mesenchymal stem cells (pMSC) that propagate from contaminating pMSC and not from EMT of other pancreatic cells. The origin of pMSC is extrapancreatic

both in human and in mouse and by using GFP+ bone marrow transplantation in the mouse model, we were able to demonstrate that these cells derive from the CD45+ component of bone marrow. pMSC express negligible levels of islet-specific genes both in basal conditions and after serum deprivation or exogenous growth factor exposure, and might not represent optimal candidates for generation of physiologically competent beta cells. On the other hand, when cotransplanted with a minimal pancreatic islet mass pMSC facilitate the restoration of normoglycemia by increasing neovascularization. **Conclusion** These results suggest that pMSCs are not optimal candidates to generate physiologically competent beta cells, but considering the large number of pMSCs obtainable from digested pancreas, they could be useful as islet ‘helper’ cells.

Duodenopancreatic Traumatic Injuries: Statistical Analysis of Prognostic Factors Can Lead Surgeon's Therapeutic Challenge

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Context Abdominal trauma rarely cause injuries involving duodenum and pancreas. The estimated incidence of pancreatic lesions ranges between 1% and 2% whilst duodenal injuries are around 0.2% of all abdominal trauma. Associated pancreatoduodenal injuries ranges from 30% to 87% and their management should be strictly related and is still controversial. Morbidity and mortality of pancreatoduodenal injuries remains high and no significant improvements have been noted in the last decades. **Objective** The Trauma Center in Maggiore Hospital in Bologna has been active since 1989. Surgical activity has been developed up to 1998 by a general surgical team while in the second ten years (1998-2007) surgical activity has been developed by an autonomous and dedicated surgical trauma unit. The aim of this

work is to introduce our experience from 1989 to 2007 in theme of surgical treatment of traumatic duodenopancreatic lesions with the purpose to stratify the results obtained during the two different periods and emphasize the impact of a dedicated surgical trauma unit in order to reach the best outcomes. **Methods** We retrospectively reviewed the demographics, clinical and intraoperative data, overall and distinguished by decade of occurrence, available from our trauma registry. Morbidity and mortality were calculated and all the demographics, clinical and therapeutic factors were analyzed in comparison between the survivor and non-survivor groups and univariate and multivariate analyses of prognostic factors by logistic regression were carried-out. **Results** In the last decade (1998-2007) patients were older

(mean age 44.2 vs. 34.9 years in the first decade), and male in a higher percentage of cases (71.4% vs. 63.6% in the first one). An increased number of blunt trauma (90.5% in the second decade vs. 81.8% in the first one) in contrast to penetrating was observed (P NS). During the second decade, mean operative time decreased (119 min vs. 133 min; P NS) without a significant difference in procedures performed with exception of a wider use of feeding jejunostomy (47.6% vs. 15.2%; P<0.01). The comparison between survivors and non-survivors showed the first group to have lower age (36.1 years vs. 47.2 years), shorter operative time (122 min vs. 149 min) and less severe AAST grade (P NS). Survival rate significantly differs comparing grade I-II lesions with ductal involving injuries (grade III-V) (P<0.01). Patient with gunshot injuries showed a higher mortality rate (33.3% vs. 23.9% and 0% of blunt trauma and stab wound, respectively). When feeding jejunostomy was performed, mortality was 6.7% vs. 28.2% (P=0.05). The patients who developed complications had a longer operative time (138 min vs. 108 min), worse AAST grade (P<0.05) as well as complex definitive surgical procedures (vs. damage control and/or diverting procedures). Combined pancreatico-duodenal injuries showed a higher morbidity rate (80% vs. 41.4% and 50.0% for isolated pancreatic and duodenal injuries, respectively) requiring a second look laparotomy in 60% of cases significantly higher (P<0.01) than

pancreatic or duodenal lesion (6.9% and 12.5%). Gunshot wound injuries suffered the highest incidence of complications (100% vs. 60% for stab wound and 42.9% for blunt trauma) and all of them required re-intervention (100% vs. 11.4 for blunt trauma and 0% for stab wound; P<0.01). Among the surgical procedures performed distal pancreatectomy showed the higher complication rate and worse survival rate. In the subset of injuries with ductal involvement (grade III-V) combined pancreaticoduodenal lesions strongly predicted morbidity (P<0.01). Operative time, last decade injuries, age and combined lesions remained strongly predictive of mortality in the multivariate analysis. **Conclusion** The presence of ductal involvement within the AAST classification, massive combined pancreaticoduodenal injuries, and hemodynamic status are significant indicators of worse injuries, requiring a careful therapeutic strategy. Optimal management and better outcome of these severe pancreaticoduodenal injuries seems to be associated with shorter operative time, simple and fast damage control surgery in contrast to complex definitive surgical procedures and feeding jejunostomy adjunct. Finally, we emphasize the crucial role of a devoted trauma team to reach the best outcome in term of mortality, morbidity and appropriate surgical strategy.

Acute Pancreatitis Complicating Transcatheter Arterial Chemoembolization of Hepatocellular Carcinoma: Report of 5 Cases

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Context Acute pancreatitis (AP) represents a rare complication after transcatheter arterial chemoembolization (TACE) of primary and secondary liver tumors (1-2%), with a significant morbidity and mortality. Direct ischemic mechanisms, as well as toxicity of antineoplastic utilised drugs, are likely to be the main etiological factors of acute pancreatic damage after TACE. **Objective** Aim of the present study was to present clinical features of five consecutive patients with hepatocellular carcinoma (HCC) who develop AP after TACE procedure. **Patients** We observed these patients during the last 10 years; 3 were males, 2 females; mean age was 62.5±14.3 years; all patients presented a long-lasting HCV-related liver cirrhosis complicated by the occurrence of HCC (ultrasonographic and contrast-enhanced CT-scan data confirmed by fine needle aspiration cytology in all cases). TACE was performed according to standard protocol (one procedure in 3 patients, two procedures in 2 patients; selective embolization of the hepatic branches feeding the tumor with a mixture of lipiodol

and farmorubicin followed by polyvinyl alcohol-particles injection); diagnosis of AP was established according to the Atlanta criteria. Abdominal pain developed soon after TACE (within 2 hours in 3 patients, and 6 hours in 2 patients). All patients presented organ failure (4 multi-organ failure, 1 single organ failure) and all needed admission to intensive care unit. Four patients (80%) developed pancreatic necrosis and peri-pancreatic fluid collections. In-hospital mortality was 60% (3 patients); mean hospital stay was 34.2±16.7 days. All patients were managed with standard medical treatment for severe AP; two of them required percutaneous aspiration/drainage procedure; none of them was operated on. **Conclusion** AP complicating TACE in patients with HCC presents a severe outcome with multiple complications and high mortality. Systematic measurement of serum pancreatic enzymes should be performed in cases of abdominal pain following TACE in order to confirm AP, which can clinically mimic a less severe postembolization syndrome.

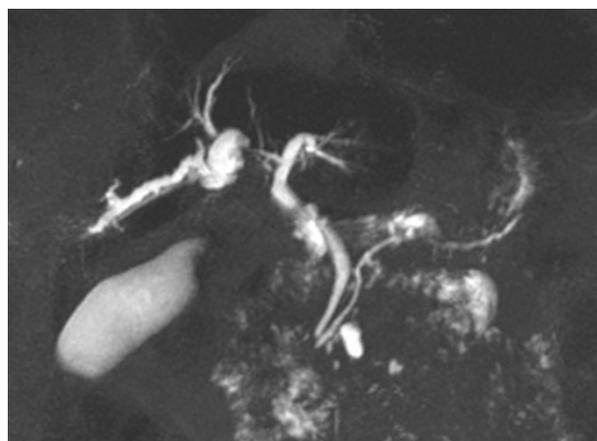
A Case of Mucin-Hypersecreting Intrahepatic Bile Duct Tumor Occurring Simultaneously with a Pancreatic Intraductal Papillary Mucinous Tumor

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Context A subtype of cholangiocarcinoma showing a papillary proliferation pattern with mucin secretion in the bile duct lumen was recently classified as biliary intraductal mucinous papillary tumor (IPMT-B). IPMT-B account for a small fraction of cholangiocarcinomas and resemble pancreatic IPMT(-P). To the best of our knowledge, there are been just two reported cases of patients with synchronous IPMT-B and IPMT-P. **Case Report** We hereby report the case of a 76-year-old woman who was incidentally diagnosed with an asymptomatic mass in the liver at a routine abdominal US. A CT-scan rose the suspect of a cholangiocarcinoma. She was healthy except for hypertension and type II diabetes. Her sister died for HCC. She never smoked nor drank alcohol. A magnetic resonance colangiopancreatography with secretin (s-MRCP) demonstrated a 3 cm bulky fluid lesion occupying the bile duct lumen (see Figure), in the right liver, and synchronous multiple pancreatic cystic lesions (1-1.3 cm) communicating with an irregular Wirsung, diagnosed as BD-IPMT-P. An EUS confirmed the clinical picture, but several biopsies were negative. After 3 months, a second s-MRCP demonstrated disease progression, with increased bilirubin and GGT levels. ERCP was performed and a

biliary stent inserted. A citobrush diagnosed IPMT-B cells (mucinous adenocarcinoma cells). Surgery was ruled out and the patient received chemotherapy (5-FU) and radiotherapy (50.4 Gy). She is alive at 12 months from diagnosis. **Conclusions** IPMT-B is considered the biliary counterpart of IPMT-P since they share several features. In this rare case both IPMT-B and IPMT-P occurred simultaneously. Further studies will be required to define whether this association is accidental or part of a typical phenotype.



Prognostic Relevance of Lymph Node Metastases and Adjuvant Treatment for Patients with Invasive Intraductal Papillary Mucinous Neoplasms (IPMNs) of the Pancreas

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Context IPMNs of the pancreas are a group of intraductal mucin-producing cystic neoplasms with clear malignant potential. However, the natural history of invasive IPMNs (papillary mucinous carcinomas) is not well known and there are few data regarding the prognostic factors and the role of adjuvant treatment for these patients. **Objective** The purpose of our retrospective analysis was to evaluate clinical and pathological factors associated with prognosis following pancreatic resection for invasive IPMNs. **Methods** The database of pancreatic surgical

resections at our institution was explored from 1/2004 to 3/2009 and matched with the pathological data on the resected specimens to identify patients resected for an invasive IPMN. A retrospective review of clinical and pathological features and outcome was conducted. **Results** Thirty-two evaluable patients (15 men and 17 women) who underwent a radical surgical resection for an invasive IPMN were selected. Median age was 68 years (range 37-87 years). Most patients (26.8%) had a T3 tumor. Eighteen (56%) patients had positive nodes (median number 4; range 1-12). The median number of

resected nodes was 31 (range 11-97). Two postoperative deaths occurred within two months of surgery related to cardiac complications. Eighteen (56%) patients received gemcitabine as adjuvant chemotherapy; four cases were treated also with adjuvant radiotherapy mainly because of inadequate surgical margins. After a median follow-up of 18 months, 13 patients experienced a disease progression and 7 died; the sites of progressive disease were: lung and liver in 3 cases each, peritoneum in 2, pancreas remnant and abdominal lymph nodes in 1 case each, multiple site in the remaining 3 patients. The estimated median disease-free survival (DFS) was 24.9 months. The presence of lymph nodes metastases was the main

prognostic factor in our series with a median DFS of 30 months for node negative vs. 12.8 months for node positive patients. Adjuvant chemotherapy seemed beneficial for node positive patients (DFS 16.5 vs. 8.5 months for treated vs. untreated patients). Among node positive patients, a lymph node ratio >0.1 resulted associated with worse outcome (DFS 11.9 vs. 16.7 months with ratio <0.1). **Conclusions** Our results confirm that node positive invasive IPMNs has a dismal prognosis. The role of adjuvant treatment for these patients seems promising but should be further investigated. An early surgical approach for this disease should be advocated.

Value of Ultrasound-Guided Pancreatic Needle Aspiration Biopsy in Cystic Lesions of the Pancreas

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Context. Pancreatic cysts are increasingly identified, due to the higher diagnostic accuracy of current imaging techniques, and they often account for diagnostic and therapeutic challenges. Pathology ranges from non-neoplastic lesions to benign and malignant neoplasms. **Objective** To plan an appropriate treatment in patients with suspicion of malignancy progression, percutaneous US-guided needle aspiration can be considered as a good option to perform cytological and chemical analyses of the cystic fluid collected from pancreatic lesions. **Methods** The study started on January 2005 and is still in progress. It includes 14 patients (9 females and 5 males, with a median age of 68 years, range 34-86 years); the diagnosis of cystic pancreatic mass was made by a combination of imaging findings (EUS, CT, and MRCP) and was confirmed by surgery in 5 patients. Aspiration was performed with a 18-Gauge needle to obtain cytological specimens and assess intra-cystic levels of CA 19-9 and CEA. **Results** The cystic lesions were located in the pancreatic head in 9 cases (64%), in the body-tail of the gland in 2 cases (18%) and diffuse through the gland in 2 cases (18%). Median size was

20 mm (range 7-80 mm). Diagnosis by imaging techniques was cystadenocarcinoma in 2 patients, mucinous cystadenoma in 5 patients, serous cystadenoma in 2 patients, intraductal papillary mucinous neoplasms (IPMN) in 3 patients, pseudocysts in 1 patient, and undetermined cystic neoplasm in 1 patient. In all cases but three adequate material for cytology was obtained. In the remaining 4 cases the presence of mucus in the liquid withdrawn did not allow for any chemical determination. The cytological analyses were: cystadenoma in 4 patients, IPMN in 2 patients, and normal cells in the remaining 5 patients. A marked elevation of CA 19-9 (>50,000 U/mL) in the cystic fluid was found in 3 patients (1 with cystadenocarcinoma and 2 with cystadenoma) and of CEA (>200 ng/mL) in 5 (1 with cystadenocarcinoma, 3 with cystadenoma, and 1 with IPMN). No major complications were observed after the procedure. **Conclusions** Preliminary results of our study seem to demonstrate that cytological and chemical analyses of pancreatic fluid collected by ultrasound-guided percutaneous needle aspiration are of limited help in the diagnosis of pancreatic cystic lesions.

Gem-Resistant Pancreatic Carcinoma Cells Capan-2 Are Enriched in Cancer Stem Cells That Can be Targeted by Disulfiram

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Context The poor response rate and short progression-free survival interval obtained with gemcitabine (GEM) suggests pancreatic carcinoma either rapidly

develops or intrinsically possesses GEM chemoresistance. Emerging data have shown that these tumors are heterogeneous, comprising a small subset of

distinct cancer cells, the so-called cancer stem cells (CSC), that are responsible for tumor initiation and propagation. Recently, highly-tumorigenic cancer cells expressing the cell markers CD44, CD24, epithelial-specific antigen (ESA) and aldehyde dehydrogenase (ALDH) have been identified within human pancreatic carcinoma. The drug disulfiram (DSF), used for over 50 years to treat alcoholism, has been shown to inhibit ALDH and NF-kappaB, induce apoptosis, exert antineoplastic activity, arrest angiogenesis and play a role in synergistically-enhancing the potency of anticancer drugs, by disabling multi-drug resistance pumps. **Objective** The study aimed to test *in vitro* whether: i) GEM-treatment results in the enrichment of a minor fraction of resistant pancreatic malignant cells with a stem cell phenotype, and ii) DSF can be employed as a new therapeutic approach by targeting CSC in pancreatic carcinoma. **Methods** The pancreatic-carcinoma cell-line Capan-2 was cultured in

serially increasing concentrations of GEM. Stable cultures of GEM-resistant cells were obtained whose resistance was 20-fold that of the parent cells. Flow cytometry was performed to examine stem cell markers (CD44, CD24, ESA and ALDH). Untreated and GEM-resistant Capan-2 cells were exposed to DSF and cell viability was determined by the Neutral Red uptake assay. **Results** In comparison to the parent cells, a higher percentage of GEM-selected cells expressed the putative phenotype of the pancreatic carcinoma CSC: CD24+, CD44+, ESA+ (triple positive: 0.12% vs. 1.7%, P=0.023) and were ALDH+. DSF treatment had no significant cytotoxic effect on untreated Capan 2 cells even at the higher concentration (1,000 µM), but demonstrated a strong growth inhibitory potential for GEM-resistant cells. **Conclusion** These results suggest that DSF may be capable of eliminating pancreatic CSC and encourage further investigation.

Survival and Prognostic Factors in Metastatic Tumors of the Pancreas. A Single-Center Experience and a Systematic Review of the Literature

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Context Pancreatic metastases are rare. The role of surgery is poorly defined and data on long-term survival are lacking. **Objective** To analyze the clinical and pathological characteristics of pancreatic metastases based on a series of consecutive patients observed in our department and on data from the medical literature. To evaluate the role of surgery and the weight of other possible prognostic factors in determining the long-term survival of these patients. **Methods** Data from patients with pancreatic metastases observed in our division from 2003 to 2008 were retrospectively analyzed. In addition, the English medical literature was reviewed regarding series of patients with pancreatic secondary tumors. **Results** Data from 235 patients including 10 consecutive patients observed in our department were retrieved. Metastasis from renal cell carcinoma accounted for 67.9% of all cases. Overall 5-year survival was 53.2%. Factors predictive of worse survival, as determined by

multivariate analysis, were: symptoms at diagnosis (HR=2.46, 95% CI: 1.38-4.38; P=0.002), synchronous tumors (HR=2.18, 95% CI: 1.11-4.27; P=0.024), radical-intent surgery not performed (HR=4.64, 95% CI: 2.73-7.87; P<0.001), and pathology of the primary tumor. In particular, compared to pancreatic metastases from renal cell cancer, metastases from melanoma (HR=4.14, 95% CI: 1.88-9.14; P<0.001) and lung cancer (HR=4.86, 95% CI: 1.80-13.2; P=0.002) were associated with worse survival. The differences in survival of patients with renal cell cancer metastases and those with either breast cancer, colorectal, or sarcoma metastases did not reach statistical significance. **Conclusions** There may be a subset of patients with pancreatic metastases who are able to benefit from surgery with respect to improved long-term survival. Symptoms at diagnosis, presentation with primary tumor, surgical resection, and pathology seem to be important prognostic factors.