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ORAL COMMUNICATIONS

A 13-Year Single Institution Experience with 4-Drug Regimens in Patients with Advanced Pancreatic Adenocarcinoma (PA)

Belli C, Balzano GP, Cereda S, Passoni P, Ghidini M, Rognone A, Cappio S, Nicoletti R, Arcidiacono PG, Villa E, Di Carlo V, Reni M

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Context The combination of cisplatin, epirubicin, gemcitabine and 5-fluorouracil (F; PEFG) was shown to improve the outcome of patients with stage III-IV PA in a phase III trial. In 2005, 5-FU was replaced by capecitabine (X; PEXG) in the clinical practice. **Objective** To report the outcome of a single institution series of 319 patients receiving either PEFG or PEXG between April 1997 and June 2010. **Methods** Chemo-naïve patients with stage III-IV PA, age 18-75 years, Karnofsky performance status (PS) >50 received PEFG until June 2005 and PEXG thereafter for a maximum of 6 months. At the end of chemotherapy, stage III patients without systemic progressive disease (PD) received concomitant chemoradiation. Computed tomography of the abdomen and chest was made at baseline, every 8 weeks during treatment and then every 2-3 months or when PD was clinically suspected. CA 19-9 measure was done on a monthly basis. Progression-free survival (PFS) was calculated as the interval between start of treatment and PD or death, and overall survival (OS) was measured from initiation of treatment to date of death or to the last follow-up assessment. **Results** One-hundred and 55 patients received PEFG (group A) and 164 PEXG (group B). Patients' characteristics were (A/B): median age 60/60 years, median PS 80/90, metastatic disease 63/60%; CA 19-9 greater than the upper limit of laboratory reference 82/88%. Disease control (complete response + partial response + stable disease) was yielded in 81% of patients in both groups. A CA 19-9 reduction >89% was observed in 30% and 26% and a reduction of 50-89% in 42% and 38%. In stage III patients, median PFS was 10.9 and 9.8 months (P=0.29); 1-year OS was 66% and 69% and median OS 16.4 and 17.9 months (P=0.17). In stage IV patients, median PFS was 6.0 and 6.0 months (P=0.5); 1-year OS 32% and 43% and median OS 8.8 and 10.7 months (P=0.05). No difference was observed in grade 3-4 toxicity. **Conclusions** PEXG is more suitable for use in the clinical practice and yielded similar results when compared to PEFG. The present study confirmed the remarkable impact of 4-drug regimens on PA outcome and feasibility on an outpatient basis. Further investigation on PEXG regimen in the peri-operative setting is warranted.

Long-Term Study of Residual Pancreatic Function After Pancreogastric or Pancreojejunal Pylorus-Preserving Pancreaticoduodenectomy

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Context No long term study has compared the residual pancreatic function after pancreogastric (PGA) or pancreojejunal anastomosis (PJA). **Methods** We studied patients operated 5-7 years ago as part of a randomised study comparing PGA and PJA in a single, high-volume referral centre. Exocrine pancreatic function was evaluated, after enzyme withdrawal, by secretin-enhanced pancreatic RNM, faecal elastase-1, and serum levels of p-amylase and lipase. Malabsorption was quantified by faecal fat balance. Endocrine function was studied by postprandial glycemic sticks and by Hb1Ac; nutritional status by

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BMI, BMI variation over the five years, serum albumin, prealbumin, vitamin D and B_{12}. Mean ±1 SEM are shown. Student's t test was used for statistical analysis, when necessary after log transformation to normalize data distribution. **Results** Fifteen PGA and 13 PJA entered the study. No difference was found in demographic parameters. An overt diabetes was found in 3 PGA and 1 PJA but Hb1Ac was the same in the two groups. PGA showed a more severe deterioration in exocrine function (fecal elastase 18.2±7.9 *vs.* 202±49.3 µg/g, P<0.01; s-lipase 12±1.22 *vs*. 24±4.25, P<0.01). Faecal fat was pathological in all but three patients. Steatorrhea was similar in PGA (27±3.79 g/day) and in PJA (22.0±4.38 g/day, P NS). No difference was found in nutritional parameters. **Conclusions** 1) Malabsorption is found in most operated patients, even in patients with normal values of elastase-1. 2) Pancreogastric anastomosis causes a more severe deterioration of exocrine capacity than PJA. 3) The malabsorption produced by PGA and PJA are of a similar severity. 4) Body weight and biochemical markers of the nutritional status are well preserved in both groups, to suggest that pancreatic insufficiency is effectively controlled by pancreatic supplements even in operated patients.

Laparoscopic Robot-Assisted Pancreas Transplantation

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Context Surgical complications are a major disincentive to pancreas transplantation, despite the undisputed benefits of restored insulin independence. The da Vinci surgical system, a computer assisted electromechanical device, provides the unique opportunity to test whether laparoscopy can reduce the morbidity of pancreas transplantation. **Methods** Pancreas transplantation was performed by robot assisted laparoscopy in three patients. The first patient received a pancreas after kidney transplant, the second a simultaneous pancreas kidney transplantation, and the third a pancreas transplant alone. Operations were carried out through an 11 mm optic port, two 8 mm operative ports, and a 7 cm midline incision. The latter was used to introduce the grafts, handle vascular crossclamping, and create exocrine drainage into the jejunum. **Results** The two solitary pancreas transplants lasted 3 and 5 hours, respectively, the simultaneous pancreas kidney transplantation lasted 8 hours. Mean warm ischemia time of the pancreas graft was 34 minutes. All pancreata functioned immediately, making their recipients insulin-independent. The kidney graft, revascularized after 35 minutes of warm ischemia, also functioned immediately and fully. No patient had complications during or after surgery; mean hospital stay was 21 days. After a mean follow-up period of 3.7 months, all recipients are alive with optimal graft function. **Conclusion** We have shown the feasibility of laparoscopic robot-assisted solitary pancreas and simultaneous pancreas and kidney transplantation. If the safety and feasibility of this procedure can be confirmed in larger series, laparoscopic robot assisted pancreas transplantation could become a new option for diabetics needing beta-cell replacement.

Management of Insulinomas: Perioperative and Long-term Outcomes Following Enucleations and Pancreatic Resections in 198 Patients

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Context Enucleation usually represents the procedure of choice for the treatment of insulinomas. However, depending on the site and size of the lesions, pancreatic resections may be required. **Objective** To analyze perioperative and long-term outcomes following enucleation/pancreatic resection for insulinomas at two high-volume centers. **Methods** One-hundred and 98 patients (116 females, 58.5%; median age: 48 years) underwent surgery for insulinomas between 1990 and 2008. Demographics, surgical procedures, complications, pathology and long-term outcomes were evaluated. **Results** All patients had symptoms of hyperinsulinism with positive fasting glucose test. Eleven patients (5.5%) had MEN-1 syndrome. No "blind resections" were performed. Surgical procedures included 106 enucleations (54%) and 92 pancreatic resections (46%). There was no mortality, overall morbidity was 52%. Eighteen percent of patients had clinically significant pancreatic fistula. The rate of overall, morbidity, overall and grade B-C pancreatic fistula did not differ

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between enucleations and pancreatic resections, but enucleations had a higher reoperation rate (8.5% *vs*. 1%, P=0.018). According to the 2000 WHO classification there were 129 benign insulinomas (65%), 62 tumors with uncertain biological behavior (31.5%) and seven well differentiated carcinomas (3.5%). All insulinomas were G1 or G2 endocrine tumors. Multiple insulinomas were found in 8% of patients. Patients with MEN-1 syndrome were significantly younger than non-MEN-1 syndrome patients (31 *versus* 48 years, P=0.013). MEN-1 syndrome was significantly (P<0.005) associated with a higher rate of malignancies, with the presence of multiple lesions, larger tumors and with a higher rate of pancreatic resections. Median follow-up was 65 months. Six patients (3%) (three WDEC and three uncertain behavior tumor) developed nodal or liver metastases during follow-up. Four patients (2%) died of disease. Three patients (1.5%) developed new exocrine insufficiency and eight (4%) new onset of diabetes. Pancreatic resections were associated with a higher risk of developing postoperative diabetes. **Conclusion** Insulinoma is a benign and unifocal tumor in most cases. Surgical resection is associated with no mortality, acceptable morbidity and very good functional outcomes in the long-term follow-up. Recurrence following surgical resection is uncommon and is more likely associated to the presence of WDEC and G2 tumor.

Functional Characterization of Genetic Susceptibility to Pancreatic Cancer

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Context In 2009 the PanScan project, a genome-wide association study (GWAS) identified various pancreatic susceptibility loci. Several single nucleotide polymorphisms (SNPs) in *ABO*, sonic hedgehog (*SHH*), telomerase reverse transcriptase (*TERT*), nuclear receptor subfamily 5, group A, member 2 (*NR5A2*), and two loci located in gene deserts (on chromosomes 13q22.1 and 15q14) were found to be associated to pancreatic cancer risk. **Objective** The aim of this study was to evaluate the possible associations between genetic variation and the risk of developing pancreatic cancer and the survival of the patients, and in the meanwhile to functionally characterize the genetic susceptibility loci. A secondary aim was to assess whether chronic pancreatitis and pancreatic cancer share some genetic risk factors. **Methods** Nineteen SNPs mapping to six regions identified by PanScan were genotyped in 690 patients with PDAC, 130 patients with chronic pancreatitis and 2,200 healthy controls recruited from Heidelberg and Liverpool. For 154 PDAC, 63 cases of chronic pancreatitis and 35 normal subjects, gene expression was evaluated using an Illumina array. **Results** Most of the SNPs identified by PanScan were significantly associated with PDAC risk in our study. In addition, we found one SNP in chromosome 15 that may influence overall survival of PDAC patients. Several SNPs were associated with differential expression of various genes, in particular SNP rs657152, mapping to *ABO*, and the *ABO* gene expression (P=0.001) in PDAC, and SNP rs8176720, mapping to *ABO*, and the *TNF* gene expression (P=0.001) in normal pancreatic tissue. **Conclusion** This study clearly indicates that a better understanding of the interplay between genetic variation in PC risk loci and gene expression could be an important step to shed light to the predisposition to the disease. Moreover, we have already recruited several other centers that will provide samples in order to test the findings in a larger population. Recognizing the need for further expansion of this network, the recruitment of collaborators and partner institutions is continuously ongoing.

Molecular Characterization of Primary Pancreatic Adenocarcinoma Cell Cultures

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Context Pancreatic adenocarcinoma is a highly aggressive malignancy with extremely poor prognosis characterized by rapid progression, invasiveness, and profound resistance to treatment. Moreover it is

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typically diagnosed at an advanced stage and the 5-year survival rate for pancreatic cancer is <5%. Because the molecular mechanisms contributing to the development of pancreatic cancer are still not fully understood, additional information about the biology of pancreatic cancer is highly valuable and might indicate novel tools for the clinical management of this disease. **Objective** To better analyze both phenotypic and genotypic features of pancreatic adenocarcinomas, we aimed to established pancreatic adenocarcinoma *in vitro* cell cultures from primary tumors. **Methods and Results** We have established 19 primary pancreatic adenocarcinoma *in vitro* cell cultures from surgically resected tumor masses with an efficiency of 70%: briefly, sterile non necrotic tumor samples were selected by the pathologist, samples were enzymatically dissociated for 2-16 hours, and cell suspension was plated with standard media, supplemented with different concentrations of hydrocortisone, insulin, transferrin, EGF, pituitary bovine extract and fetal bovine serum. After 1-4 weeks, depending on both the amount of the initial cells and their growth rate, cultures were morphologically and immunophenotypically characterized and, when possible, cryopreserved. Furthermore we have been also able to efficiently grow cells out of these tumors upon thawing, demonstrating banking possibility. Genotypic features of 7 pancreatic adenocarcinoma DNA samples and their corresponding *in vitro* cell culture DNAs were analyzed using multiplex MassARRAY mutation analysis which screened 19 oncogenes commonly altered in solid tumors (Sequenom OncoCarta panel v1.0). Thus we were able to prove that the established cell lines maintain the key genomic signatures of their primary tumors: out of the 238 somatic mutations tested we found completely overlapping data. **Conclusions** Our model system could enormously facilitate the efforts in both drug testing and molecular profiling for evaluating candidate anticancer agents and predicting their clinical efficacy in pancreatic adenocarcinoma.

The Burden of Grade C Pancreatic Fistula After Pancreaticoduodenectomy

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Context Pancreaticoduodenectomy (PD) still carries a high morbidity rate also in high volume institutions. Patients requiring relaparotomy, especially due to pancreatic fistula (PF), are exposed to a high risk of mortality. **Objective** To describe incidence, clinical consequences and mortality of grade C PF after PD, in comparison with re-laparotomies for other causes. Further, we compared the outcomes of different surgical strategies to treat pancreatic anastomosis failure. **Methods** Data from 778 consecutive patients undergoing PD in our department between 2001 and 2010 were prospectively collected in our pancreatic surgery database. We divided the population in three groups according to the time period: (A) 2001-2004, (B) 2005-2007, (C) 2008-2010. Data are reported in percentage and median (interquartile range). **Results** Sixty-five patients (8.3%) underwent relaparotomy after PD. Overall mortality rate was 32.3% (n=21) and was similar throughout time (group A 27.3%, B 28.6%, C 40.9%). The main cause of relaparotomy was grade C PF (4.9%, n=38; late bleeding n=26, sepsis n=12); other causes of relaparotomy included early bleeding (1.8%, n=14), biliary leakage (0.6%; n=5), and other rare events. Patients with grade C PF showed a slightly higher mortality when compared to the others (36.8% *vs*. 25.9%) and more frequently required a second relaparotomy (21.1% *vs*. 3.7%). They underwent reoperation at a later time from resection (10 *vs*. 2 days), had longer length of stay (31 *vs*. 20 days) and a longer intensive care unit stay (3.8 *vs*. 0.5 days) According to intraoperative findings and/or Ethiblok availability, PF was treated as follows: duct occlusion (DO) (n=15, 39.5%; mortality 26.7%), completion pancreatectomy (CP) (n=14, 36.8%; mortality 50%), simple drainage (SD) (n=9, 23.7%; mortality 33.3%). Length of stay after different procedures was respectively: 20 (16), 17 (12), 37 (42). Only 1 patient who underwent CP needed a further surgical procedure, compared to 4 (44.4%) patients with SD and 3 (20%) with DO. Pancreatic fistula persisted at discharge in 4/6 patients of SD group and 8/11 of DO group. During the years CP became more frequent (A n=2, B n=4, C n=8) and mortality for this procedure decreased (100%, 75%, 25%). Since 2008, CP was associated with pancreatic islet autotransplantation in 6/8 patients. **Conclusion** Patients reoperated for PF had a worse outcome with longer hospitalization and further procedures with respect to other relaparotomy causes. In recent years, owing to the availability of islet autotransplantation to reduce the metabolic impact of the procedure, CP was the favourite technique, allowing to prevent further sequelae due to persistent PF.

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A Real-World Analysis of the Outcome of Patients with IPMN and Indication for Surgery According to IAP Criteria in Whom Surgery Is Not Performed Due to Advanced Age or Comorbidities

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Context According to IAP guidelines, surgery is indicated in all main duct (MD-IPMN) and mixed variant IPMNs and in branch-duct IPMNs (BD-IPMN) if sized >30 mm or with high risk signs. These indications are valid if the patient is a good surgical candidate with a reasonable life expectancy, and may be hardly applied to elderly patients with incidental detection of IPMN, and/or major comorbidities. However, the natural history and prognosis of such patients is unclear. **Objective** To assess the outcome of patients with IPMN and indication for surgery, who did not receive surgery. **Methods** Retrospective cohort analysis of prospectively enrolled IPMNs patients. **Results** One-hundred patients (61 women, mean age: 68.8; 38-95 years) recruited; diagnosis of BD-IPMN in 76, mixed type in 21 and MD-IPMN in 3 patients. For the present analysis, patients are divided into 4 groups: Group 1: 4 patients (4%) non operable due to invasive, locally advanced or metastatic IPMN. Group 2: 63 patients (63%) with BD-IPMNs, and no features of malignancy, without indication for surgery. The remaining 33 patients (33%) had IPMNs with resectable disease and surgical indication. Of these patients, 18 (10 men, mean age: 65.7, 47-80 years; 5 BD-IPMNs, 12 mixed IPMNs and 1 MD-IPMN) received surgery (Group 3) with histologic findings of severe dysplasia or cancer in 5. In 15 patients (7 men, mean age: 75.5, 66-87 years; 7 BD-IPMNs, 8 mixed-IPMNs) resection was not performed because of the presence of comorbidities or advanced age (Group 4). In a mean follow-up period of 24.4 months 10/100 patients died, 5 of them due to IPMN (3 in Group 1, 2 in Group 4). The median survival in patients with surgical indication and resection (Group 3) compared with those patients with surgical indication and no resection (Group 4) did not differ (26 *vs*. 21.5 months; P=0.4). Survival assessed by Kaplan-Meier curve was not significantly different in these two groups (P=0.1). Risk factors for death related to IPMN in the whole population of 100 patients were age (OR: 1.1 for year; P=0.01) and MD involvement (OR: 11.,5; P=0.01). In the 33 patients with surgical indication (Groups 3 and 4), we have not identified factors associated with worse prognosis. **Conclusions** In patients with IPMN and indication for surgery, the option not to operate elderly patients and/or with major comorbidities, although not codified, may not lead to a worse outcome, and should be accurately discussed with the patient.

Meta-Analysis of the Placebo Rate of Abdominal Pain Remission in Clinical Trials of Chronic Pancreatitis

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Context Abdominal pain is the main clinical manifestation of chronic pancreatitis. The benefit of currently available therapies for pain management is uncertain. Knowledge of placebo outcomes and understanding the specific study features that influence these outcomes may aid the design of future trials. **Objective** The aim of this study was to investigate the placebo effect on abdominal pain remission rates in patients with chronic pancreatitis, and to identify influencing factors. **Methods** The MEDLINE, Embase and Scopus databases were searched and randomized placebo-controlled trials in chronic pancreatitis patients providing data on abdominal pain remission rates in placebo arms were included. Pooled estimates of the placebo rate were calculated using random-effects logistic regression analysis. Stratum-specific rates for different patient and study-level covariates were calculated to account for heterogeneity. **Results** Six randomized controlled trials (172 placebo-treated patients) met the predefined criteria. The pooled estimate of the placebo rate for abdominal pain remission was 19% (95% CI: 8-39%). There was a statistically significant heterogeneity among the studies (I^2=78%; P<0.001). A multicenter study design, a run-in period of <2 weeks, and the absence of a wash-out period in crossover trials were all significant sources of

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heterogeneity associated with higher placebo responses. **Conclusions** This meta-analysis identifies for the first time the efficacy of placebo for pain in chronic pancreatitis. A multicenter design, the length of the run-in period, and the absence of a wash-out in crossover trials explain the heterogeneity between studies. These data provide a sound basis for designing future placebo-controlled randomized clinical trials for the treatment of pain in chronic pancreatitis.

Markers of Tissue Hypoperfusion and Short-Term Outcomes After Major Pancreatic Surgery

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Context Tissue hypo-perfusion in the immediate postoperative period after major pancreatic surgery is associated with adverse outcomes. **Objective** The aim of this study was to evaluate the role of unmeasured anions in arterial blood, byproducts of anaerobic metabolism, in predicting short term outcome after pancreatic surgery. **Methods** Patients undergoing major pancreatic surgery between January 2008 and March 2011 were studied using prospectively maintained databases. Arterial blood gas analysis performed on admission to the high dependency unit after surgery was used to calculate the calculated ion gap (CIG) and non-lactate gap (NLG) using a simplified modification of the Stewart-Figge equation. Length of stay in critical care and hospital, renal dysfunction, anastomotic leak and 30-day mortality were used as short-term outcome measures. **Results** One-hundred and thirty-five patients were included in the study. Raised CIG and NLG were significantly associated with prolonged cumulative critical care stay (P=0.001 and P=0.002) as well as postoperative stay in hospital (P=0.002 and P=0.003), renal dysfunction on third postoperative day (P=0.010 and P=0.018) but not with anastomotic leak (P=0.730 and P=0.982) or 30-day mortality (P=0.513 and P=0.748). **Conclusion** Tissue hypoperfusion as measured by the calculated ion gap and non-lactate gap on the day of surgery is associated with adverse outcomes in patients undergoing major pancreatic surgery. The CIG and NLG are novel markers that can be used for goal driven optimisation of these patients in combination with other established haemodynamic parameters.

Outcome	Calculated ion gap (CIG)		Non-lactate gap (NLG)	
	Median (range)	P value	Median (range)	P value
Length of critical care stay:		0.001		0.002
- Less than, or equal to, 7 days	2.51 (-12.98 to 11.06)		1.48 (-13.58 to 9.36)	
- More than 7 days	4.54 (-12.92 to 11.90)		3.14 (-14.12 to 9.58)	
Length of postoperative stay:		0.002		0.003
- Less than, or equal to, 14 days	2.55 (-12.98 to 11.06)		1.56 (-14.12 to 9.36)	
- More than 14 days	5.30 (-11.93 to 11.90)		3.50 (-13.03 to 9.58)	
Renal dysfunction on 3rd day:		0.010		0.018
- eGFR greater than, or equal to, 60 mL/min	3.21 (-12.98 to 11.90)		1.60 (-14.12 to 9.58)	
- eGFR less than 60 mL/min	6.12 (-2.17 to 11.17)		4.16 (-3.07 to 8.47)	
Anastomotic leak:		0.730		0.982
- No	3.29 (-12.98 to 11.17)		1.81 (-14.12 to 9.58)	
- Yes	3.43 (-11.93 to 11.90)		1.75 (-13.03 to 7.18)	
30-day mortality:		0.513		0.748
- No	3.43 (-12.98 to 11.90)		1.78 (-14.12 to 9.58)	
- Yes	4.27 (-1.48 to 10.87)		2.57 (-2.38 to 6.89)	

Pancreatic Exocrine Insufficiency in Advanced Pancreatic Cancer: Fecal Elastase-1 (FE-1) Value Is a Strong Independent Predictor of Poor Survival

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Context The relationship between prognosis of advanced pancreatic cancer (APC) and exocrine insufficiency (PEI) has been poorly investigated. **Objective** Aim of the present study is to investigate a

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possible correlation between FE-1 value and survival in APC patients. **Methods** A prospective non-randomized study was conducted between 2007 and 2009. All patients with a diagnosis of APC were enrolled. FE-1 was measured at the admission. PEI was defined as "absent" (FE-1: >200 µg/g of stool), "moderate" (FE-1: 100-200 µg/g), "severe" (FE-1 <100 and >20 µg/g) and "extremely severe" (FE-1 ≤20 µg/g). Univariate and multivariable analyses were performed. **Results** One-hundred and ninety-four patients with APC were enrolled. The median FE-1 was 204 µg/g (IQR: 19-489 µg/g), being normal in 97 patients (50%). Overall, 48 (25%) had an extremely severe PEI, 28 (14%) a severe PEI and 21 (11%) a moderate PEI. Patients with extremely severe PEI had higher incidence of albumin values <40 g/L (44% *versus* 29% *versus* 14%, P<0.01), higher pancreatic head localizations (96% *versus* 73.5% *versus* 59%, P<0.01), higher rate of jaundice (70% *versus* 37% *versus* 34%, P<0.01). The median overall survival was 10.5 months. Patients with FE-1 ≤20 µg/g had a worse prognosis (median survival: 7 *versus* 11 months, P=0.031). By multivariate analysis, presence of metastases (HR 1.81, P<0.0001), haemoglobin ≤12 g/L (HR 2.12, P=0.001), albumin ≤40 g/L (HR 1.64, P=0.010) and FE-1 ≤20 µg/g (HR 1.59 P=0.023) resulted as independent predictors of survival in APC patients. **Conclusions** A low value of FE-1 is strongly correlated with a poor survival in patients with APC.

Hypofractionated Stereotactic Body Radiotherapy for Non-Metastatic Locally Advanced Unresectable Pancreatic Cancer: Preliminary Results

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Context For patients with exocrine pancreatic cancer, the only curative treatment is complete surgical resection, but less than 20% are eligible for surgery at presentation. For these patients with locally advanced disease, treatment typically consists of chemoradiation, or initial chemotherapy followed by chemoradiation if there is no progression. Stereotactic body radiation therapy (SBRT) represents a relatively new development in the field of radiation therapy and is now beginning to deliver impressive results in the treatment of deeply situated tumors of various organ sites. **Objective** To report the feasibility and early clinical results of stereotactic body radiotherapy (SBRT) delivered with modulated volumetric arc therapy (VMAT) for the treatment of patients with locally advanced unresectable pancreatic cancer. **Methods** From June 2010 to May 2011, 21 patients with unresectable pancreatic cancer and no systemic disease were treated in our Division. Patients were immobilized during multi-phases CT simulation with personalized body mask. Daily cone beam CT was performed before each fraction to minimize the set-up uncertainties. SBRT was delivered with VMAT by RapidArc technique. The prescription dose was 45 Gy in 6 consecutive fractions of 7.5 Gy each. The organs at risk (OAR) considered were: duodenum and stomach (1% and 3% of the volume receiving <36 Gy, respectively), kidneys (15 Gy to less than 35%), liver (dose at 700 cm^3 <15 Gy) and spinal cord (Dmax <18 Gy). One patient received concomitant chemotherapy (capecitabine *per os*). Local response was defined using modified RECIST (Response Evaluation Criteria in Solid Tumor) to describe the change in the irradiated lesion. **Results** At a median follow-up of 6 months, evaluable patients are locally controlled (11 stable disease, 7 partial response); six patients failed distantly, one died for other cause. There was no acute toxicity like nausea, pain or diarrhea; late toxicity is not reported due to short follow-up. **Conclusions** SBRT using VMAT is feasible, safe and effective for patients with unresectable pancreatic cancer, with minimum toxicity and good local control.

Clinical, Morphological and Functional Aspects of Patients Suffering from Pancreatitis Associated with Mutations of CFTR and SPINK1 Genes

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Context Sporadic pancreatitis may be associated with mutations of CFTR and SPINK genes. The clinical and instrumental outcome of pancreatitis associated with gene mutations (GM) differ from pancreatitis not

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associated with GM. Few data are present in literature about clinical, instrumental and functional profiles of pancreatitis associated with CFTR GM compared to those of pancreatitis associated with SPINK1 GM. **Objective** Aim of this study was therefore to compare patients suffering from pancreatitis associated with CFTR and SPINK1 GM. **Patients and Methods** Clinical, instrumental and functional data from our prospective database of patients suffering from pancreatitis associated with GM were selected. The diagnosis of GM was gathered by investigation on 35 more common CFTR GM and the two main SPINK1 GM (N34S and P55I) on leukocyte DNA extracted from anticoagulated blood specimens. Patients with clinical history strongly suggestive for cystic fibrosis underwent HPLC and, if abnormal, a complete sequence of CFTR gene was performed. Patients were divided in 3 groups: CFTR-S (single CFTR GM), CFTR-D (compound CFTR GM) and SPINK1 (single or double SPINK1 GM). **Results** Eighty-six patients (54 M, 32 F; mean age at clinical onset 29.8±15.3 years) were studied, 57 (66%) in CFTR-S group (35 M, 22 F; mean age 31±13.9 years), 12 (14%) in CFTR-D group (8 M, 4 F; mean age 24.2±15.8 years) and 17 (20%) in SPINK1 group (11 M, 6 F; mean age 30±19.2 years). Eleven patients (13%) suffered from painless pancreatitis. No differences were observed in episodes of pancreatitis, need for an endoscopic approach, evolution toward pancreatic insufficiency. However, a diagnosis of chronic pancreatitis (P=0.007) and onset of calcifications (P=0.002) were more commonly observed in SPINK1 group. Twenty-four patients (27%) underwent surgery, 12 derivative-type and 12 demolitive-type. Six patients developed a pancreatic neoplasia (4 adenocarcinoma and 2 IPMNs) at a mean age of 58 years (range 48-72 years), and 4 patients died for pancreatic adenocarcinoma. **Conclusions** Pancreatitis associated with SPINK1 gene mutations seems to differ from that associated with CFTR gene mutations.

Pancreatectomy Plus resection of Peripancreatic Arteries: A Single Institution Experience

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Context Involvement of large peripancreatic arteries, either alone or in combination with a vein segment, is considered a contraindication to pancreatic resection. **Objective** To evaluate the outcome of pancreatectomy plus resection of isolated arterial segments (AR) or concurrent resection of arterial and vein segments (AVR) at a single institution. **Methods** From November 1987 to October 2010, resection of peripancreatic vessels was performed in 246 patients along with different types of pancreatic resections. Main peripancreatic arteries, excluding the splenic artery, were resected in 67 patients (27.7%) either alone (n=27; 10.9%) or simultaneously with a vein segment (n=40; 16.3%). There were 31 males (46.3%) and 36 females (53.7%), with a mean age of 62.4 years (range 38-84 years). **Results** Forty-eight patients were diagnosed with ductal adenocarcinoma (71.6%) and 17 with either other pancreatic tumors or periampullary neoplasms. In one patient no tumor was identified and the final diagnosis was chronic pancreatitis (1.5%). Overall post-operative mortality and morbidity rates were 8.9% and 53.7%, respectively. No statistically significant difference was detected when comparing patients undergoing AR to AVR, in either morbidity (55.5% *vs*. 52.5%) or mortality (3.7% *vs*. 12.5%). Survival at 1, 3, and 5 years was not different between patients diagnosed with ductal adenocarcinoma (45.3%, 18.6% and 0) and other tumor types (73.8%, 29.5% and 29.5%). However, within the former group, patients undergoing AR had higher probabilities of survival at 1 and 3 years (56.5% and 30.1%) as compared to patients undergoing AVR (39.2% and 10.5%) (P=0.03). Histologic evidence of actual vessel infiltration was not associated to worse outcome at 1 and 3 years (37.1% and 13.3%) when compared to tumor adherence (68.6 and 22.8%). Patients requiring aggressive resection of mesenteric root, resulting in small bowel auto-transplantation, had decreased survival rates at the same time points (37.5% and 8.3%) when compared to the remaining patients irrespective of the number of vessels resected (50.4% and 26.7%), although the difference was not statistically relevant (P=0.09). Neoadjuvant treatments did not improve survival at 1 and 3 years (28.1% and 18.7% *vs*. 50% and 21.5%). **Conclusion** Pancreatectomy plus AR or AVR, carries a 4-fold increase in the risk of post-operative complications as compared to standard pancreatectomy. In the occasional patient diagnosed with ductal adenocarcinoma involving an isolated arterial segment, resection might be worth pursuing. Simultaneous involvement of artery and vein segments spells inoperability. Pre-operative medical treatments do not seem to improve survival. Actually, most of them were initially deemed inoperable, treated by chemotherapy or chemoradiation, as permanent treatment modalities, and eventually reconsidered for surgery because of survival exceeding expectations and relatively good clinical conditions without evidence of distant metastasis.

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Long-Term Survival of Patients Undergoing Pancreatectomy Plus Vein Resection and Suffering Postoperative Complications

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Context Although tumor adherence to or segmental infiltration of superior mesenteric/portal vein (SM/PV) is no longer considered a contraindication to pancreatectomy, there is no detailed information on the oncologic outcome of patients developing complications after these extended operations. **Objective** To evaluate the impact of post-operative complications on the long-term survival of patients undergoing pancreatectomy plus resection of SM/PV. **Methods** A retrospective analysis, including all consecutive patients undergoing pancreatectomy plus resection of SM/PV, was carried out at two referral centers for pancreatic diseases located in Pisa and in Stockholm, respectively. Survival was calculated for the entire cohort, for patients without *vs*. patients with post-operative complications, and for patients with medical therapies *vs*. patients undergoing surgery alone. Post-operative complications were graded according to Clavien's classification. **Results** Overall, 241 patients were included. The final diagnosis was ductal adenocarcinoma (DA) in 187 patients (77.6%), other tumors types (OTT) in 51 (21.2%) and chronic pancreatitis in 3 (1.2%). The overall morbidity and mortality rates were 47.3% and 5.3%, respectively. Repeat surgery was necessary in 21 patients (8.7%). According to the Clavien scale, 27.4% of patients developed grade 1-2 complications, 5.8% grade 3a complications, 5.4% grade 3b complications, 2.5% grade 4 complications and 5.3% grade 5 complications. There were no differences in morbidity and mortality according to tumor type (DA: 45.4% and 4.3%; OTT: 54.9% and 7.8%) or patient age (≥70 years: 45.5% and 5.2%; <70 years: 48.2% and 5.5%). A significant survival advantage at 1, 3 and 5 years was found in patients with OTT compared to DA (94.9%, 73.7% and 52% *vs*. 74.3%, 19.4% and 13.7%; P<0.0001). In patient diagnosed with DA the occurrence of post-operative complications was not associated with worse prognosis as compared to patients undergoing an uneventful post-operative course. A survival disadvantage did not became evident even considering patients with higher Clavien's grades. A significant difference in 1, 3 and 5 years survival was found in patients treated with adjuvant treatments (86.2%, 23.3% and 15.9%) as compared to those undergoing surgery alone (63.1%, 18.5% and 10.6%) (P=0.03). As opposed, neo-adjuvant treatments did not improve survival (77.7%, 43.2% and 21.6%) as compared to surgery alone (73.9%, 17.8% and 13.2%).**Conclusion** Major post-operative complications (Clavien grade ≥3b) develop in some 13% of patients after pancreatectomy plus resection of SM/PV, but do not worse long-term survival. This observation, although drawn in a multi-institutional retrospective series with all its inherent limitations, underscores the central role of surgery in the treatment of DA adherent to or infiltrating the SM/PV.

148 Consecutive Patients with LAPC Treated with RFA: Results of Long-Term Follow-up

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Context RFA is a local ablative technique which we recently demonstrated as feasible and safe when applied to Stage III pancreatic carcinoma. Controversial data in literature are disorienting about results on survival. **Objective** In this prospective observational study we carried out a preliminary assessment of RFA efficacy (in terms of survival) by considering only those patients with a minimum follow-up of 12 months. Overall (OS), disease-specific (DSS), and progression-free survival (PFS) were analyzed along with the morbidity rate. **Results** Eighty-two patients consecutively treated with pancreatic radiofrequency ablation (RFA), with a minimum follow-up of 12 months, were analyzed; 35 patients (42.7%) underwent RFA after chemo- and/or radio-therapy, while 70 patients (85.4%) received adjuvant treatment (either chemotherapy or chemo-radiotherapy) after the procedure. Forty patients (48.8%) succumbed to disease, 3 for causes related to the procedure (3.7%). Median disease-specific survival

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(DSS) was 20 months (95% CI: 13-26.3 months), with an expected 2-year survival rate of 46%. Progression of disease occurred in 68.3% of patients (n=56). Progression-free survival at 1 year was 33%, with a median of 9 months (95% CI: 6.3-11.7 months; range: 1-25 months). Within those patients with recurrence of disease, median DSS was 16 months (95% CI: 12.8-18.7 months), with a 2-year rate of 34%. During follow-up, within those patients who were judged to be downstaged (n=12; 14.6%), 4 underwent a R0 pancreatic resection. At univariate analysis, timing of RFA (before or after chemo-radiotherapy) did not significantly correlate with a better survival rate, (median: 13.4 *vs*. 17 months, respectively; P=0.556). **Conclusion** RFA seems to provide a promising outcome in patients affected by unresectable locally advanced pancreatic cancer. To address this issue, a phase III trial comparing RFA *versus* surgical exploration along with palliative procedures (when needed), both sequentially integrated with chemo-radiotherapy, is currently ongoing.

The Effect of Prophylactic Transpapillary Pancreatic Stent Insertion on Leakage Rate After Distal Pancreatectomy: Results of a Randomized, Clinical Trial

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Context Pancreatic fistula (PF) causes major morbidity after distal pancreatectomy (DP). Transpapillary pancreatic stenting has been suggested to be beneficial in treating established PF and also prophylactically, to reduce the risk of PF after DP. **Objective** To determine if prophylactic pancreatic duct stenting reduces PF formation after DP. **Methods** Patients scheduled for DP during October 2006 to December 2010 were assessed and, if eligible, randomized to DP without or with stenting before transection of the neck of the gland (DP + stent). The DP procedure was standardized and the follow-up period included the first 30 postoperative days. The outcomes were assessed according to the intention-to-treat analysis principle. **Results** Sixty-four patients were assessed and 58 randomized to either DP (n=29) or DP+stent (n=29). Mean operating time for DP was 218.8±94.1(SD) *vs*. 283.3±131.9 for DP + stent (P=0.052). A clinically significant PF (ISGPF classification grade B or C) occurred in 6 DPs (22.2%) and 11 (42.3%) DP stent patients (OR: 2.57; 95% CI: 0.78-8.48; P=0.122). The mean hospital stay for patients without a stent was 13.4±6.4 days, compared to 19.4±14.4 days for those provided with a pancreatic stent (P=0.071). **Conclusion** The results from this trial show that prophylactic pancreatic stenting does not reduce PF when performing a standardized resection of the body and tail of the pancreas.

Microvascular Density (MVD) in Pancreatic Neuroendocrine Tumors (pNET): Correlation with MDCT Post-Contrastographic Pattern and the Neoplasms Nature

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Context Couvelard *et al*. demonstrated that benign tumor (ADN) showed higher MVD with respect to borderline tumor (BRD) and well differentiated carcinomas (WDC). **Objective** Aim of our study was to correlate MDCT post-contrastographic patterns of PNET with their MVD and biological behaviour (ADN, BRD and WDC). **Methods** We compared 12 patients, who underwent quadriphasic MDCT study in early arterial (15"), pancreatic (30"), venous (70"), delayed (180") phases. Three different post-

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contrastographic patterns were identified: pattern A (early arterial/pancreatic enhancement and rapid wash-out, 4 cases); pattern B1 (early wash-in and no wash-out, 4 cases) and pattern B2 (enhancement only in venous or delayed phase, 4 cases). Greatest lesion dimension was measured. CT findings were compared with MVD in surgical pathological specimens (expressed by number of vessels/surface unit after CD34 staining; six fields for each patient) after pancreatic surgical resections. **Results** After surgical resection, pathological analysis demonstrated 2 ADN, 5 BRD and 5 WDC. We demonstrated that all ADN were associated with pattern A, showing high MVD (average level: 463 vessels/mm^2); 3/4 lesions showing pattern B1 were BRD, with middle level of MVD (average level: 373 vessels/mm^2) while 3/4 lesions with pattern B2 were WDC, demonstrating low level of MVD (average level: 237 vessels/mm^2). We obtained statistically significant differences (P<0.0001) among the 3 different CT patterns and their MVD. **Conclusions** In our opinion the MDCT post-contrastographic pattern and the MVD of PNET can suggest their biological behavior.

Minor Papilla Sphincterotomy Is an Effective Therapy in Recurrent Pancreatitis Due to Santorinicele: Experience of a Single Centre

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Context Santorinicele is a focal cystic dilatation of the terminal portion of the dorsal pancreatic duct at the minor papilla in patients with pancreas divisum that results from a combination of a weakness of the duodenal wall and a minor papilla obstruction that prevents the outflow of pancreatic juice causing recurrent pancreatitis. Pancreatic sphincterotomy could relieve obstruction, facilitating the outflow of the pancreatic juice throw the papilla reducing pancreatitis recurrences. **Objective** To evaluate the clinical outcome of patients affected by santorinicele after endoscopic treatment for reduction of acute pancreatitis frequency. **Patients and Methods** From December 2008 to June 2011 12 patients (4 male and 8 females, mean age of 57.83±13.69 years) with symptomatic santorinicele (recurrent pancreatitis), were diagnosed by MRCP with secretin stimulation. Ten patients underwent to pancreatic sphincterotomy of minor papilla: 9 *de novo* sphincterotomy and 1 re-sphincterotomy were performed. In 2 patients cannulation of the minor papilla was unsuccessfully due to not recognition of the minor papilla. Time interval between the onset of symptoms and endoscopic treatment was 6.3±7.39 years. Injection of secretin during endoscopic examination facilitate recognition of minor papilla. Minor papilla sphincterotomy was performed using a standard minor papilla sphincterotomy; prophylactic pancreatic stent was not routinely inserted (6 patients: 7 Fr 5 cm stent; 1 patient: nasopancreatic drainage). **Results** Mean follow-up after endoscopic treatment was 11.5±8.8 months. Mortality of procedure was 0% and morbidity 16.6% (one case of mild acute pancreatitis and one case of retroperitoneal perforation). There were no episodes of recurrent pancreatitis. Three patients undergone MRCP follow-up with secretin stimulation with a complete normalization of morphological and functional test. **Conclusion** Minor papilla sphincterotomy is a successful therapy in patients with recurrent pancreatitis due to santorinicele.

Cefazolin is Inappropriate as Antibiotic Prophylaxis in Pancreatic Surgery

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Context Italian guidelines recommend cefazolin for perioperative pancreatic surgery prophylaxis. **Aim** To assess the effectiveness of cefazolin as perioperative prophylaxis in pancreatic surgery. **Materials** From January 2010 to June 2011, we prospectively enrolled 72 patients that underwent surgery for periampullary diseases. Surgical procedures were: 57 pancreatico-duodenectomies, 3 total pancreatectomies, 7 biliary and

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gastric bypasses, 5 ampullectomies. Intraoperative bile samplings for culture and perioperative prophylaxis with cefazolin 2 g were performed. Forty out of 72 (56%) patients underwent ERCP before surgery (group A) and 35 (87%) of them received a stent; 32 (44%) were not submitted to any endoscopic maneuvers (group B). **Results** All patients of group A had positive bile culture while only 19% of patients of group B had infected bile (P<0.01); in group A there were 97 isolated germs and in group B 10 bacteria (overall: 46 Gram+ and 56 Gram-). Cefazolin was effective against 15% of isolated bacteria, but potentially able to sterilize bile in only 4 patients (6%). Complications were: 15 pancreatic fistulas (21%), 5 intra-abdominal abscess (7%), 4 biliary fistulas (6%), 3 duodenojejunal fistulas (4%), 16 wound infections (22%). Even if the overall incidence of complications was similar in both groups, wound infection rate was higher in group A than in group B (27% *vs*. 12%, P=0.3). Forty-two percent (27/64) of bacteria isolated from drainages of patients with abdominal infection were already present in the intraoperative bile culture. As Italian guidelines recommend repeating antibiotic administration in operation longer than twice of antibiotic half-life, from September 2010 we began to administer cefazolin every three hours during surgery. The comparison of the rate of infectious complications does not show any difference between single-dose prophylaxis group (30 patients: 42%) and multiple doses prophylaxis group (42 patients: 58%) **Conclusion** Cefazolin is effective against very few bacteria present in the bile of patients undergoing surgery for pancreatic disease. Multiple intra-operative administrations of cefazolin did not affect the rate of infectious complications. A different antibiotic prophylaxis seems therefore advisable in patients undergoing pancreatic surgery. We are going to test penicillin combined with a beta-lactamase inhibitor recommended as second choice prophylaxis by Italian guidelines.

Synergistic Interaction of Novel Lactate Dehydrogenase Inhibitors with Gemcitabine in Hypoxic Models of Pancreatic Cancer

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Context Hypoxia is a driving force in pancreatic cancer growth and metastasis. Since the muscle isoform of lactate dehydrogenase (LDH-A) constitutes a major checkpoint for the switch from aerobic to anaerobic glycolysis, we tested a series of novel N-hydroxy-2-carboxy-substituted indoles with Ki values for LDH-A reaching the low micromolar range [1]. **Methods** *In vitro* studies were performed in 14 pancreatic cancer cells lines, characterized by differential HIF-1alpha and LDH-A mRNA expression. The cytotoxic activity of the three most promising inhibitors (PI-FLY#21, 31 and 124) was evaluated with the SRB assay, whereas modulation of LDH-A mRNA, protein and activity was investigated by RT-PCR, western blot and enzymatic activity assays. Perturbation of cell cycle and apoptosis induction were studied with flow cytometry, while pharmacological interaction with gemcitabine was investigated with the combination index (CI) method. All these experiments were performed in both normoxic and hypoxic conditions (1% O_2). **Results** LDH-A expression was detected in all the pancreatic cancer cells, and significantly increased under hypoxic conditions. The novel LDH-A inhibitors demonstrated a good antiproliferative activity, with IC_{50} values ranging between 9.9 and 20.3 μM in normoxic conditions, and they proved to be particularly effective under hypoxic conditions, with 100- and 2-fold reduction of IC_{50}s in PP78 and PANC-1 cells, respectively. Furthermore, these compounds induced apoptosis, and synergistically enhanced the cytotoxic activity of gemcitabine (CI values <0.5). **Conclusion** These data provide evidence that LDH-A is a viable target in pancreatic cancer cells, and novel LDH-A inhibitors display synergistic cytotoxic activity with gemcitabine, offering an innovative tool for optimizing chemotherapy in hypoxic pancreatic tumors.

Reference

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Significant Association Between DNA Repair Polymorphisms and Survival in Pancreatic Cancer Patients Treated with Gemcitabine/Platinum Combination Chemotherapy

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Objective This multicenter study was aimed at evaluating the association of candidate polymorphisms with outcome of pancreatic cancer patients treated with the equivalent polychemotherapeutic regimens cisplatin-epirubicin-capecitabine-gemcitabine (PEXG), cisplatin-docetaxel-capecitabine-gemcitabine (PDXG) and gemcitabine-capecitabine plus epirubicin-cisplatin intra-arterial infusion (EC-GemCap). **Methods** We examined 11 polymorphisms in 8 genes (*ERCC1*, *XPD*, *XRCC1*, *CYP1B1*, *ABCB1*, *TS*, *CDA*, and *RRM1*) in 122 stage-III/IV pancreatic cancer patients treated upfront with PEXG, PDXG or EC-GemCap. Univariate/multivariate analyses compared clinical (age, sex, PS, stage, CA 19-9) and genetic parameters with overall-survival (OS), progression-free-survival (PFS) and toxicity using Fisher's, log-rank test and Cox's proportional hazards model. **Results** Patients harbouring *XPD-Gln751Gln*, *XPD- Asp312Asn* + *Asn312Asn* or *XRCC1-Arg399Gln* + *Gln399Gln* genotype had a worse prognosis. A strong combined genotype effect was observed: patients with 0-to-2 and 3-to-4 risk-genotypes had median OS of 13.5 and 10.3 months, respectively (P<0.001). *XPD-Gln751Gln* (HR=1.9, P=0.003) as well as combination of >2 risk-genotypes (HR=2.7, P<0.001), emerged as independent predictors for death-risk at multivariate analysis. No correlations were observed with toxicity. Conversely, *XPD-Gln751Gln* was associated with shorter PFS, and comparison with gemcitabine-alone-treated patients suggested its predictive significance for platinum-based regimens. **Conclusion** Polymorphisms of DNA-repair genes appear to be candidate biomarkers of primary resistance to gemcitabine/cisplatin-based polychemo-therapeutic regimens, and may offer an innovative tool for optimizing chemotherapy in advanced pancreatic cancers.

Growth Pattern of Serous Cystic Neoplasms of the Pancreas: Observational Study with Long-Term Magnetic Resonance Surveillance and Recommendations for Treatment

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Context The natural history and growth pattern of pancreatic serous cystic neoplasms (SCN) is not well understood. **Objective** This study was designed in order to get insight into the growth rate of SCN and to suggest recommendations for their management. **Methods** Patients with well-documented incidentally-discovered or minimally symptomatic SCN who underwent yearly surveillance magnetic resonance imaging were analyzed using a linear mixed model. The growth rate and the effects of different fixed factors (sex, personal history of other non-pancreatic malignancies, radiological pattern, clinical presentation, tumor site) and random factors (age and tumor diameter at the time of diagnosis) on tumor growth were investigated. **Results** Study population consisted of 145 patients. Estimated overall mean growth rate was 0.28 cm/year, but the growth curve analysis showed a different trend between the first seven years after the baseline evaluation (growth rate of 0.1 cm/year) and the subsequent period (years 7 to 10, growth rate of 0.6 cm/year, P<0.0001). Tests for fixed effects demonstrated that an oligo/macrocystic pattern and a personal history of other tumors are significant predictors of a more rapid mean tumor growth (P<0.0001, and P=0.022, growth rates of 0.34 cm/year). Furthermore, tumor growth increased with age (P=0.0001). **Conclusion** Overall, SCN grow slowly, and an initial non-operative approach is feasible in all the asymptomatic or minimally symptomatic patients. The oligo/macrocystic variant

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and a past history of other non-pancreatic malignancies impact on tumor growth. In any case, a significant growth is unlikely to occur before seven years from the baseline evaluation. Tumor size at the time of diagnosis should not be used for decisional purposes.

Pancreatic Tumors in Childhood and Adolescence: Uncommon Neoplasms with Favorable Outcome

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Context Pancreatic tumors in children and adolescents are uncommon and may show different histological patterns. Little information is available on their actual incidence, natural history and surgical management. **Objective** Aim of the present paper is to analyze the experience with surgical treatment of primary pancreatic neoplasms in children and adolescents at a single, high-volume centre for pancreatic diseases. **Methods** Retrospective review of medical records and pathology reports of patients younger than 18 years who underwent surgery at the Verona University Hospital from 1990 through 2010. **Results** Study population consisted of 20 patients. Abdominal pain and palpable mass were the most common presenting symptoms. No patient had a locally-advanced, unresectable or metastatic disease. Complete resection (R0) was achieved in 19 patients. There was no postoperative mortality, postoperative complications occurred in 5 (25%) cases. Histological examination revealed 12 solid pseudopapillary tumors, 5 neuroendocrine tumors, 2 cystadenomas, and 1 epithelial malignant tumor. At a median follow-up of 49.5 months (range 7-234 months), there was no tumor recurrence. As per long-term complications, postoperative diabetes was diagnosed in one patient, four other patients developed pancreatic exocrine insufficiency. **Conclusion** In the setting of a high-volume surgical centre, radical resection of pancreatic tumors in children and adolescents is associated with acceptable morbidity and favourable long-term outcome.

Comparing RECIST and Choi's Criteria After Neoadjuvant Chemoradiotherapy in Patients with Resectable Pancreatic Cancer

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Context Assessment of response after neoadjuvant therapy for solid tumours is based on RECIST criteria. In 2007 Choi *et al*. published a new classification system. **Objective** To evaluate the accuracy of the two classification systems for pathological response to neoadjuvant therapies. **Methods** From 2008 to 2010, 11/27 patients (40.7%) affected by pancreatic adeno-carcinoma underwent neoadjuvant therapy with gemcitabine and radiotherapy within a randomized study comparing chemoradiotherapy plus surgery *vs*. surgery alone. We assessed radiological response after neoadjuvant therapy applying RECIST criteria, that evaluate differences in CT size, and Choi's criteria that consider changes both in size and density at CT. We compared restaging with intraoperative and pathologic data of the patients undergone surgery. A statistical analysis was made with Kendall's concordance test. **Results** Ten out of 11 (90.9%) patients completed the neoadjuvant therapy while 1/11 (9.1%) died for acute myocardial infarction. At restaging, using RECIST criteria, we registered 8 (80%) patients with stable disease and 2 (20%) cases of progression of the disease with development of liver metastases. Instead Choi's criteria assessed 5 (50%) partial responses, 3 (30%) stable diseases and 2 (20%) progressive diseases. Eight patients were considered to be resectable but 2 (25%) underwent palliative surgery for locally advanced neoplasm. For 6 patients undergone resection the pathologic examination showed 2 cases (33.3%) of partial macroscopic response and 4 (66.7%) partial microscopic responses. The concordance test showed that the two systems matched (P=0.023). Comparing concordance between each classification with intra-operative and pathological findings, we found a significant concordance for Choi's criteria (P=0.006) while RECIST criteria did not show any correlation

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(P=0.094). **Conclusion** In our experience, Choi's criteria seem to evaluate response after neoadjuvant therapy in patients with resectable pancreatic cancer better than RECIST. Due to the small number of patients, larger prospective studies are needed.

Hyperglycemia-Induced S100A8 and S100A9 Target Akt and NF-kB Signaling in Pancreatic Cancer Cells

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Context In pancreatic cancer (PaCa) S100A8 is highly expressed by stromal cells when SMAD4 is not mutated or by cancer cells when SMAD4 is mutated, suggesting the existence of a link between TGF-b and S100A8 pathways. Moreover S100A8 and its binding partner S100A9 are suggested to be involved in cancer progression and in cancer-associated diabetes mellitus. **Objectives** To analyze S100A8 and S100A9 expression levels in peripheral blood mononuclear cells of patients with PaCa, chronic pancreatitis (ChrPa) or pancreatobiliary tract tumors (PBT) and to ascertain S100A8/S100A9 interactions with TGF-b1 on PaCa Akt and NF-kB signalling. **Methods** Fifty-five PaCa, 12 ChrPa and 15 PBT were studied. S100A8 and S100A9 mRNA expression levels were quantified by RT-PCR (Taqman chemistry). Capan-1 (SMAD4 mutated) and MiaPaCa2 (SMAD4 wild type) cell lines were used to analyze S100A8, S100A9 and TGF-b1 effects on Akt (pAkt473) and NF-kB (pIkBa) signalling by western blotting. **Results** S100A8 and S100A9 expression levels were correlated with each other (r=0.637, P<0.0001), but none of these proteins vary between groups (F=0.65, P NS; F=2.75, P NS) or, in PaCa, between tumor stage (t=1.24, P NS; t=0.56, P NS). S100A8, but mainly S100A9, were directly correlated with fasting plasma glucose (r=0.22, P=0.05; r=0.46, P<0.0001), HbA1c (r=0.11, P NS; r=0.37, P=0.002), and insulin (0.37, P=0.008; r=0.46, P=0.001). The heterocomplex S100A8/S100A9, not any single molecule, induced Akt473 phosphorylation, which was enhanced by TGF-b1. IkBa phosphorylation of MiaPaCa 2 was slightly affected by S100A9 treatment only. In Capan-1 S100A8 was ineffective, while S100A9 and S100A8/S100A9 complex induced a highly significant increase of IkBa phosphorylation, which was not modified by TGF-b1. **Conclusions** Blood expression levels of S100A8 and S100A9 do not reflect the presence of malignancy, but a poor glycemic control. In PaCa associated diabetes mellitus higher levels of these proteins might favour cancer cell growth by inducing Akt and NF-kB signalling. TGF-b1 might act as a S100A8/S100A9 co-factor when SMAD4 mutations occur.

Branch Duct Intraductal Papillary-Mucinous Neoplasia: Thin Red Line Walking Between Surgery and Surveillance

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Context Performing pancreatic resection or surveillance in patients affected by branch duct intraductal papillary mucinous neoplasms (BD-IPMN) is mainly based on radiological features. **Objective** To identify whether different subgroups of BD-IPMN display a characteristic clinical behavior, and to investigate clinical and radiologic predictors of dysplasia/invasiveness. **Patients and Methods** Fifty-two specimens of resected BD-IPMN were reviewed by a dedicated pathologist. A correlation between histologic subtypes (gastric, intestinal, pancreatobiliary and oncocytic) and degree of dysplasia/ invasiveness (mild, moderate, severe dysplasia and invasive carcinoma) was made. For the purposes of the present study, histologic subtypes were dichotomized into gastric and non-gastric, and the degrees of dysplasia into adenomas and borderline-to-invasive IPMN. Furthermore, family history of cancer, symptoms, tumor markers, and magnetic resonance cholangiopancreatography (MRCP) features were correlated with pathological findings. **Results** A non-gastric subtype was associated with borderline-to-invasive BD-IPMN (P<0.01). This association was independent of tumor diameter. Adenomas arose only

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from the gastric subtype, in borderline-to-invasive BD-IPMN arisen from a gastric epithelium, a correlation with tumor diameter (>3 cm) was found. Furthermore, a dilated main pancreatic duct, the presence of mural nodules and thickness of the cystic wall on MRPC were significantly associated with borderline to invasive BD-IPMN (P<0.05). The dilation of the main pancreatic duct is highly correlated to the risk of degeneration at the multivariate analysis (P<0.05). **Conclusion** BD-IPMNs encompass a group of neoplasms with different biological behaviors. Mainly, gastric type IPMNs show a more indolent behavior and the risk of malignancy seems to increase with the diameter (as opposed to the intestinal type). We confirm the role played by the radiological features (mural nodules, thickness of the cystic wall, dilation of the main pancreatic duct on MRPC) as predictors of malignancy. A particular role is played by the dilation of the main pancreatic duct highly related to the risk of degeneration also at the multivariate analysis.

Pattern and Clinical Predictors of Lymph Node Involvement in Neuroendocrine Neoplasms of the Pancreas

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Context Well differentiated pancreatic neuroendocrine neoplasms (PNENs) are often indolent neoplasms without pathological lymph node metastasis (pN1). Therefore, in patients with low risk of pN1 a lymphadenectomy could be avoided. **Objective** To construct a model for predicting the risk of pN1 prior to surgical resection. **Methods** Databases from the University of Verona and the Beaujon Hospital were queried. Data of all patients with resected (R0 or R1) non-functioning PNEN between 1993 and 2009 were analyzed. **Results** Data were analyzed for 194 patients. Metastases were present in the dissected lymph nodes of 58 patients (30%). The 5-year disease free survival for pN1 patients was significantly lower than for pN0 (66% *vs*. 93%, P<0.0001). Multivariate analysis suggested the independent predictors of pN1 were radiological nodal status (rN) (odds ratio (OR) 3.4, P=0.008), localization in the pancreatic head (OR 3.4, P=0.002) and the degree of differentiation (G2 *vs*. G1, OR 3.5, P=0.001). When the degree of differentiation was excluded, on multivariate analysis rN1 (OR 4.1, P=0.001), localization in the pancreatic head (OR 3.2, P=0.002), and radiological size >4 cm (OR 2.5, P=0.012) were independent predictors of pN1. **Conclusion** Patients with PNEN-G1 of the pancreatic body, in the absence of radiological node involvement, have a low risk of pN1. If a preoperative cytological diagnosis is not achieved, radiological size of the lesion is a powerful alternative predictor of pN1.

Does Preoperative Chemotherapy Affect Short-Term Outcome After Pancreatic Resection? A Case-Match Analysis

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Context Preoperative chemotherapy (PCHT) has recently been suggested also in patients with resectable disease. Apart from the risk of tumor progression because of delay in surgical treatment, one of the most important concerns about PCHT in resectable pancreatic cancer patients is the potential risk of increasing postoperative morbidity and mortality, as reported in rectal cancer and liver metastatic patients. No comparative study is available at present on the impact of PCHT on short-term postoperative outcome after pancreatic resection. **Objective** To assess the impact of PCHT on short-term postoperative outcome after pancreatic resection. **Methods** Between 2003 and 2010, 40 patients with locally advanced pancreatic cancer received gemcitabine-based chemotherapy and successfully underwent resection. Each patient was matched with two control patients with pancreatic adenocarcinoma selected from our prospective electronic database. Match criteria were age (±3 years), gender, ASA score, type of resection, pancreatic duct diameter (±1 mm), and tumour size (±5 mm). Primary endpoint was morbidity rate. Secondary endpoints were mortality rate and length of hospital stay (LOS). Additionally, the degree of fibrosis and fatty infiltration of the pancreatic specimen were assessed by an experienced pathologist blinded to both surgeon

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judgment and preoperative treatment, in order to analyze structural changes related to PCHT. **Results** Overall morbidity rate was 45.0% in the PCHT group *vs*. 50.0% in the control group (P=0.62). Pancreatic fistula rate was 17.5% in the PCHT group *vs*. 25.0% in the control group (P=0.49). Mortality rate was 5.0% in the PCHT group and 2.5% in the control group (P=0.60). Mean length of hospital stay was 11.8 days in the PCHT group *vs*.12.8 days in the control group (P=0.31). There was no difference in resection margin status, while the rate of patients without nodal involvement (N0) was higher in the PCHT group (47.5% *vs*. 18.8%, P=0.001). PCHT did not cause structural changes in the pancreas in terms of degree of fibrosis and interlobular fat infiltration. **Conclusion** PCHT did not adversely affect short-term outcome after pancreatic resection.

Single Step EUS-Guided Transmural Drainage of Pancreatic Pseudocysts: Analysis of Technical Feasibility, Efficacy, and Safety in a Single Center

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Context Endoscopic ultrasound (EUS)-guided drainage of pancreatic pseudocysts (PPs) has become a first line therapy in many centers. This is due to the ability of the EUS instrument to assess the wall thickness, identify major vessels and find the closest access to the fluid cavity. Surgery may be avoided in cases when successful EUS-guided drainage is performed, with no recurrence of the cyst. However, acute surgery may be needed in some cases of complications such as perforation or major bleeding. **Objective** The aim of this retrospective study was to evaluate technical feasibility, efficacy, and safety of single-step EUS-guided transmural drainage of PPs in our centre. **Methods** Over a three-year period, endoscopic drainage of PPs was performed in 36 patients (mean age 53±11.9 years) by using interventional echoendoscopes (Pentax EG-3830 UTK) with a single step device for enter, dilate and stent the cavity. Technical success of the transmural procedure was defined as complete access and successful placement of one or more stents within the pseudocyst with no immediate complication. Clinical success was defined as complete resolution of the pseudocyst, documented at 3 months with CT scan or MRI control. **Results** Endoscopic stent placement was successful in 94% (34/36) of patients (89% transgastric approach 32/36; 11% transduodenal approach 4/36) and failed in 2 patients because of acute angulation (n=1) and because of rapid decompression of the pseudocyst after penetration of the cystotome, that dislodged the guidewire and it was impossible to regain access to the cavity (n=1). Clinical success was achieved in 89% of patients (32/36), two patients had recurrent PP and both were successfully treated by a second EUS-guided drainage. Post procedure, one patient (2.7%) complained of severe pain and physical examination revealed abdominal distension. A CT of the abdomen revealed free air consistent with perforation. The patient underwent emergency surgery, the perforation was repaired and a cyst-enterostomy was performed with successful outcome. One patient who had necrotic collection, developed post-procedural infection one week following discharge and underwent surgery with successful outcome. No bleeding occurred. No procedure-related mortality was observed. **Conclusion** Single step EUS-guided transmural drainage was feasible in 94% of cases, with an efficacy of about 90%. Complications are rare during EUS-guided drainage of PPs and can be managed successfully. Our results are comparable to previously published data.

Electroporation of Pancreatic Adenocarcinoma Cell Lines Enhances the Anti-Tumor Effect of Bleomycin and Cisplatin

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Context Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive tumor for which no effective therapeutic treatments are available so far. Recent evidence suggests that electroporation (EPN) can be used *in vivo* to increase the uptake of chemotherapeutic agents by tumour cells, thus leading to enhanced response rate. **Objective** We aimed at defining the optimal parameters for electrical pulses and concentration of drugs (bleomycin and cisplatin) by *in vitro* analysis of PDAC cell lines. **Methods** Two cell

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lines were used: PANC1 and MiaPaCa2. Cell lines received eight pulses of 100 µs with different electric field strength (0.5 and 1 kV/cm). Permeabilization was determined by flow cytometry after simultaneous exposure of cells to electric pulses and lucifer yellow, whereas cell viability was measured by MTT assay. The cytotoxicity of bleomycin and cisplatin on pulsed cells was determined using the optimal permeabilization conditions, and IC_{50} values were calculated. **Results** The optimal electric conditions was defined as 1 kV/cm, eight pulsed of 100 µs duration. In these conditions the mean value of viability of the pulsed controls was 95% of that of the unpulsed controls with a permeabilization of 90% of pulsed cells. Using these optimized parameters for EPN, cell lines showed enhanced sensitivity to both bleomycin and cisplatin. After EPN, the IC_{50} of bleomcycin could be reduced by a factor of 160 and 50 for PANC1 and MiaPaCa2, respectively. The IC50 value for cisplatin could be reduced by factors ranging from 4-10 in the cell lines after EPN. **Conclusions** We established an optimized protocol for EPN *in vitro* suggesting that bleomycin rather than cisplatin may be effective *in vivo* as part of EPN treatment.

Pancreas-Preserving Duodenectomy is a Safe Alternative to High-Risk Pancreaticoduodenectomy for Premalignant Duodenal Lesions

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Context Pancreaticoduodenectomy (PD) with pancreaticojejunal anastomosis to a normal pancreas with small duct reflects an increased risk for development of pancreatic fistula (PF) and overall morbidity, particularly in overweight patients. Pancreas-preserving duodenectomy (PPD) for pre- or low-malignant duodenal tumors, where pancreas is normal, could be a safer alternative to high-risk PD (HR-PD). **Objective** To compare the postoperative outcome after PPD and HR-PD. **Methods** All patients who underwent PPD and HR-PD between 2006 and 2010 in Karolinska University Hospital were retrieved from a prospective data registry. The demographics, length of stay (LOS), and postoperative morbidity and mortality were analysed. **Results** Forty patients operated with HR-PD and 15 with PPD were identified. PPD patients were younger (48 *vs*. 64 years), more overweight (67% *vs*. 30%, P=0.01), and none had adenocarcinoma on pathology. There were no differences in total morbidity between PPD and HR-PD. PPD patients, however, exhibited fewer PF (13 *vs*. 38%), fewer severe (Clavien grade ≥3b) complications (13 *vs*. 38%), less ICU stay (6.8 *vs*. 20%), less reoperations (6.8 *vs*. 25%), lower mortality (0 *vs*. 2.5%), and shorter LOS (17 *vs*. 26 days), but the numbers was too small to reach statistical significance. PPD was performed with shorter operative time than HR-PD (319 *vs*. 422 min) and with less intraoperative blood loss (616 *vs*. 1,027 mL, P<0.001). **Conclusion** PPD can be performed with shorter operative time, less intraoperative loss and with comparable, if not slightly better, postoperative outcome than HR-PD in this small series. Hence, PPD is the preferable surgical alternative for resection of pre- and low-malignant duodenal lesions.

PTEN Loss is a Marker of Poor Prognosis in Surgically Resected Chemotherapy Treated Pancreatic Ductal Adenocarcinoma

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Context The PTEN (phosphatase and tensin homolog) gene encodes a ubiquitously expressed tumor suppressor dual-specificity phosphatase that antagonizes the PI3K signaling pathway through its lipid phosphatase activity and negatively regulates the MAPK pathway through its protein phosphatase activity. PTEN is involved also in the maintenance of genomic stability. PTEN loss of function is a common genetic aberration in several tumor types. PTEN role in pancreatic ductal adenocarcinoma (PDCA) is still poorly investigated, although PTEN is relevant in suppressing early development of pancreatic adenocarcinoma in a mouse model, its loss abrogates ras induced senescence and alterations of the PTEN locus at chromosome 10q23.3 are frequently observed in human PDCA. **Objective** To investigate PTEN prognostic role in PDCA evaluating its protein expression by immunohistochemistry **Materials** Between 2002 and 2008, 63 patients, median age 60 year, with stage IB/III underwent curative surgery at our institution. These patients were enrolled in a clinical trial and randomly assigned to receive adjuvant

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chemotherapy with either gemcitabine (n=30) or with a combination of cisplatin, epirubicin, 5-fluorouracil, gemcitabine (PEFG regimen; n=33), followed in both arms by chemoradiation if systemic recurrence was not evident at the end of chemotherapy. Resection margins were microscopically negative in 37 patients (59%); 21 patients (33%) had grade 3 disease; 51 (81%) had nodal involvement. PTEN expression was graded as 0 (absence of immunoreactivity), 1+ (weak immunoreactivity), 2+ (preserved staining) in neoplastic cells. **Results** After a median follow-up for living patients of 42 months (range 36-108 months), 52 patients had recurrence and 47 died of disease. Median OS was 30 months (23.4 months in gemcitabine arm and 32.0 months in PEFG arm) and 3-year OS was 38%. Median DFS was 13.5 months. For patients with PTEN 0 (n=18) median survival was 18.3 months and 3-year OS 17% while for patients with PTEN 1 or 2 median survival was 32 months and 3-year OS 47% (P=0.023). **Conclusions** PTEN loss identifies PDCA patients with the worst prognosis. However, considering that in addition to its well-described role in cell signaling, PTEN is involved in the maintenance of genomic stability and loss of PTEN function causes defects in repair of DNA double-strand breaks by homologous recombination, the possibility that PTEN negative PDCA could benefit of PARP inhibitors must be explored.

New WHO Classification for Pancreatic Endocrine Tumors: A Better Model?

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Context In 2010 WHO released a new classification (NWHO) system for endocrine pancreatic tumours (NETs). **Objective** To compare the NWHO and previous one (WHO) in patients affected by NETs. **Methods** From January 1980 to December 2010, 89 consecutives patients underwent surgical intervention for NETs. Data regarding sex, age, presence of symptoms, hormonal status, presence of MEN1, surgical procedure, R status, TNM stage, older and new WHO classification and disease specific survival (DSS) were collected. Multivariate analysis, including WHO and NWHO, was carried out to evaluate the independent factors related to DSS. A sensitivity analysis was performed to include patients in which NWHO was impossible to be calculated. **Results** Mean age of patients was 54.7±14.2 years. There were 46 (51.7%) females and 43 (48.3%) males. Symptoms were present in 68 (76.4%) patients. Fifty-two (58.4%) patients had non-functioning NETs. Left pancreatectomy was performed in 48 (53.9%) cases, atypical resection in 22 (24.7%), pancreatico-duodenectomy in 12 (13.5%), total pancreatectomy in 2 (2.2%) and palliative surgery in 5 (5.6%). R0/1 resection was carried out in 79 (88.7%) cases. According TNM stage there were: I, 27 (30.3%); II, 29 (32.6%); III, 22 (24.7%); IV, 11 (12.4%). According WHO, 46 (51.7%) patients had a well differentiated tumours (WDT), 32 (36%) well differentiated carcinoma (WDCa), 11 (12.4%) poorly differentiated carcinoma (PDCa). The NWHO was available only in 49 (55.1%) patients: 20 (22.5%) NET G1, 25 (28.1%) NET G2, 4 (4.5%) neuroendocrine carcinomas (NEC) G3. At multivariate analysis WHO and R2 status were the only independent factors related to DSS (RR=6.7, P<0.001; RR 2.0, P=0.018; respectively). WHO stratifies DSS better than NWHO: RR 0.12 (95%CI: 0.01-0.99; P=0.049) and RR 0.16 (95% CI: 0.16-0.05; P=0.002) comparing WDT *vs*. WDCa and WDCa *vs*. PDCa, respectively. The sensitivity analysis confirmed in two models the superiority of WHO while in others two we did not find any difference. **Conclusion** In our experience WHO still remains the best prognostic factor to predict DSS in patients with NETs.

Post-Operative Analgesia After Pancreatic Surgery: Safety and Efficacy of Continuous Wound Infusion of Ropivacaine

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Context Continuous wound analgesia (CWA) is used in various surgical settings and several studies had demonstrated a satisfactory pain control after abdominal surgery, reduction of opioids requirements

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and earlier return to normal bowel function in colorectal surgery. The analgesic efficacy of continuous local preperitoneal anaesthetic instillation after pancreatic surgery is not widely reported in literature, while is often used epidural analgesia or intravenous morphine infusion. **Objective** To evaluate the efficacy of CWA to control post-operative pain, the incidence of complications related to wound catheter and the differences between epidural analgesia (EA) and CWA and opioids, after elective pancreatic surgery. **Materials** From October 2010 to May 2011, 68 patients undergoing elective subcostal laparotomy for pancreatic surgery received post-operative analgesia: 32 with CWA of ropivacaine, 12 with continuous EA of ropivacaine and fentanyl, 24 with continuous intravenous morphine infusion. We evaluated the following parameters: quality of analgesia by static and dynamic (coughing) VAS, use of rescue drugs, timing of first bowel movement (flatus and stool), procedure complications. **Results** The mean static VAS at first postoperative hours (<12 h) was 1.5±2.2 in CWA, 4±3 in EA and 0.58±1.7 in morphine group. We did not register statistically significant difference in rest or dynamic pain scores among the 3 groups. In the first post-operative day, 8 patients (25%) with CWA needed other analgesic drugs (ketorolac or opioids), while 5 out of 12 with EA (41%) (P=0.29). The median time of first flatus in CWA group was 64±21 h, in EA group 77±18 h and in morphine group 76±28 h; there was not any statistical difference, although CWA allows a more rapid stool canalization (mean 88 h) than morphine (117 h) and EA (110 h) (P<0.05). Three patients (9%) of CWA group had therapeutic failure of analgesia, while 25% of patients with EA. We observed the accidental removal of catheter in 3 EA and in 1 CWA. No procedure related complications were registered. **Conclusion** Local anaesthesia infusion at the fascial plane is an effective analgesia alternative to epidural or opioids infusions. CWA is a safe procedure with a more rapid bowel function recovery that influences the post-operative patient rehabilitation.

A Twist in the Tale After Pancreatic Resection for Cystic Neoplasms: When Histological Examination Reveals a "Whipple for Nothing"

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Context While surgical timing and management of pancreatic cystic neoplasms have not been extensively assessed yet, diagnostic patterns of such incidence increasing entities appear nowadays clearly defined especially in high volume centres. **Objective** To analyze the potential mismatch between preoperative diagnosis and final pathological report of resected pancreatic cystic neoplasms. **Methods** Data pertaining to patients observed from January 2000 till December 2010 for pancreatic cystic neoplasms at the authors' institution were retrieved. Diagnostic pathways and indication to surgery were critically reconsidered. All histological examinations were re-reviewed. Patients presenting with a mismatch between preoperative diagnosis and postoperative histological report were the focus of the analysis. Mismatched diagnoses were then divided into "worsening" and "ameliorative" prognosis. Finally, critical re-examination of such cases was done to identify avoidable and non-avoidable mistakes. **Results** Four-hundred and 51 (43.3%) out of the 1,041 patients observed underwent a pancreatic resection. In 41 cases (9%) we found a divergence between preoperative diagnosis and histological report. Of these, 20 where preoperatively diagnosed as IPMN, 13 as MCN, 3 as SCN and 5 as other cystic neoplasms. In 23 cases (56%) histological report showed an ameliorative o similar prognosis than preoperatively expected, and 15 of these (36.5%) were non-neoplastic ("Whipple for nothing"). In contrast, in 18 patients (44%) a worsening diagnosis in terms of postoperative prognosis was found. In particular 11 (26,8%) patients had an underlying ductal adenocarcinoma. From critical analysis of the data, 33 resections (80%) were unavoidable, while 8 (20%) could have been avoided through a more accurate diagnostic evaluation and/or preoperative observation. **Conclusions** Even in high volume centres, preoperative diagnosis of pancreatic cystic neoplasms is affected by a certain degree of inaccuracy which was in the waste majority of cases unavoidable. A moderate risk of an unpredicted underlying ductal adenocarcinoma has to be taken into account.

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Positron Emission Tomography *vs.* International Consensus Guidelines in Detecting Malignancy of Intraductal Papillary Mucinous Neoplasms of the Pancreas

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Context The main problem in management of intraductal papillary mucinous neoplasms of the pancreas (IPMNs) remains the correct diagnosis of malignancy. International consensus guidelines (ICG) have been widely used to select patients candidates to surgery or suitable for surveillance, but their low specificity increases the number of benign IPMNs undergoing resective surgery. Positron emission tomography (PET) has been proved highly sensitive and specific in detecting malignancy in pancreatic IPMNs [1]. **Objective** Aim of this study was to assess the reliability of ICG and PET in distinguishing benign from malignant IPMNs of the pancreas. **Methods** Patients with suspected IPMNs of the pancreas observed from January 1989 to July 2010 were collected and classified as cases of main duct, mixed type, and branch type IPMN. The indication for resection or surveillance was reviewed retrospectively for all patients according to ICG. PET was considered positive for a standardized uptake value (SUV) >2.5. Surveillance included clinical examination, laboratory tests, CA 19-9 serum levels, and CT and/or MR every 6 months for 2 years and yearly thereafter. PET was repeated in clinically or radiologic suspected cases, or if tumor markers increased. EUS was rarely performed. **Results** Sixty-one main duct or mixed type and 101 branch type IPMNs were included. Histological diagnosis of IPMN was available in 81 patients, missing for 1 locally-advanced IPMN, while 80 patients are under surveillance. Conservative surgery was performed in 16/68 patients with benign IPMNs. The sensitivity, specificity, PPV, NPV, and accuracy of the ICG in detecting malignancy were 93.2%, 22.2%, 59.4%, 72.7%, 61.2%, while for PET they were 83.3%, 100%, 100%, 84.6%, 91.3%. **Conclusion** PET is more accurate than the ICG in distinguishing benign from malignant (invasive and non invasive) IPMNs. Prophylactic IPMN resection in young patients fit for surgery should be guided by the ICG, whereas PET should be performed in older patients, cases at increased surgical risk, or when the feasibility of parenchyma-sparing surgery demands a reliable preoperative exclusion of malignancy.

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The Heterotrimeric G15 Protein May Support Sustained PKD1 Activation

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Context Protein kinase D1 (PKD1) involvement has been documented in a variety of cellular processes important to cancer development. Inhibiting PKD1 activity blocks pancreatic carcinoma (PaCa) growth *in vivo* and PKD1 is being evaluated as a novel therapeutic target in this deadly disease. PKD1 is typically activated by the phospholipase C pathway which is on turn activated by heterotrimeric Gq/11 proteins. We previously described the exceptional resistance of the Gq/11 family member G15 to arrestin-dependent desensitization, the universal regulatory mechanism that acts on receptors to prevent overstimulation of other G proteins. More recently, we confirmed microarray data describing G15 expression in pancreas adenocarcinoma. **Objective** Here we investigated if G15 could be responsible for sustaining PKD1 activation in response to receptors that were either acutely stimulated or that had reached full desensitization. **Methods** PKD1 activity was monitored in COS-7 cells upon co-transfection with Galphaq-family proteins and G protein coupled receptors (GPCRs). PKD1 activation was measured by immunoblot, assessing the phosphorylation levels of two sites (Ser744 and Ser748) part of the activation

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loop that controls PKD1 catalytic activity. Similar experiments were performed in the PaCa cell line PT45 determining the functional consequences of silencing endogenous G15 alpha subunit by specific shRNA sequences. **Results** PKD1 was activated when G15 was stimulated either directly, by Al_3F_4, or by agonist activation of a GPCR. Furthermore, G15 sustained prolonged activation of PKD1 collecting signals generated by desensitized GPCRs. By converse, inhibiting the expression of G15 alpha subunit in PT45 cells reduced PKD1 tonic activation. **Conclusion:** We conclude that G15 ectopic expression may support prolonged activation of the signalling pathway leading to PKD1 and thus may contribute to support oncogenic signalling.

POSTER SESSION

Activation of MNK2/eIF4E Pathway by the Splicing Factor SRSF1 Supports Pancreatic Cancer Cell Survival to Genotoxic Stress

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Context eIF4E is a key regulator of translation initiation. Increased eIF4E levels are often observed in cancer and its overexpression elicits cell transformation by enhancing cell cycle progression and cell survival. Phosphorylation of eIF4E by the MNK kinases seems required for its oncogenic potential. The MNK family comprises two proteins, MNK1 and 2, whose mRNAs are alternatively spliced in two variants, a and b. **Objective** We have investigated the role of eIF4E phosphorylation in pancreatic cancer cell proliferation and survival. We concentrated on eIF4E modulation and discriminated between MNK1 and MNK2 activity during chemotherapeutic treatment. **Methods** Western blot analysis to detect changes in the phosphorylation status of eIF4E under gemcitabine exposure. Immunofluorescence against capsase3 and clonogenic assay to analyze apoptotic rate and toxicity. RNAi to obtain MNK1/2 or SRSF1 gene silencing and RT-PCR to analyze splicing variants of MNK2 mRNA. IHC for phosphorylated eIF4E. **Results** We found that eIF4E phosphorylation is stimulated in response to chemotherapeutic treatment of pancreatic cancer cells, in concomitance with the promotion of MNK2b variant that overrides upstream regulatory pathways. The modulation of MNK2 splicing was exerted by upregulation of the oncogenic SRSF1 splicing factor. Preventing eIF4E phosphorylation by pharmacological inhibition of MNKs, depletion of endogenous MNK2 or SRSF1 synergistically enhanced the cytotoxic effects of gemcitabine. Moreover, immunohisto-chemistry of patient specimens indicated that eIF4E phosphorylation represents an independent prognostic factor of pancreatic cancer, which predicts early disease onset and worse prognosis. **Conclusions** Treatment of pancreatic cancer cells with gemcitabine triggers a positive feedback through SRSF1-mediated splicing of MNK2b and phosphorylation of eIF4E, which protects cancer cells from drug-induced genotoxic stress. These results suggest that inhibition of MNKs activity might represent a novel therapeutic strategy for this deadly disease.

Contribution of HLA-DRB1*04 Allele to the Genetic Susceptibility of Autoimmune Pancreatitis: Preliminary Data

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

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was to investigate the role of HLA in the development of autoimmune pancreatitis in order to contribute to the understanding of the pathophysiology. **Methods** Allelic polymorphisms at the DNA level were investigated in the genes of MHC region (HLA B, DRB, DQB) with PCR based methodologies (PCR-SSP; PCR-RFLP) in 57 AIP patients (38 males, 19 females) and 183 healthy normal controls (78 males, 105 females) of the same ethnical group. All patients and controls gave their informed consent. **Results** Among HLA-DRB1 genes, we found a trend to significance for DRB1*04. PCR reactions were performed to determine the DRB1*04 specificities in the DRB1*04 positive patients: a trend to significance for HLA DRB1*0408 allele was found. Neither HLA-B nor HLA-DQB1 associations with the disease were found. **Conclusions** This study supports a role of HLA-DRB1*04 as susceptibility factor for AIP. T cells may be triggered in the pancreatic tissue upon exposure to foreign peptides similar enough to cross-react and to break immunological tolerance.

Accuracy and Safety of US guided FNA in One-Day Hospital Setting

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Context Every year in Italy 8,250 patients have a diagnosis of unresectable pancreatic cancer and need a cyto/hystological confirm to begin as soon as possible the proper medical treatment. **Objective** The purpose of this study was to assess accuracy and safety of ultrasound-guided FNA cytological sampling in one-day hospital (DH) recovery for focal pancreatic lesions in a single pancreatic centre. **Material and Methods** We reviewed 177 consecutive ultrasound-guided FNA cytological sampling procedures for focal pancreatic advanced lesions alone or with liver metastasis from January 2010 to May 2011. The procedures were performed with a contrast enhanced sonography and the diagnosis was made by a cytopathologist immediately after. We computed the sensibility, specificity and accuracy to obtain a final diagnosis, the radiological records, the presence of other morbidity and the onset of complications. **Results** The study sample included 74 (42%) women and 103 (58%) men (mean age 65.8 years). The location of the tumor was 54.8% in the head, 44.6% in the body-tail and 1 patient in all the gland; 43% had metastatic disease. The mean dimension of the tumor was 4.5 cm (range 2-8.5 cm). The histology was: pancreatic adenocarcinoma 147 (83%), endocrine tumor 7 (0.04%), pancreatitis 3 (0.02%), anaplastic carcinoma 3 (0.02%); others 6 (0.03%). In 138 (78%) the FNA was performed only on the pancreatic gland, in 39 (22%) on pancreas and liver. Sampling was diagnostic at the first FNA attempt in 151 cases (85.3%) and consequently with the use of different technique (mainly EUS) 97.7% of our patients obtained a final diagnosis. Cytologic sampling had 97.8% sensitivity, 100% specificity, and 87% accuracy. In 171 cases (97.8%) the procedure was uneventful. Only 5 (2.82%) minor complications happened (2 clinically significant pain, 2 hyperamylasemia and 1 mild pancreatitis). The 151 patients (85.3%) receiving the diagnosis at first attempt were discharged after 10 hours. Forty-four patients (24.8%) required more than a DH hospitalization either to obtain the final diagnosis with a second line diagnostic procedure or to treat comorbilities mainly cholestasis. **Conclusion** The DH ultrasound-guided FNA cytological sampling in a pancreatic centre obtains accurate and safe diagnosis in 10 hours in the most majority of cases with a consequent speed process towards medical treatment.

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

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Context Scanty data are available on diabetes mellitus associated with exocrine pancreatic disease. **Objective** 1) To define the prevalence, risk factors, and etiopathogenetic aspects of diabetes mellitus associated with exocrine pancreatic disease. 2) To evaluate the role of glucose metabolism, insulin resistance and insulinemia in prognosis of cancer patients. **Methods** A prospective observational study was performed on patients proposed for pancreatic surgery from 1/2008 to 6/2011. Four-hundred and 79 patients were characterized for gender, age, weight, BMI, history of diabetes, hypoglycaemic therapy, family history, blood glucose, insulinemia, HbA1c, GADA, IA-2A, IAA, ZnT8A, b cell function (HOMA2B), insulin resistance (HOMA2-IR and -S). In patients undergoing cancer resection disease-free and overall survival were

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assessed. **Results** 35.3% of patients were diabetic (28% with known and 7.3% with newly diagnosed diabetes); normoglycaemia was present in 45.8% of patients while impaired fasting glucose (IFG: 101-125 mg/dL) was present in 8.9%. In patients with known diabetes, onset was 34 months before admission (median). The treatment was insulin in 42.6%, OHA in 38.3%, insulin + OHA in 4.3% and diet in 14.9%. In a multivariate analysis, significant risk factors for diabetes were age, familiarity for diabetes and diagnosis of ductal adenocarcinoma. HOMAs showed that in diabetic patients the main defect is insulin secretion, being insulin resistance less affected. Islet autoantibodies were present in a subgroup of patients. Finally, in cancer patients insulinemia and insulin resistance (HOMA2IR) were independent risk factor for tumor progression by Cox regression analysis. **Conclusion** diabetes associated with exocrine pancreas disease is a complex clinical entity with unique characteristics. Insulin resistance is a determinant of biological behaviour of pancreatic cancer.

Patterns of Recurrence After Curative Resection of Pancreatic Ductal Adenocarcinoma

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Context Despite curative surgery for pancreatic ductal adenocarcinoma (PDAC), most patients develop cancer recurrence. **Objectives** The aim of the present study is to describe the patterns of failure after curative resection of PDAC. **Methods** A retrospective analysis of 411 consecutive radical resections (R0/R1) for PDAC between 1998 and 2008 was performed. The location of the first recurrence and the time to recurrence after surgical resection were considered. First recurrences were defined as local (LR), hepatic (HR) or systemic (SR). A comparison between different groups of recurrence was performed. A multivariate analysis for predictors of disease-free survival (DFS) was carried out. **Results** The recurrence was LR in 111 patients (38.2%), HR in 139 (48%) and SR in 40 patients (13.2%). The type of recurrence significantly influence overall (OS) and disease-free (DFS) survival. The median (95% CI) OS and DFS survival was 33 months (28.9-37.0 months) and 14 months for patients with LR, 18 months (15.9-20.0 months) and 9 months for those with HR, 27 months (21.5-26.4 months) and 13 months for those patients with SR. Microscopic positive residual margin (R1) is significantly associated to LR (P=0.011) whilst tumour grading (G3-4) is more related with HR (P=0.031). Nodal status influences time but not type of recurrence (P=0.212). By multivariate analysis nodal status (N1), microscopic positive residual margin (R1) and microvascular invasion were independent predictors of DFS. **Conclusion** After curative resection for PDAC a half of the patients experience a liver recurrence within 1 year after resection and quickly die of metastatic disease. Nodal involvement, positive margin status and microvascular infiltration could suggest whose part of patients are at high risk of early failure.

FDG-PET Incidental Detection of Second Cancer During Investigation for Pancreatic Diseases

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Context Positron emission tomography/computed tomography (PET/CT) is a unique imaging technique that aids in the detection of cancerous lesions. It is currently and widely used for cancer staging (both initial and follow-up), including pancreatic neoplasms. In the course of performing whole-body FDG-PET, an unexpected region of FDG uptake may be identified known as an incidentaloma: this raises the possibility of a separate primary malignancy which may require further evaluation. **Objective** This study evaluated our findings of second primary cancer incidentally discovered during PET/CT examination of patients initially investigated or followed-up for pancreatic disease. **Methods** We performed a retrospective evaluation of a prospectively collected data base of 305 patients with pancreatic pathology who were evaluated by whole body PET/CT imaging from January 2004 to December 2010. In this series 274 patients were scanned before treatment and 31 during the course of their follow-up (pancreatic cancer). Median follow-up time was 29 months (range 14-124 months). **Results** Twenty-nine patients (9.5%) had pathologic uptake of FDG in other organs, and 24 (7.8%) had second primary cancers revealed by PET/CT imaging. Of

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these, 15 tumors (62.5%) were synchronous (found at initial evaluation). Pancreatic diseases included: pancreatic cancer (n=5), IPMNs (n=9), mucinous cystadenoma (n=1). Second cancer was located in the colon (n=12), right ureter (n=1), duodenum (n=1) and breast (n=1): 13 patients underwent surgical resection and 2 endoscopic excision (colonic adenoma with high grade dysplasia). Six patients died for pancreatic cancer or colon cancer progression, and 9 are alive from 6 to 84 months. Nine tumors (37.5%) were metachronous, found at follow-up staging for pancreatic cancer (n=8) or chronic pancreatitis (n=1). Second cancer involved the colon (n=5), lung (n=3), and larynx (n=1). All but one second tumors were resected: 2 patients died for pancreatic cancer progression, 7 are alive and free of disease from 6 to 101 months. **Conclusion** Synchronous or metacronous second primary cancers may be identified by PET/CT in a small, but significant proportion of patients with pancreatic diseases. An additional diagnostic work-up is essential when abnormal findings, indicative for a second primary cancer, are obtained on PET/CT images to rule out the presence of a second malignancy.

Fecal Elastase-1 and Steatorrhea in Patients with Chronic Pancreatic Disorders or with Pancreatic Resections

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Context Limited data exist on the operative characteristics of FE1 not for the diagnosis of pancreatic diseases but for malabsorption. Moreover, the relationship between FE1 and fat losses has never been compared in malabsorption due to chronic disorders or pancreatic resection. **Objectives** 1) To clarify whether a previous pancreatic resection modifies the relationship between FE1 and steatorrhea. 2) To select the value of FE1 that better identifies the presence of steatorrhea in operated or non operated patients. **Design** Fecal fat balance (reference value: <7 g/day) and FE1 (reference value: >200 μg/g; mildly impaired: 100-200 μg/g; severely impaired: <100 μg/g) were studied in patients with pancreatic disorders and a suspicion of malabsorption. Student's t test and ANOVA were used (0.05 as limit for significance). The relationship between steatorrhea and FE1 was evaluated by a power regression analysis with a dummy variable identifying operated or non operated patients. **Results** We studied 72 patients (29 submitted to pancreatic resection). Steatorrhea (18.3±2.5 g/day) was pathological in 42 patients. FE1 (154±23.4 μg/g) was consistent with exocrine impairment in 48 (severe 42, moderate 6). Steatorrhea was greater when FE1 was severely reduced (28.2±3.61 g/day) than when it was normal (2.1±0.38 g/day) or moderately reduced (9.3±3.33 g/day) (P<0.001). The power regression line between FE1 and steatorrhea was significantly different in operated and non operated patients (P<0.001). According to our mathematical model, a steatorrhea ≥7 g/day is expected when FE1 is lower than 15 μg/g in non operated patients, lower that 225 in operated patients. The cut off value of 100 μg/g of FE1 showed a 92.1% sensitivity and a 82.7% specificity for steatorrhoea. In non operated patients, equivalent results are obtained with a more strict cut off of 15 μg/g. **Conclusions** In non operated patients, steatorrhea is expected only for extreme reductions of FE1 (lower than 15 μg/g). After pancreatic resections, steatorrhea is almost the rule even in the presence of a moderate impairment of pancreatic function (FE1 lower that 225 μg/g). Pancreatic supplements may be considered in all patients after pancreatic resections.

Development and Molecular Characterization of a Gemcitabine-Resistant Pancreatic Adenocarcinoma Cell Subpopulation

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Context The limited effect of conventional chemotherapy in pancreatic adenocarcinoma (PDAC) suggests the need for novel therapies that more directly target molecular aberrations of the disease. To date, no clear molecular characterization of drug resistant phenotype of pancreatic cancer cells is available, even if some evidence suggests a correlation with the expression of mesenchymal markers. Epithelial to mesenchymal transition (EMT) contributes to cell invasion and seems to affect the sensibility to chemotherapeutic drugs. Interestingly, the splicing factor SRSF1 has an important role in the EMT and its overexpression is sufficient to transform fibroblast. **Objective** We analyzed the protein expression of

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cancer related genes after chronic exposure of PDAC cells to gemcitabine to characterize the molecular events that could lead to chemotherapeutic resistance. **Methods** We chronically exposed PDAC cells to gemcitabine and then released them to select a drug resistant cell subpopulation. We performed western blot and mass spectrometry analyses to assay the expression of cancer related protein. We analyze the survival after drug administration by cell count with trypan blue staining. **Results** Chronical exposure of PDAC cells to gemcitabine leads to a mesenchymal phenotype and also causes an activation of ERKs pathway. Mass spectrometry analysis also showed changes in the expression of a subset of proteins, like alpha-actinin-1 and GAPDH. Moreover, this treatment selects a cell subpopulation morphologically different from the control cell line, less sensible to drug-induced cell death and which expresses higher levels of SRSF1 proto-oncogene. **Conclusion** Our results show that chronic exposure of PDAC cells to gemcitabine leads to selection of a subpopulation of drug resistant cells, which undergoes EMT and overexpresses the SRSF1 splicing factor. These features could be essential for the development of drug resistance and might highlight possible molecular targets for treatment.

A Prognostic Score to Predict Major Complications After Pancreaticoduodenectomy

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Context PD still carries a high rate of severe postoperative complications. No score is currently available to help identify the patient's surgical risk. **Objective** To develop and validate a prognostic score to predict major postoperative complications after pancreaticoduodenectomy (PD). **Methods** We prospectively collected in an electronic database preoperative, intraoperative and outcome data of 747 patients undergoing PD in our Institution from 2001 to 2010. We used a multivariate logistic regression analysis to create a new score to predict major complications defined as Clavien-Dindo classification III-V. The score was developed using a random two-thirds of the population (469 patients), and was then validated and calibrated in the remaining third of the patients (231 patients). **Results** Major complication rate was 16.7% (117/700). Independent predictors of major complications were identified as ASA score, texture of the pancreatic stump, diameter of the pancreatic duct and operative blood loss. A prediction score based on these parameters was calculated. In the validation population the risk could be predicted accurately, with a mean predicted risk of 15% versus an observed risk of 17%, and with a significant C-statistic index of 0.74. The risk to develop severe postoperative complications was 7% in "low risk" patients (0-3 points), 13% in "intermediate risk" (4-7 points) patients, 23% in "high risk" patients (8-11 points), 36% in "very high risk" patients (12-15 points). Predicted and observed risks were similar throughout the different categories. **Conclusion** This novel score may accurately predict the patient's postoperative outcome. Early identification of high risk patients could help the surgeon to adopt different intraoperative and postoperative strategies tailored on the single patient.

MR Analysis and Evolution Over Time of Multifocal Intraductal Papillary Mucinous Neoplasms Confined to Secondary Ducts

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Context Multifocal intraductal papillary mucinous neoplasms (IPMN) confined to secondary ducts are reported to be less aggressive than the main-duct type. Therefore, because of their slow evolution, are monitored over time. **Objective** The goal that our study aims is to follow the evolution over time of multifocal intraductal papillary mucinous neoplasms (IPMN) of the side branches by means of MR imaging. **Materials and Methods** Were evaluated 108 patients with multifocal IPMN of the side branches examined with MRI and MRCP (MRI/MRCP). The inclusion criteria of the study included patients with the presence of two or more dilated side branches involving any site of the parenchyma; presence of communication with the main pancreatic duct and previous investigations by MRI/MRCP after at least six months. Median follow-up was 25.8 (range 12-217) months. Exclusion criteria: MPD and mixed IPMNs; previous pancreatic surgery, lack of MRI/MRCP control performed at our institute and at least 12-month follow-up. Images were assessed

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qualitatively and quantitatively. Quantitative image analysis included: number of dilated side branches; maximum diameter of the largest branch duct; maximum diameter of main pancreatic duct in the head and body-tail, annual change of the largest lesion. Qualitative image analysis included: presence of malformations/anatomical variants of the pancreatic ductal system; site of the lesions (head-uncinate process, body-tail, ubiquitous, bridge morphology); presence of intraluminal dependant defects; presence of mural nodules. All patient were asymptomatic. **Results** At diagnosis, the mean value of cystic lesions of the side branches was 7.09. The mean diameter of the cystic lesions was 13.7 mm. The mean diameter of the pancreatic main duct was 3.6 mm. At follow-up, the mean number of cystic lesions of the branch-duct was 7.76 (P<0.05). The mean diameter of the cystic lesions was 13.9 (P<0.05). The mean diameter of the pancreatic main duct was 3.7 mm. Intraluminal filling defects in the side branches were seen in 18/108 patients (16.6%); mural nodules were seen in 3/108 patients (2.7%). **Conclusions** Multifocal IPMN of the branch-duct shows a very slow growth and evolution over time. In our study, only 3/108 patients showed mural nodules. Hence, careful non-operative management seems to be safe and effective in asymptomatic patients.

Obstructive Jaundice Negatively Impairs Dynamic Exercise Performance in Patients Undergoing Major Pancreatic Surgery

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Context Obstructive jaundice is common in patients undergoing surgery for periampullary cancer and is associated with adverse postoperative haemodynamic events. **Objective** The aim of the present study was to evaluate the effect of jaundice on preoperative cardiopulmonary function in patients undergoing major pancreatic surgery. **Methods** Patients undergoing major pancreatic surgery between August 2008 and March 2011 were studied using prospectively maintained databases. Cardiopulmonary function was assess using a symptom-limited, incremental work load exercise test on a cycle ergometer. Cardiac and pulmonary functional parameters measured at the anaerobic threshold and peak exercise were compared in jaundiced and non-jaundiced patients. Data on preoperative patient factors including demographics, body habitus and blood tests were collected. **Results** Ninety-six patients were included in the study. Obstructive jaundice was present in 53 patients (55%). Jaundice was associated with lower exercise load (P=0.006) minute ventilation (P=0.007) and oxygen consumption (P<0.001) at the anaerobic threshold as well as lower exercise load (P<0.001), minute ventilation (P<0.001), peak oxygen consumption (P<0.001) and oxygen pulse (P<0.001) at peak exercise. Lower oxygen consumption at the anaerobic threshold (P<0.05) and at peak exercise (P<0.05) were associated with jaundice independent of other preoperative factors (sex, BMI, serum albumin, serum haemoglobin and POSSUM physiology score). **Conclusion** Obstructive jaundice in patients undergoing major surgery for periampullary cancer is associated with poorer dynamic exercise performance as measured by cardiopulmonary exercise testing. Further studies are needed to explore the physiological and metabolic effects of bilirubin on cardiopulmonary function as well as peripheral oxygen utilisation and will improve perioperative optimisation of jaundiced patients undergoing major surgery.

Contrast Enhanced Ultrasonography (CEUS) and Quantitative Perfusion Analysis in the Assessment of Neuroendocrine Liver Metastases

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Context Enteropancreatic neuroendocrine tumours (EP) are rare neoplasms with a high rate of liver metastases. The gold standard for the detection of EP lesions are MRI, CT scan, and somatostatin receptor scintigraphy. Nevertheless, after an accurate diagnostic work-up, in about 10% of patients the primary site remains unknown. Contrast enhanced ultrasonography (CEUS), allows the visualization of tumour microvascular system improving characterization of liver metastases. **Objective** To evaluate, in EP liver metastases, CEUS findings in relationship with the site of primary tumour and the proliferative index (Ki67).

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Patients and Methods The present single-center prospective study enrolled 40 patients (median age 61 years, range 39-78 years) with histologically proven WDEC EP liver metastases. Median Ki67 value was 5% (range 1-30%). All examinations were performed by Toshiba AplioXV equipment, after i.v. injection of 2.4-4.8 mL of ultrasound contrast agent (UCA; Sonovue®). On the basis of the findings of the arterial phase, lesions were defined as hyper- or hypo-enhanced respective to UCA uptake of the surrounding parenchyma. Using a specific software (Qontrast®) quantitative hemodynamic parameters (peak and regional blood volume; RBV) were also obtained. **Results** CEUS showed arterial hyper-enhancement of the lesion in 29/40 patients (72.5%) and arterial hypo-enhancement in 11/40 patients (27.5%). Twelve out of 14 patients (86%) with pancreatic primary tumour (PETs) showed arterial hyper-enhancement of the liver lesion, while 13/20 patients (65%) with intestinal carcinoids tumors (CTs) had arterial hyper-enhancement of the liver metastases (P NS). No difference was observed in the proportion of hyper-enhanced liver metastases in patients with Ki67 >2 respective to patients with Ki67 ≤2 (76% *vs*. 58%; P NS). Quantitative parameters such as peak and RBV were significantly higher in patients with hyper-enhanced metastases than in patients with hypo-enhanced metastases (58% *vs*. 25.5%, P=0.0004; 2,757 *vs*. 981 P=0.0011). Moreover, Peak and RBV resulted significantly higher in patients with PETs than in patients with CTs (65.8% *vs*. 44.2%, P=0.02; 3,540.59 *vs*. 1,760.2, P=0.02). **Conclusions** The hyper-enhanced pattern showed in the arterial phase and the lack of portal-venous enhancement are the prevalent CEUS pattern of EP liver metastases both from pancreatic and intestinal tumor. Determination of quantitative CEUS parameters (peak, RBV) confirms the visually pattern of vascularisation of EP liver metastases and allows to highlight different vascular behaviour depending on the primary tumour site. Thus, quantitative analysis seems to be a promising tool to improve the CEUS characterization of EP liver metastases, especially in patients with unknown primary site.

Immune Suppression in Pancreatic Cancer Patients

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Context Pancreatic cancer represents an enormous therapeutic challenge as it naturally resists to standard therapies. Among the alternative approaches, immunotherapy seems to be one of the most promising. However, a limitation can be the severe immune dysfunction due to combinatory mechanisms present in pancreatic cancer patients. Some tumors escape mechanisms are directly associated to antigen recognition, while others act on the immune status activation, by stimulating suppressive populations as T regulatory cells (Treg) or myeloid derived suppressor cells (MDSC). In addition, immune dysfunctions due to alteration in the immune receptor signaling pathways have been described. The overall effect is a generalized immune suppression. **Objective** With the present study, we wanted to evaluate to what extent each mechanism could operate in each single cancer patient. To test the patient specific immunological status, we recruited 30 patients diagnosed with locally advanced pancreatic ductal adenocarcinoma and 20 healthy donors. **Methods and Results** We performed a phenotypical analysis in peripheral blood mononuclear cells to assess the presence of Tregs (CD4 CD25 Foxp3 positive cells), monocytic-MDSC (CD14 and IL4R-alpha positive cells) and granulocytic-MDSCs (CD15 and IL4R-alpha positive cells). In some patients we also tested the immune suppressive properties of MDSC subpopulations in an antigen-unspecific as well as in an antigen-specific setting, demonstrating in some patients the inhibitory activity of the monocytic subset by restoring the T cell proliferation capability after depletion of CD14+ cells. To assess the capability of patients' lymphocytes to respond to different stimuli, we performed a proliferation assay stimulating peripheral blood mononuclear cells with OKT3 plus CD28. Furthermore, we evaluated the speed of STAT1 phosphorylation following IFN-alpha stimulation. **Conclusion** We noticed that this phenotypic as well as functional profile classified the patient population under several subgroups. Our study suggests that each pancreatic adenocarcinoma patient, at diagnosis, is characterized by a patient specific immune-dysfunction setting. The understanding of its uniqueness can represent a crucial help for the choice of a suitable customized therapy, especially in the context of biological and combinatory therapies, often aimed to reinforce the patient immune system before immunotherapeutic intervention.

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O6-Methylguanine-DNA Methyltransferase Expression and Methylation Status in Non-Functioning Pancreatic Neuroendocrine Carcinomas

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Context Pancreatic neuroendocrine tumors (pNET) show heterogeneous clinical presentation and behavior. Recent studies suggest that temozolomide (TMZ) based treatments have activity in neuroendocrine tumors showing O^6-methylguanine-DNA methyl-transferase **(**MGMT) deficiency. **Objective** We addressed the relevance of TMZ based treatment in non-functioning (NF) carcinomas by analyzing MGMT protein expression and DNA methylation. **Methods** The expression of MGMT protein was investigated by immunohistochemistry (IHC) on paraffin embedded tissues of 64 NF carcinomas. Methylation of MGMT was evaluated on a subset of 20 tumors by pyrosequencing analysis of 5 CpG sites that are supposed to be involved in the transcription regulation of MGMT. Mean methylation level across the five CpG sites for each sample was next directly correlated with MGMT expression. **Results** Lack of MGMT expression was observed in 27 of 64 (42%) tumors, whereas the remaining tumors displayed variable degree of antigen staining. As DNA methylation is tissue specific, we first determined the background methylation in two non-neoplastic pancreatic extracts as well as two microdissected islets preparation, which showed average methylation of about 6%. Eleven tumors (55%) had a methylation level higher than non-neoplastic controls. Among these, five tumors (45%) lacked MGMT staining. On the other hand, all tumors showing homogeneous MGMT-staining (5/20) had a mean methylation level less than 6%. **Conclusion** Our data show that more than one third of NF carcinomas (42%) lacked MGMT expression measured by IHC. We also observed a discrepancy between IHC and DNA methylation analysis in defining MGMT deficiency, thus suggesting that appropriate prospective trials are mandatory to define the best predictive parameters of response to TMZ based therapies.

Leakage of Biliojejeunostomy After Pancreaticoduodenectomy. Is It Possible to Recognize Risk Factors?

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Context Biliary fistula (BF) is rarely reported in literature as a complication after pancreatico-duodenectomy (PD). **Objective** To evaluate potentially factors related to BF . **Methods** From January 2006 to December 2010, data from 104 PD were collected. The main outcome was BF rate. The following potential risk factors were evaluated: sex, age, co-morbidities, ASA score, presence of preoperative biliary stent, recent history of cholangitis, preoperative level of bilirubin, type of resection, characteristics and management of pancreatic remnant, use of T tube, pathological diagnosis. Univariate analysis was carried out using appropriate test. Multivariate analysis was performed with logistic regression. **Results** Mean age of patients was 66.9±11.2 years. There were 40 (38.5%) female and 64 (61.5%) male. One or more co-morbidities were present in 68 (65.4%) patients; 26 patients (25%) were ASA 2, 69 (66.3%) ASA 3 and 9 (8.7%) ASA 4. Forty-seven (47.5%) patients had preoperative biliary stent; a recent episode of cholangitis was present in 30 cases (28.8%). Mean level of preoperative bilirubin was 4.5±6.2 mg/dL. A pylorus preserving PD was performed in 75 (72.1%) patients. An extended resection was carried out in 10 (9.6%) cases. Wirsung duct was dilated in 43 cases (41.3%) and pancreatic stump was soft in 54 (51.9%) cases. Pancreatic anastomosis was carried out in 75(72.1%) patients. Malignant disease was present in 91 (87.5%) cases. BF rate was 12.5%. At univariate analysis level of preoperative bilirubin was related to BF (1.7± 2.1 mg/dL *versus* 4.9±6.5 mg/dL in patients with and without BF, respectively; P=0.001). Logistic regression does not find risk factors related to BF. **Conclusion** Bilirubin level could be related with BF but preoperative stent and the use of a T tube do not prevent BF in patients underwent PD.

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Total Pancreatectomy *Versus* Pancreaticoduodenectomy (Whipple Procedure): Morbidity and Mortality in Short and Long Time

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Context Pancreatic resection can be a challenging procedure, reporting actually a consistent frequency of complications. **Objective** To report our experience between two types of pancreatic resection focusing on morbidity and mortality. **Methods** At the Sant'Orsola-Malpighi Hospital in Bologna, between 2001 and 2010, we performed 134 pancreas resections. Of them 73 patients underwent Whipple pancreaticoduodenectomy procedure (WP) and 37 total pancreatectomy (TP). Indication for WP and TP were respectively adenocarcinoma of the pancreas (22 cases *vs*. 24), cancer of the papilla (18 cases *vs*. 0), biliary tract cancer (15 cases *vs*. 2), neuroendocrine tumors (8 cases *vs*. 0), benign diseases (3 cases *vs*. 4), metastatic cancer (1 case *vs*. 3) and other malignancies (6 cases *vs*. 4). Morbidity and mortality reported in the two groups were compared. **Results** Vascular resection of the portal vein/mesenteric vein was necessary in 18 cases (9 *vs*. 9): histological confirmation found cancer invasion in 4 cases out of 9 in WP and 3 cases out of 9 in TP. Patients who underwent WP developed more complications, with a statistic significance (P=0.019). Reported complications, respectively for WP and TP, were: pancreatic leak (13 *vs*. 0), biliary leak (2 *vs*. 0), post-operative bleeding (4 *vs*. 0), gastro-intestinal fistulas (2 *vs*. 0), sepsis (3 *vs*. 1), pneumonia (3 *vs*. 0). Logistic regression did not show any risk factor other than type of procedure related to morbidity. Survival was similar in both groups. R0 resection was obtained in 57 out of 73 of WP (78%) and 18 out of 34 of TP (53%); considering only pancreatic cancer R0 was 59% *vs*. 40% with no significant relevance. Perioperative mortality was reported in 3 cases of WP, none in TP. Considering only pancreatic cancer, long-term survival did not show any statistical difference between the two procedures (1-year survival 66% in WP *vs*. 57% in TP). **Conclusions** Total pancreatectomy can be a valid surgical option in case of pancreatic malignancies, reporting a lower incidence of surgical complications and can be proposed in selected cases.

Advanced Age Should Not Exclude Patients from Pancreaticoduodenectomy

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Context Is today accepted that prognosis of pancreas cancer is the life-time limiting agent also in old patients underwent to pancreaticoduodenectomy (PD). However, sometime, the age is considered a contraindication for the increased risk of complications and for peri-operative costs. **Objective** To analyze the peri-operative costs and outcome of PD in elderly patients (group 1 ≥75-year-old) compared to younger individuals (group 2 <75-year-old). **Methods** The post-operative results and costs of 367 consecutive PD (201 males and 166 females) done from 2004 to 2010 at Karolinska University Hospital was done comparing patients from group 1 (n=65) to patients from group 2 (n=302). The two groups were comparable regarding mostly of general characteristics, excluding age (mane age of group 1: 78.7 years; mean age of group 2: 61.5 years) and pre-operative anesthesiologic risk (ASA 1: 8.1% *vs*. 7.7%; ASA 2: 42.9% *vs*. 57.5%; ASA 3 42.9% *vs*. 32.1%; ASA 4 8.1% *vs*. 2.7%). **Results** The mean post-operative stay was not different in group 1 compared to group 2 (16 *vs*. 16.7 days; P NS). The overall post-operative complication rate was similar in the two groups (55.3% *vs*. 56.6%; P NS). No differences were found comparing the two groups for surgical and medical post-operative complications. Even analyzing major complications (Clavien score ≥3b), no statistically significant differences were found between group 1 and 2 (16.9% *vs*. 16.5%; P NS). No differences were found comparing group 1 and 2 regarding the reoperation rate (6.1% *vs*. 7.9%; P NS). No statistically significant differences in the post operative mortality rate were found comparing group 1 (1.5%) to group 2 (3.3%). Comparing the overall cost of the procedures, no statistically significant differences were found comparing group 1 to group 2 (30,570 Euro *vs*. 32,176 Euro; P NS). **Conclusion** PD is a safe procedure in elderly patients also. In our experience no differences were found concerning length of hospital stay, post-operative complications and mortality. No differences were found regarding the cost of the procedures also. On the basis of these results patients should never excluded from a PD only on the basis of the age.

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Circulating Lymphocyte Subsets in Pancreatic Adenocarcinoma

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Context Alterations of the immune system are frequently associated with solid organ malignancies. **Objective** To evaluate the immune response in patients with pancreatic adenocarcinoma (PA) as compared to chronic pancreatitis (CP), other malignant digestive cancer (MDC) and healthy subjects (HS) by determining circulating lymphocyte subsets. **Patients** Ninety-four subjects were studied: 25 consecutive patients with histologically proven PA (12 males, 13 females; mean±SD age 62.0±12.8 years), 17 patients with proven CP (13 males, 4 females; age 50.9±14.7 years), 14 patients with histologically confirmed MDC (4 males, 10 females; age 69.4±12.5 years) and 38 HS (18 males, 20 females; age 54.3±15.0 years). None of the study cancer patients were treated medically or surgically at the time of the study. According to the AJCC criteria, 1 PA patient was in stage I, 5 in stage II, 4 in stage III, and 15 in stage IV. **Methods** Total and subset lymphocyte counts (total T lymphocytes, T helper and T suppressor lymphocytes, activated T lymphocytes, B lymphocytes, NK cells) were evaluated using a FACScan (Becton-Dickinson, Sunnyvale, USA). Statistical analysis was carried out using the one-way ANOVA design and simple contrast. Total lymphocytes and lymphocyte subset counts are reported as mean±SD. **Results** Only T helper, T suppressor and B lymphocytes were significant different among the four groups of patients studied ($P<0.05$); these differences were due to the fact that PA patients had T suppressor lymphocytes (560.4±399.8 mm^{-3}) and B lymphocytes (227.3±106.3 mm^{-3}) significantly higher ($P<0.05$) than MDC patients (T suppressor lymphocytes 438.9±412.0 mm^{-3}; B lymphocytes 154.6±94.5 mm^{-3}). AP patients with stage I and II had B lymphocytes subset (147.0±75.0 mm^{-3}) significantly lower ($P<0.05$) than those with stage III and IV (252.6±103.4 mm^{-3}). **Conclusions** Circulating total and lymphocytes subjects of PA patients are similar to that of both patients with CP and HS. The augment of circulating B lymphocytes with the increase of the AP stages seems to play an important role in the tumor immunology of pancreatic cancer.

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

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Context Blood and spleen expansion of immature myeloid cells might compromise the immune response to cancer, enabling tumor outgrowth and metastasis. **Objective** To study the pattern of circulating and splenic lymphocyte subsets and immature myeloid cells in patients with benign and malignant pancreatic diseases. **Patients and Methods** One-hundred and three pancreatic and/or splenic surgical patients were enrolled (52 ductal adenocarcinoma (PaCa), 10 NETs, 10 IPMNs, 9 SCA, 9 non-pancreatic tumors and 13 control cases (chronic pancreatitis, splenic non neoplastic lesions)). In blood and splenic samples, flow cytometric analysis was conducted on lymphoid (CD4+, CD8+, CD4+ CD25+ T cells) and myeloid cells (CD33+ CD14+ HLA-DR+, CD33+ CD14+ HLA-DR-, CD33+ CD14- HLA-DR+ and CD33+ CD14- HLA-DR-). Inhibitory molecules PDL-1 and CTLA4 were also studied in immature myeloid cells in 30 splenic samples. **Results** In PaCa a significant reduction was found in circulating cytotoxic CD8+ T cells ($P=0.015$) and CD33+ CD14- HLA-DR+ dendritic cells ($P=0.01$), whereas in spleen samples these latter cells were increased in patients with both exocrine and endocrine malignant pancreatic tumors ($P=0.077$). Circulating and splenic CD33+ CD14+ HLA-DR- cells, potentially immunosuppressive, were increased in patients who developed disease recurrence or died after surgery for the disease ($P=0.0023$). In PaCa, splenic dendritic cells had a higher PDL-1 expression ($P=0.028$) while CD33+ CD14+ HLA-DR- cells had a lower CTLA4 expression ($P=0.029$) than in samples from other diseases. **Conclusion** Among exocrine and endocrine benign or malignant pancreatic tumors, PaCa mainly imbalances immune cells pattern. Reduced circulating dendritic and cytotoxic T cells might favour PaCa growth, while the expansion of

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CD33+ CD14+ HLA-DR- cells, potentially immunosuppressive, might favour tumor progression. PaCa might affect immune cells by targeting PDL-1 and CTLA4 molecules.

Outcome of a Short Term Chemotherapy in Stage III Pancreatic Carcinoma: A Selection for Local Ablative Treatment?

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Context Systemic chemotherapy (CHT) with neo-adjuvant intent in stage III pancreatic carcinoma aims to achieve resectability in so called CT responder patients, to reduce occult micrometastasis and to obtain a R0 resection when surgery can be performed. Same stage of disease can be treated with a local ablative therapy (RFA) with no significant difference in prognosis whether RFA is performed as first line treatment or after other therapies. In our series of RFA as first line treatment we observed 15% of early progression (within 3 months) and therefore those patients could not benefit of any local therapy. **Objective** To evaluate the outcome of a short systemic CHT in a stage III pancreatic carcinoma in order to identify those patients eligible for a local ablative therapy. **Patients and Methods** All patients with a diagnosis of stage III ductal carcinoma were eligible for the study. In all cases stadiation was obtained by CT scan or MRI, and CEUS. They were all sent to oncologist with a planned re-evaluation after 3 months of CHT chosen by the oncologist. Re-staging was performed with CT scan and CA 19-9 serum marker. Local or systemic progression, stable disease or partial response were the three possible event. **Results** Between March and June 2009, 65 patients were evaluated with the requested criteria. Tumor was located in the head in 43 patients (66%) and in body/tail in 22 patients (34%) and median CA 19-9 was 246 U/mL. All patients were sent to oncologist previous consent about the ongoing trial. Two patients died within 2 months with no therapy and 5 patients were drop out. Three patients (4.6%) underwent to early surgical palliation of jaundice not responsive to stenting. Fifty-five patients (85%) received venous CHT. Three patients died during therapy. After 3 months 25/55 patients (45%) had progression of disease (local progression in 25% and distant metastasis in 20%); in 17/55 patients (31%) stable disease was confirmed at re-stadiation and 10/55 patients (18%) had radiological downstaging. RFA was performed in 65% of patients with stable disease and in 30% of patients with radiological downstaging (understadiation) whereas resection was conducted in 6% and 50% of the two groups, respectively. All patients who received RFA were afterwards treated by other associations of different therapies. Median survival of CHT responders undergone to RFA is 15 months (IQR 13-18 months) and at this time 43% of them are alive with controlled disease 16 months after diagnosis. No early progressions were observed in this subgroup of patients. **Conclusions** A short term CHT may help to identify those patients who can benefit of a local ablative treatment.

Preoperative Pancreas CT/MRI Characteristics Predict Fistula Rate After Pancreaticoduodenectomy

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Context Pancreatic fistula (PF) is considered to be the main cause of morbidity after pancreatico-duodenectomy (PD). A recent study from our institution suggested the risk for pancreatic fistula after distal pancreatectomy to be closely related to the pancreatic remnant volume (PRV). The hypothesis was formulated that also after PD the PRV is an important determinant of the risk for PF formation. **Methods** All patients undergoing PD between September 2007 and November 2010 at the Karolinska University Hospital Stockholm were included. Preoperative multidetector CT or MRI was used to calculate the PRV and the pancreatic duct width (PDW) at the alleged resection line. **Results** One-hundred and 82 patients (mean age 65.8 years) undergoing PD were included. The diagnosis was malignant in 144 patients (79.1%) and benign in 38 (20.9%). PF defined according to the International Study Group of Pancreatic Fistula

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(ISGPF) criteria was diagnosed in 37 (20.3%). The mean PRV was 36.9 cm^3 (SD 15.4 cm^3) and the mean PDW was 4.5 mm (SD 3.0 mm). In a univariate analysis a large calculated volume of the pancreatic remnant increased the subsequent risk of PF (OR: 3.712; 95%CI: 1.582-8.710; P=0.003), as did a small duct width (OR: 8.459; 95% CI: 3.106-23.04; P<0.001). The size of the pancreatic remnant and width of the pancreatic duct maintained their impact on leakage risk also according to a multivariate analysis. **Conclusion** A large pancreatic volume and small pancreatic duct increase the risk of pancreatic fistula. Preoperative CT and/or MRI therefore provides a useful instrument for predicting fistula formation before PD.

Downregulation of Krüppel-Like Factor 4 Expression and P53 Mutation Are Associated with High Frequency of Pancreatic Intraepithelial Lesions in Pancreatic Ductal Adenocarcinoma

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Context The transcription factor Krüppel-like factor 4 (KLF4) may act both as an oncogene and a tumor suppressor in a tissue-dependent manner. **Objective** Further studies on its role in pancreatic ductal adenocarcinoma (PDAC) progression and clinical outcome are warranted. **Materials and Methods** We investigated the loss of heterozygosity (LOH) in the 9q22.3-32 region and loss of KFL4 gene expression in epithelial cells from 35 PDAC, 6 pancreatic intraductal neoplasias (PanINs) and 6 normal ducts, isolated by laser microdissection, as well as their correlation with overall survival (OS) in patients treated with gemcitabine in the adjuvant setting. LOH was evaluated with 4 microsatellite markers and *in situ* hybridization, while KLF4 expression was studied by reverse transcription-PCR and immunohistochemistry. p53 mutation analyses was also performed. **Results** LOH in at least 1 locus was observed in 25 of 35 PDAC cases and in 5 of 6 PanINs, respectively. In particular, the loss of the D9S105 marker was present in 46.9% of PDAC and 83.3% of PanINs, becoming the most deleted marker, while no LOH in D9S105 was observed in normal Wirsung pancreatic duct. Lack of KLF4 mRNA expression was significantly associated with: 1) genomic deletion flanking KLF4 in PDAC and in PanINs; 2) lack of KLF4 protein expression; and 3) shorter OS. KLF4 and p53 alterations were associated with high frequency of low-grade PanINs PDAC-associated. **Conclusion** These results strongly suggest a relationship between D9S105 deletion and downregulation of KLF4 gene expression as an early event in PDAC progression, as well as a possible role of KLF4 as a prognostic biomarker in gemcitabine-treated patients.

PMP22 Genetic Alteration and Modulation of PMP22 Expression by NSC-631570 in Pancreatic Ductal Adenocarcinoma (PDAC)

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Context Peripheral myelin protein 22 gene (PMP22) encodes a membrane protein of myelin in the peripheral nervous system, and PMP22 duplication causes the Charcot-Marie-Tooth 1A (CMT1A) phenotype. PMP22 is also capable of delaying the transition from G0/G1 to S phase (growth arrest specific gene 3, GAS3). However, growth factors involved in PMP22 regulation, such as insulin-like growth factor-II (IGF-II), are up-regulated after radiation in fibroblast cells, and might influence chemo-radiosensitivity. Since the compound NSC-631570 had a protective effect on human fibroblasts but not human tumour cells against ionizing radiation, and showed beneficial effects in phase II studies in

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metastatic and locally advanced PDAC patients. **Objective** The aim of this study was to evaluate the interaction between PMP22, IGF-II and NSC-631570 in PDAC primary cell cultures (PCCs). **Methods** DNA duplication of PMP22 gene was evaluated by PCR and specific digestion by the endonucleases EcoRI and NsiI in 13 PDAC tissues, 2 PCCs and PBMCs from 3 healthy subjects (used as negative controls in genetic tests for the CMT1A syndrome). PMP22 protein expression was evaluated in tissues and cells by immunohistochemistry (IHC), using a quantitative scoring (e.g., 0 absent, 1 low, 2 intermediate and 3 high expression). The PCCs were also exposed to IGF-II, NSC-631570, and their combination. Finally, expression of PMP22 was correlated with cell proliferation index. **Results** The PMP22 duplication was observed in 44% (7/16) of PDAC patients and in both PCCs. PDAC duplicated samples showed significantly higher score of PMP22 protein expression (P=0.0262). PMP22 protein was correlated with decreased cell growth, whereas 400 nM IGF-II reduced PMP22 expression and increased cell proliferation. Conversely, the addition of 1 μM NSC-631570 increased PMP22 expression, and overcame IGF-II induced proliferation. **Conclusion** This is the first study reporting PMP22 duplication in PDAC specimens and cells. This duplication was correlated with PMP22 expression. PMP22 protein was inversely related to cell proliferation and its inhibition by IGF-II might explain chemo-radioresistance caused by PDAC associated fibroblasts. However, NSC-631570 increased PMP22 expression and might synergize with anticancer treatments against PDAC.

Critical Role of Laser Microdissection for Genetic and Epigenetic Analyses in Pancreatic Cancer: Ten Years of Monocentric Experience

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Context Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease, and molecular studies to unravel novel biomarkers and therapeutic targets are warranted. However, PDAC is characterized by different precursor lesions, as well as by an intense desmoplastic reaction, with islet of neoplastic cells often representing a minor population. Moreover, normal ductal cells, which are considered to be the normal counterpart of pancreatic adenocarcinoma cells, comprise about 5% of the total populations of cells making up this organ. For all these reasons, molecular techniques to identify critical mutations, as well as pattern of altered mRNA/microRNA expression should be performed on selected pancreatic cell subpopulations. **Methods** Therefore, the use of laser microdissection (LMD) is critical for the analysis of PDAC biological characteristics, and we performed LMD on 113 PDAC samples including 81 cases analyzed in two pharmacogenetic studies on expression of determinants of gemcitabine and miR-21 [1, 2]. LMD was also performed on 5 specimens from normal ducts, and the cells from these tissues were used to obtain a normal tissue pool, whereas in 28 randomly selected PDAC cases the sampling was performed on whole tissue, without laser microdissection, using 3 cryostatic sections. **Results** For each sample, LMD allowed to pick up specimens of 5,000 cells. The precision of the narrow focus of the laser beam resulted in the capture of individual cells with high degree of accuracy and extremely low risk of contamination. The analysis of protein contamination by absorbance reading demonstrated that most samples were pure, showing an optimal 260/280 ratio (1.8-2.0). The comparison of dCK, 5'-NT, CDA, RRM1, hENT1, TS and FPGS expression levels among the non-microdissected tumour tissues and the respective microdissected samples with the paired Student's t test demonstrated a meaningful statistical variation in 6 out of the 7 genes analyzed. The statistical analysis revealed significant differences also in mRNA expression levels between microdissected tumour tissues and normal pancreatic tissues for all the studied determinants. Similarly, the study of miR21 expression revealed that mean miR-21 expression of normal pancreatic duct samples was about 1,000-fold lower than the levels in microdissected tumors. Furthermore, the non-microdissected tumor tissues had a significantly lower expression of miR-21 than their respective microdissected samples (P=0.014). **Conclusion** These results suggest that LMD succeeded in eliminating the stroma, that can mask the true expression of possible biomarkers of drug activity, and help in the rational selection of more effective therapies.

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Hepatic Artery Variants Do Not Affect Outcome in Pancreatic Surgery

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Context The classical visceral arterial anatomy of the pancreas occurs in only 55-60% of the population. Unexpected aberrant right hepatic artery (aRHA) has an incidence of 10-20% and its importance has been underlined in several reports. **Objective** To assess the incidence and type of aRHA in our series of pancreaticoduodenectomy and investigate its relationship with the outcome of the surgical procedure. **Methods** From January 2010 to June 2011 we realized 62 consecutive pancreaticoduodenectomies for periampullary benign and malignant disease: 24 pancreatic adenocarcinoma, 10 ampullary adenocarcinoma, 15 IPMN, 4 chronic pancreatitis, 4 distal bile duct adenocarcinoma, 3 endocrine tumors, 1 duodenal adenocarcinoma and 1 pancreatic liposarcoma. We retrospectively analyzed operation reports of all 62 pancreaticoduodenectomies and compared patients with (group A) and without aRHA (group B). **Results** The aRHA group consisted of 14 patients (23%), while group B of 48 (77%). In the group A we had 2 patients with common hepatic artery originating from the superior mesenteric artery (SMA) (Michels type 9) and 12 with accessory right hepatic artery arising from SMA (Michels type 6). Preoperatively examination of CT scan by the surgeon revealed aRHA in 60% of cases. None of the patients in the two groups experienced injury of the arterial vessels during the dissection of the hepatic pedicle. The characteristics of patients in groups A and B were comparable: male to female ratio was 2:1 in both group, the median age was 71 years in group A and 68 years in group B, histological diagnosis were homogeneously distributed in both groups. Groups A and B had no differences in intraoperative data: median operative time was 456 and 445 minutes respectively, median blood loss was 300 mL in both groups, average red cells volume transfused was 330 mL in group A and 217 mL in group B (P=0.25). Surgical complications (42.8% in group A and 52% in group B), mortality (nihil in both groups) and the number of lymph nodes harvested (median 12 in group A and 14.5 in group B) were similar in both groups. **Conclusion** In our series the presence of aRHA is more frequent than usually reported; pre-operative knowledge of the presence of an arterial variant makes easier its intraoperative detection and preservation. The presence of an aRHA does not affect surgical mortality and morbidity.

Circulating Metalloproteinase-3 and Tissue Inhibitor of Metalloproteinase-2 in Patients with Ductal Pancreatic Neoplasms

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Context There is increasing evidence regarding the involvement of inflammation in patients with intraductal papillary mucinous neoplasms (IPMNs) of the pancreas. **Objectives** To evaluate the circulating concentrations of MMP-3 and TIMP-2 in patients with IPMNs and in those with ductal adenocarcinomas (ADAC). **Patients** Sixty patients (32 males, 28 females, mean age 69.3±11.3 years) were enrolled: 31 (51.7%) had IPMNs and 29 (48.3%) had histologically confirmed ADAC. Thirty blood donors were also studied as controls. **Methods** The serum concentrations of MMP-3 and TIMP-2 were determined in all study subjects using commercially available kits. **Results** Serum concentrations of MMP-3 were significantly higher both in patients with ADAC (14.8±11.3 ng/mL) and in those with IPMNs (18.2±19.8 ng/mL) as compared to the healthy subjects (5.9±2.9 ng/mL, P=0.001) whereas serum levels of TIMP-2 were significantly lower both in IPMN patients (91.3±23.5 ng/mL) and in patients with ADAC (84.7±18.2 ng/mL) than in those of the healthy subjects (141.3±47.9 ng/mL, P<0.001). No significant differences in the serum levels of both MMP-3 and TIMP-2 were found between patients with IPMNs and those with ADAC as well as in the patients with branch type IPMN (MMP-3: 20.0±16.5 ng/mL; TIMP-2: 94.7±24.4 ng/mL) as compared to those with main duct IPMN (MMP-3: 16.2±23.3 ng/mL, P=0.220; TIMP-2: 87.7±22.7 ng/mL, P=0.607). **Conclusions** IPMNs have a pattern of extracellular matrix factors and their inhibitors are similar to those of ADAC; MMP-3 and TIMP-2 cannot be utilized to routinely differentiate IPMNs from ductal adenocarcinomas.

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Do Risk Factors for Pancreatic Fistula Really Exist? A Fifteen-Year Single Institution Experience

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Context Distal pancreatectomy (DP) is the surgical procedure of choice for pancreatic tumors in the body-tail of the pancreas. Even though in high volume centers the mortality is less than 2%, morbidity remains high. Pancreatic fistula (PF) is the most important clinical complication and its incidence is around 30%. The optimal management of pancreatic remnant during DP is still unknown. **Objective** We retrospectively reviewed our 15-year experience (January 1996 to December 2010) with distal pancreatectomies to find parameters potentially associated with pancreatic fistula. The International Study Group for Pancreatic Fistula classification was used. **Methods** Pre- and post-operative details were analyzed using uni- and multivariate models. **Results** Five-hundreds and 96 DP were performed at author's institution. Of these 544 were distal pancreatectomy with splenectomy (DPS) and 52 were spleen-preserving distal pancreatectomy (SPDP). Indications for surgery were ductal adenocarcinoma (19.5%), cystic lesions (42.7%), endocrine neoplasms (24.8), and other conditions (including chronic pancreatitis, pseudocyst, trauma, 13%). The pancreatic remnant was sutured in 50% of cases, stapled alone 47% and both stapled and sutured in 3%. Median operative time was 228 min (IQR 180-265 min). The median hospital stay was 12 days (IQR 10-15 days). The overall morbidity rate was 51%. PF developed in 24.4% of patients. At the univariate and multivariate analysis, no risk factors for PF emerged. **Conclusion** Our experience demonstrated that management of the pancreatic remnant (stapler, manual suture, multivisceral resection) does not influence pancreatic fistula after distal pancreatectomy.

Role of CA 19-9 Concentration as an Independent Prognostic Factor in Unresectable Pancreatic Ductal Adenocarcinoma (PDCA) Treated with GemOx

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Context To date, gemcitabine (GEM) doublets remains the cornerstone of chemotherapy for PDCA. Some trials seem to confirm that GEMOX regimen (GEM plus oxaliplatin) could increase median overall survival (OS) and progression free survival (PFS) in PDCA patients. **Objective** To evaluate PFS and OS in patients affected by unresectable PDCA treated with GEMOX regimen. **Methods** From May 2005 to December 2010, 61 consecutives patients affected by unresectable PDCA, histologically confirmed, were treated with GEMOX schedule as first line treatment in our centre. Data regarding sex, age, preoperative level of CA 19-9, site of the tumor (head or body-tail), involvement of mesenteric or hepatic or celiac arteries, presence and site of distant metastasis, TNM stage, OS and PFS were collected. OS and PFS were calculated using Kaplan Meier method. Univariate analysis was carried out using the log-rank test. Cox regression analysis was used to perform multivariate analysis. **Results** Mean age of patients was 66.6±10.3 years. There were 22 (36.1%) females and 39 (63.9%) males. Tumor was located in head of the pancreas in 33 (54.1%) patients, and in the body-tail in the other 28 patients (45.9%). Encasement of one or more arteries was present in 36 (59%) cases. Distant metastases were found in 46 (75.4%): 41 (67.2%) hepatic metastases, 3 (4.9%) patients with pulmonary metastasis and 2 (3.3%) with peritoneal spreading. According to TNM stage there were: stage II 2 (3.3%); stage III, 13 (21.3%); stage IV, 46 (75.4%). Median OS and PFS were 8.9±1.0 months and 3.5±0.3 months, respectively. A lower baseline value of CA 19-9 (<100 U/mL) represented a prognostic factor related to longer OS at the univariate analysis (OS: 10.1±0.7 *vs*. 6.5±0.9 months; P=0.018). Multivariate analysis confirmed the results of univariate analysis. **Conclusion** In our experience pretreatment serum CA 19-9 concentration is an independent prognostic factor for survival in patients treated with GEMOX regimen as first line treatment, as recently reported in literature.

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Methylation-Associated Down-Regulation of *RASSF1A* and Up-Regulation of *RASSF1C* in Pancreatic Endocrine Tumors

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Context Ras-association domain family 1A (*RASSF1A)* gene silencing by DNA methylation has been suggested as a major event in pancreatic endocrine tumor (PET) but *RASSF1A* expression has never been studied. The *RASSF1* locus contains two CpG islands (*A* and *C*) and generates seven transcripts (*RASSF1A*-*RASSF1G*) by differential promoter usage and alternative splicing. **Objective** To identify the putative role of *RASSF1A* methylation as a marker lesion for PET. **Methods** We studied 20 primary PETs, their matched normal pancreas and three PET cell lines for: i) the methylation status of the *RASSF1* CpG islands using methylation-specific PCR and pyrosequencing; and ii) the expression of *RASSF1* isoforms by quantitative RT-PCR in 13 cases. **Results** *RASSF1A* methylation showed a high variability in terms of distribution and level within and among samples, with PETs having average methylation higher than normal in 12/20 (60%) cases (P=0.01). *RASSF1A* was always expressed in PET and normal tissues, but it was, on average, expressed 6.8 times less in PET (P=0.003); interestingly, *RASSF1A* methylation inversely correlated with its expression. *RASSF1* isoforms were rarely found, except *RASSF1C* whose expression was 11.4 times higher in PET than in normal tissue (P=0.001). *RASSF1A* methylation and gene expression correlated in two of the three PET cell lines, which also showed a significant increase in *RASSF1A* expression upon demethylating treatment. **Conclusions** *RASSF1A* gene methylation in PET is higher than normal pancreas in only 60% of cases and as such it cannot be considered a marker for this neoplasm. *RASSF1A* is always expressed in PET and normal pancreas and its levels are inversely correlated with gene methylation. Isoform *RASSF1C* is overexpressed in PET and the recent demonstration of its involvement in the regulation of the Wnt pathway points to a potential pathogenetic in tumor development.

RASSF1A Methylation and Chromosome 3p Alterations in Pancreatic Ductal Adenocarcinoma

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Context Ras-association domain family 1A (*RASSF1A*) is frequently inactivated by promoter methylation in various types of cancer, including pancreatic ductal adenocarcinomas (PDAC). However, the *RASSF1A* promoter methylation status of single CpGs has never been described and never directly related to its loss of expression in PDAC. **Objective** To evaluate *RASSF1A* promoter methylation as a marker lesion for PDAC and its relation with transcription regulation of *RASSF1A* and its variants in PDAC. Moreover, we addressed the identification of chromosome 3p alterations in PDAC. **Methods** We investigated the methylation status of 51 CpGs within the CpG island A and of 37 CpGs within the CpG island C by pyrosequencing and the mRNA expression of *RASSF1A* and its splicing variants by quantitative RT-PCR in 14 PDAC xenografts and 8 PDAC cell lines. Fluorescence *in situ* hybridization (FISH) analysis for chromosome 3p was performed on PDAC tissue microarrays including 98 primary tumors and seven metastases. **Results** Our data showed a frequency of *RASSF1A* methylation in PDAC xenografts lower than that reported in primary adenocarcinomas (21% *vs*. 64%), while 50% of PDAC cell lines were heavily methylated along CpG island A. *RASSF1* mRNA variants were expressed in PDAC xenografts and cell lines; however, methylation was not associated with lower mRNA expression. Indeed, *RASSF1A* mRNA levels were lower in PDAC than in normal pancreas (P<0.05). FISH analysis highlighted the excess of CEP3 copy number as the best prognostic factor affecting survival of PDAC patients, despite the high frequency of 3p losses *vs*. gains among PDAC cases (52% *vs*. 20%). **Conclusions** Methylation of *RASSF1A* cannot be considered a marker lesion for PDAC. However, *RASSF1A* downregulation and alterations in copy number of chromosome 3p may represent relevant events for the pathogenesis and progression of PDAC.

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Presence of Extra-Abdominal Metastases Affects Survival in Digestive Endocrine Tumors

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Context Digestive endocrine tumors (dETs) are advanced in 60% of cases since diagnosis. Little is known about prognosis of these patients according to different site and number of metastases. **Objective** Our aim was to investigate progression-free survival (PFS) and risk factors for progression in advanced dETs according to metastatic status. **Methods** Pancreatic ETs (PETs) and intestinal carcinoids (CTs) metastatic at diagnosis were divided in 3 groups: 1) only unilobar liver metastases; 2) only bilobar liver metastases; 3) extra-abdominal metastases. PFS and risk analysis were assessed by Kaplan-Meier and Cox-proportional hazards regression model. **Results** Two-hundreds and 29 consecutive patients (59% PETs, 41% CTs): 13.9% included in group 1, 78.2% group 2 and 7.9% group 3. Median Ki67 was 4.5%. Median PFS was 81 months. Different PFS was observed for: PET/CT (P= 0.008; 5-year PFS 18.5%/26.8%), G grading (P<0.001; 5-year PFS in groups 1, 2, 3: 31.2%, 18.2%, 6.4%), metastases (P<0.001; 5-year survival in groups 1, 2, 3: 25.6%, 22.4%, 11.1%). Significant risk factors were: PET *vs.* CT (HR 1.51; P=0.01), Ki67 (for each increasing unit: HR 1.03; P<0.001), metastatic groups (HR 1.87; P<0.001), G grading (HR: 2.05; P<0.001). At multivariate analysis, independent factors were Ki67 (HR 1.03; P<0.001) and metastatic groups (HR 1.67; P=0.01). **Conclusion** In metastatic dETs, median PFS was 18 months. Pancreatic primary site is a risk factor for poor outcome. PFS was mainly affected by Ki67 and metastatic status.

Left Pancreatectomy for Neuroendocrine Pancreatic Tumors

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Context Pancreatic neuroendocrine tumors (pNET) are often localized in the body-tail of the pancreas. Left pancreatectomy is the procedure of choice and can be performed either with splenectomy or with a spleen-preserving procedure. **Objective** The aim of this study was to retrospectively evaluate postoperative complications and clinical outcome of patients submitted to laparotomic left pancreatectomy with splenectomy (DP) or spleen-preserving left pancreatectomy (SPLP) for pNET in our Unit in the last 30 years. **Methods** We reviewed clinical data of patients from January 1981 to December 2010, evaluating histological features and staging (WHO 2000, TNM 2010), type of surgical procedure and early (within 30 days) and late postoperative complications. **Results** We observed 216 patients affected by pNET: among them, 123 tumors (56.9%) were localized in the body-tail of the pancreas and 69 patients underwent laparotomic left pancreatectomy. We excluded 5 patients who also underwent an enucleation of a cephalic lesion and 5 patients operated for a more aggressive tumor in which the pNET was an incidental finding. We enrolled 59 patients in this study (29 F, 30 M; mean age 53.8 years). According to the WHO 2000 and TNM 2010 classifications, we had 33 benign tumors (55.9%, 31 stage I), 5 borderline tumors (8.5%, 4 stage IIb) and 21 malignant lesions (35.6%, 12 stage IV). We performed 29 DP (49.2%), 28 SPLP (47.4%, 23 cases with splenic vessel preservation) and 2 left pancreatectomies in previous splenectomy (3.4%). DP was performed when a malignant tumor was evident (65.5% of cases). SPLP was performed for benign lesions in 93% of cases. Post-operative mortality was 3.9%. Total post-operative morbidity was 42.4% (76% early complications), equally distributed in DP and SPLP groups. We had 10 pancreatic fistulas (16.9%, 6 in the DP group and 4 in the SPLP group), 8 abdominal fluid collections (13.6%), 5 pseudocysts (8.5%, 4 in the DP group) and 2 splenic infarctions in SPLP with splenic vessel ligation (2/5 of Warshaw operation performed). **Conclusion** Laparotomic left pancreatectomy in pNET can be performed with or without splenectomy. The complication rate is still high and it is comparable between the two surgical procedures.

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Interventional Radiology For Hemorrhage After Pancreaticoduodenectomy

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Context Mortality rate for haemorrhage after pancreaticoduodenectomy (PD) ranges from 15% to 60%. Treatment options include: relaparotomy and interventional radiology (IR). Herein, we evaluated the role of IR in 2 cases of bleeding after PD. **Case Report** A 72-year-old man was admitted to our hospital for obstructive jaundice by cholangiocarcinoma of distal common bile duct. A PD was performed. On the 2th postoperative day, emergency laparotomy was necessary for hemorrhagic shock by necrotic hemorrhagic acute pancreatitis and a total pancreatectomy was performed. The patient was discharged on the 28th postoperative day. Thirty-five days after discharge he was readmitted for abdominal pain, bleeding from Kehr's tube and melena. Upper gastrointestinal endoscopy revealed blood in the stomach and CT did not show arterial bleeding. Selective celiac and common hepatic artery (CHA) angiography revealed arterial bleeding from the right hepatic artery. A micro-catheter was inserted into the origin of the bleeding and successfully treated it by microcoil embolization. Patient was discharged 15 days after the procedure. A 82-year-old man with solid pancreatic lesion in the head of the pancreas incidentally detected by CT was admitted to our hospital. A PD was performed. Postoperative course was complicated by a pancreatic fistula, grade B, treated with CT-guided percutaneous drainage, and pleuric effusion treated with thoracic drainage. On the 36th postoperative day, the patient presented hematemesis and hemodynamic shock. CT showed massive arterial bleeding from a small vessel originating from CHA, confirmed by selective celiac angiography. A micro-catheter was inserted into the origin of the bleeding and successfully treated by microcoil embolization. The arterial flow of the hepatic artery was preserved. Patient died 8 days later for sepsis. **Conclusion** IR is effective for diagnosis and treatment of acute haemorrhage after PD.

Role of Interventional Radiology in the Management of Complications After Pancreatic Resection

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Context Although the mortality rate after pancreatic resection has decreased in most high-volume centres, the morbidity rate remains high. Recent technical advances in interventional radiology (IR) could change the management of surgical complications after pancreatic resection (PR). **Objective** To evaluate the role of IR in the management of the complications following PR. **Methods** From January 2006 to December 2010, data from 210 PR were collected. All interventional radiology procedures employed to treat the major complications after PR were considered. The main end-point was re-laparotomy avoided in the management of postoperative pancreatic fistula (POPF), biliary fistula (BF), postpancreatectomy haemorrhage (PPH) and fluid amylase negative collection. Ancillary end-points were: complications after IR procedures and types of pancreatic resections needing more frequently IR procedures. **Results** Among 210 patients reviewed, the overall mortality, morbidity and reoperation rates were 3.8%, 61%, and 6.7%, respectively. Complications considered occurred in 95/210 (45.2%) patients, of which 26 (27.3%) required IR procedure. Of those 26 patients: 17 (65.4%) underwent pancreaticoduodenectomy (PD), 6 (23.1%) left pancreatectomy (LP), 2 (7.7%) enucleoresection and 1 (3.8%) middle pancreatectomy. The IR group included the following procedures: 20 (76.9%) percutaneous CT-guided drainage for POPF grade B/C), 2 (7.6%) percutaneous biliary drainage, 3 (11.5%) angiography with or without embolization and 1 (3.8%) percutaneous CT-guided drainage for fluid amylase negative collection. No complications related to IR procedures were detected. Four (15.3%) patients underwent reoperation despite IR: 3 (75%) for POPF grade C and 1 (25%) for late PPH C. Reoperation was avoided in 22 (84.6%) of patients receiving IR. **Conclusion** The majority of complications occurring after pancreatic resection can be managed effectively and safety using IR. Reoperation was avoided in 84.6% of patients. The most important indication was clinical relevant POPF after PD or LP.

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

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Objectives To identify new serum biomarkers of pancreatic cancer (PaCa) by MALDI-TOF analysis. **Methods** Fifty-one PaCa, 38 chronic pancreatitis (ChrPa), 48 controls (24 with type II diabetes mellitus, DM) were studied. Fasting sera were purified by Sep-Pak C18 before MALDI-TOF anchorchip analysis. **Results** One-hundred and 76 features (1207-5374 m/z) were selected. Seven features were highly correlated (P<0.0001) with disease: two (m/z 3182 and 4009) with PaCa, one (m/z 2049) with ChrPa, four (m/z 1530, 1778, 2006, 2602) were less represented in PaCa and/or ChrPa as compared to controls. Ten-fold cross validation binary recursive partitioning trees for patient classification were obtained. The first tree, which included CA 19-9, age, m/z 2006, 2599, 2602, allowed to well discriminate controls (AUC=0.988) and ChrPa (AUC=0.988) from PaCa (AUC=0.974) (correct classification equal to 90.5%). The second tree (CA 19-9, age, m/z 2006, 2599, 2753, 4997), built considering only patients and controls with DM, allowed to distinguish DM (AUC=0.997) from ChrPa (AUC=0.968) and PaCa (AUC=0.980) (correct classification equal to 90.1%). While CA 19-9 alone did not discriminate localized from advanced PaCa (AUC=0.685), the tree including CA 19-9, 1550 and 2937 m/z features, achieved AUC=0.970. We obtained a successful fragmentation by MALDI-TOF/TOF analysis for three cancer-associated features (1530, 1550, 1778 m/z) which were found to be part of clusterin, apolipoprotein A1 and complement C3. ApoA1 and C3 were measured in all sera, and in a series of 76 new serum samples (26 type II DM, 50 PaCa). ApoA1 was significantly reduced in PaCa with respect to all the other groups (F=13.13, P<0.0001). At multivariate logistic regression analyses (predictors: age, gender, CA 19-9, ApoA1 and C3), only ApoA1 (P<0.0001) was confirmed to be strictly correlated with PaCa, thus further supporting its role as a potential biomarker for this tumour. **Conclusion** We demonstrated that new serum biomarkers identified using a proteomic approach, significantly enhance the diagnostic performance of CA 19-9.

Enhanced Recovery After Surgery Pathways for Pancreatic Surgery: Preliminary Result of Safety and Adherence

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Context Enhanced recovery after surgery (ERAS) programmes have been increasingly applied in different surgical specialties improving postoperative recovery and reducing morbidity. Its role on upper GI major surgery, especially pancreatic surgery, is still controversial and data on its application are few. **Objective** To test safety and feasibility of an ERAS pathway for patients undergoing pancreatico-duodenectomy (PD) and left pancreatectomy (LP). **Methods** From October 2010 to May 2011, 73 consecutive patients undergoing PD (n=40) and LP (n=33, laparoscopic 54.8%) were treated with a multimodal, inter-disciplinary perioperative ERAS pathway. The items implemented were: preadmission counselling, no preoperative bowel preparation, carbohydrate loading, epidural analgesia avoiding the use of opioids, intraoperative i.v. fluid restriction (4-5 mL/kg/h), postoperative nausea and vomiting and hypothermia prophylaxis, removal of nasogastric tube (NGT) at the end of surgery, POD 1 mobilization for at least 4 (PD) and 6 h (LP), solid food diet on POD 1, i.v. infusions stop on POD 2 (LP) and 4 (PD), removal of urinary catheter on POD 1 (LP) and 3 (PD). Complications were classified according to Clavien-Dindo classification stratified as minor (grade I-II) and major (grade III-V). Data are reported in percentage or median and interquartile range (IQR). **Results** Adherence to the pathway: preadmission counseling 76% of patients. No patients received bowel preparation. Epidural analgesia 93% for PD and 88% for LP. Only two patients in the overall population left the operating theatre with a NGT in place. Fifty-seven percent of PD patients were mobilized on POD 1 for a median of 60 minutes, 93% on POD 2. Median day of solid diet intake was day 3 (IQR: 1 day) and i.v. infusions were stopped on day 5 (IQR: 2 days); only

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7% of patients needed the repositioning of a NGT. Seventy percent of LP patients were mobilized on POD 1 with a median of 30 minutes and 90% on POD 2. The median day of solid diet intake was day 2 (IQR: 1 day) and i.v. infusions were suspended on day 4 (IQR: 1 day); only 6% of patients needed the repositioning of a NGT. Surgical outcome: overall morbidity for PD and LP was 64% and 62%, respectively; major complications 17% and 3%; and mortality 4% and 0%. Pancreatic fistula rate was 28% and 54%, respectively. Delayed gastric emptying occurred in 13.7% of PD patients. Readmission rate was 9% (PD) and 10% (LP). These data do not differ from our historical group. Postoperative length of stay was 9.5 days (IQR: 3 days) for PD and 7 days (IQR: 2 days) for LP. **Conclusion** The application of an ERAS protocol proved to be safe with no increase in morbidity and readmission rate. Adherence to most items, especially preoperative and intraoperative, was high. Compliance with post-operative items such as early stop of i.v. infusions and early solid food diet had worse results. Data on length of stay for both procedures are encouraging.

Adenosquamous Carcinoma of the Pancreas: A Series of 12 Cases

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Context Adenosquamous carcinoma (ASC) is a rare aggressive subtype of ductal pancreatic adenocarcinoma defined as a neoplasm with 30% or more malignant squamous cell carcinoma component admixed with ductal adenocarcinoma with higher potential for metastasis and an even worse prognosis. **Methods** We revised the histologic slides of all cases of pancreatic neoplasms from our archive, surgically resected between 2005 and 2010 looking for squamous cell component. Applying immunohistochemistry for two squamous cell markers (cytokeratin 5 and p63) we collected 12 cases with a squamous cell component representing the 30% or more of the neoplastic cell and so defined as ASC. **Results** The size of these tumors ranged from 2 to 6 cm, located mainly in the head of the pancreas (80% of cases). All cases showed massive perineural and lymphatic invasion and where associated to a severe chronic pancreatitis. The percentage of squamous cell component ranged from 30% to 95% of the tumor (in 8 of 12 cases; 66.67% this percentage was higher than 50%). Eight cases had lymph node metastases completely composed of squamous cells (2 cases), completely composed of adenocarcinomatous pattern (3 cases) or composed of both components (3 cases). The histological pattern of the metastases did not reflect the percentage of the two components in the primitive lesion. Preneoplastic lesions as mucinous metaplasia, intraductal pancreatic neoplasm and squamous metaplasia were found in all cases and involved either the main duct than the peripheral ducts. **Conclusion** In our cases squamous cell component seemed to be deeply intermingled in the mass of the predominant adenocarcinoma surrounded by a fibrotic pancreatic parenchyma with the main and peripheral ducts often presenting squamous metaplasia. These observations suggest the hypothesis of a possible common origin of squamous cell and adenocarcinomatous components from a pluripotent neoplastic stem cell.

Cystic "Feminine" Pancreatic Neoplasms in Men. Do Any Hormonal and/or Phenotypic Alterations Correlate with These Uncommon Entities?

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Context Mucinous cystic neoplasm (MCN) and solid pseudopapillary neoplasm (SPN) of the pancreas are uncommon hormone-related pancreatic tumours (HRPTs) with a clear predominance in young women. **Objective** To investigate the possible association between HRPT development in males and phenotypic and sex hormone alterations. **Methods** A retrospective analysis of our database was performed between the date February 1990 and February 2011 searching for male patients with HRPTs. Risk factors for sexual dysfunction (age >65 years, severe diabetes, alcoholism, atherosclerosis) were considered exclusion criteria. We investigated secondary sexual characteristics development, sex hormone level and

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overall sexual dysfunction degree according with the International Index of Erectile Function (IIEF) Questionnaire. **Results** We initially identified 25 patients: MCN: n=16 (64%); SPN: n=9 (36%). At follow-up, 5 patients were lost, 8 resulted dead and 3 were excluded according with exclusion criteria. We finally enrolled 9 patients (MCN: n=5; SPN: n=4). Puberty occurred within physiological age for 7 patients (mean±SD: 13.3±1 years) while it was mildly delayed in two cases. Signs of gynecomastia were not showed from adolescence until surgery in whole series. Three patients revealed mild sexual dysfunction at IIEF score, along with low testosterone level in two cases. Another patient with low level of testosterone was affected by secondary azoospermia. **Conclusion** In this study, the first in literature with similar aim, hormonal and/or sexual dysfunction was present in 30% of HRPTs. Unfortunately, the small sample size along with the rarity of these lesions, make further trials to be needed for reliable conclusions.

Predicting Factors of Long-Term Survival After Radiofrequency Ablation for Locally Advanced Pancreatic Cancer. Our Experience from a Series of 131 Consecutive Cases

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Context Radiofrequency ablation (RFA) represents a new and valid option in the multidisciplinary treatment of locally advanced pancreatic cancer (LAPC). Long-term survival data after RFA have never been reported in literature previously as part of a large and homogeneous series. **Objective** To investigate the presence of possible predicting factors of long-term survival for patients affected by LAPC who underwent RFA in the largest series available in literature to date. **Methods** A retrospective analysis of our database between February 2007 and April 2011 was performed searching for patients treated with RFA for LAPC. We indicated as "short-term survivors" (STS) or "long-term survivors" (LTS) those patients who showed an overall survival from diagnosis less or more than 24 months, respectively Demographics, clinical and surgical details with follow-up data were reported and statistically analyzed. **Results** We initially retrieved 131 patients. Forty-four (33.6%) of them were excluded as they were either still alive (n=40; 30.5%) or dead for non-related to surgery reasons (n=4; 3.1%) but within 2 years from diagnosis (potentially LTS). Other 3 (2.3%) patients were not considered because they died for RFA-related complications. The patients we finally included were 84, of whom 48 (57.1%) were STS and 36 (42.9%) were LTS. Median survival rate was 20 months for whole series, (95% CI: 14-26 months) and 35 (95% CI: 31-40 months) and 13 (95% CI: 10-16 months) for LTS and STS group, respectively (P<0.001). At univariate analysis AST level <30 U/L (P=0.04; OR: 2.8), CA 19-9 <600 U/mL (P=0.028; OR: 3.0) and adjuvant intra-arterial regional chemotherapy (IARC) (P=0.001; OR: 7.9) showed to correlate with long-term survival. Multivariate analysis indicated CA 19-9 level <600 U/mL (P=0.025) and IARC (P=0.003) as independent factors able to predict those patients who are candidate to be LTS. **Conclusion** Our series documented that long-term survival after RFA for LAPC is clearly possible. CA 19-9 level may predict those patients who are likely candidate to benefit from RFA in the context of a multidisciplinary environment. A prospective trial is needed for reliable conclusions.

Are Sendai's Criteria Always Effective in Management of IPMN? A Single Center Experience

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Context The correct management of IPMNs remains still uncertain **Objective** To evaluate the different strategies for the management of patients affected by IPMNs. **Methods** From January 2003 to December 2010, demographic, clinical, radiological, pathological data and type of management (surgery or follow-up), regarding 132 patients with IPMNs, were recorded in a prospective database. Indication to surgery was established according to international consensus guidelines. The patients were divided in three groups:

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group A, patients with criteria for surgery selected for surgical treatment; group B, patients without criteria for surgery selected for radiological follow-up; group C, patients with criteria for surgery but with high surgical risk selected for radiological follow-up. Failure of our strategy was a pathological diagnosis of IPMN adenoma in group 1 or deaths for malignant IPMN in groups 2 and 3. The intention to treat analysis was carried out. Finally we evaluated the quality of life (QoL) using EORTC questionnaire. **Results** Seven (5.3%) patients presented IPMN type I, 98 (74.2%) IPMN type II and 27 (20.5%) IPMN type III. Surgical treatment was proposed to 31 (23.5%) patients (group A). Radiological follow-up was suggested to 101 (76.5%) patients. Of these, 78 (77.2%) did not present criteria for surgery (group B), while only 23 (22.8%) had one or more criteria (group C). Mean follow-up, sex and presence of co-morbidities were similar among the three groups. Mean age in group C was higher than in groups A and B (74.3 *vs*. 67.4 and 69.4 years, respectively; P=0.040). Rate of the success was lower in group A than in groups B and C (83.3%, 98.7% and 100% respectively; P=0.009). Mean survival was lower in group C than in groups A and B (50.3±6.5, 61.7±6.5 and 63.1±2.2 months, respectively; P=0.035) but no patients died for malignant IPMN in groups B and C. The quality of life was similar among the three groups. **Conclusion** In older patients with radiological criteria for surgery but high surgical risk, radiological follow-up can be considered as a possible strategy for the management of IPMNs.

Is Binding Pancreaticojejeunostomy a "Panacea" for the Pancreatic Fistula? Results of a Multicentric Prospective Non-Randomized Study

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Context Binding pancreaticojejunostomy (BPJ) has been proposed in eastern countries as a safe technique that avoids anastomotic leakage (POPF) after pancreaticoduodenectomy (PD). **Objective** To evaluate the rate of pancreatic fistula in an European population underwent BPJ after PD. **Methods** From January 2009 to December 2010, data regarding 69 consecutives patients underwent PD in three centres were collected in a dedicate clinical research form (CRF). For each patient we registered sex, age, co-morbidities, ASA score, type of resection, characteristics of pancreatic remnant, pathological diagnosis, morbidity (according Clavien-Dindo classification) and mortality. The primary end point was the POPF rate. The secondary end points were overall complication, postoperative pancreatic haemorrhage (PPH), reoperation and mortality rate. Finally univariate and multivariate analysis were carried out to evaluate the factors predicting POPF. **Results** Mean age of patients was 64.5±12.4 years. There were 27 (39.1%) females and 42 (60.9%) males. One or more co-morbidities were present in 39 (56.5%) patients; 5 patients (7.2%) were ASA 1, 27 (39.1%) ASA 2, 35 (50.7%) ASA 3 and 2 (2.9%) ASA 4. A Child PD was carried out in 42 (60.9%) patients. An extended resection was performed in 5 (7.2%) cases. Pancreatic stump was hard in 36 (52.2%) cases and Wirsung duct was dilated in 31 cases (44.9%). Malignant disease was present in 65 (94.1%) cases. Thirteen patients (18.8%) had POPF (8.7% grade A, 8.7% grade B, and 1.4% grade C). Overall complication, PPH, reoperation and mortality rate were 52.2%, 18.8%, 9.0% and 5.8%, respectively. The univariate analysis showed that the presence of soft pancreatic stump was the only factor related to POPF rate (34.4%, and 5.4% in patients with soft and hard pancreatic stump, respectively; P=0.004). Logistic regression confirmed that soft pancreatic stump was the only independent factor related to POPF (OR: 9; 95% CI: 2-44; P=0.007). **Conclusion** In European population, BPJ do not reduce the risk of POPF.

Preliminary Results of Pancreatic Sphincterotomy as Treatment of Symptomatic IPMN

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Context Recurrent pancreatitis can be presenting symptoms of intraductal papillary mucinous neoplasm (IPMN) caused by a transient papillary obstruction by mucus. In main duct IPMN (MD-IPMN) surgical

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treatment is indicated for the high risk of neoplastic evolution; in side branch-IPMN (SB-IPMN) surgery is suggested only in symptomatic patients. In patients with MD-IPMN unfit for surgery or in symptomatic SB-IPMN without radiological evidence of malignancy (tumor diameter <30 mm, mural nodules, dilated main pancreatic duct or positive cytology) pancreatic sphincterotomy (PS) can be considered as an alternative treatment to reduce attacks of acute pancreatitis by facilitating drainage of mucus through the papilla. **Objective** To reduce the frequency of acute pancreatitis attacks performing PS in patients affected by symptomatic SB-IPMN without radiological evidence of malignancy or in patients with MD-IPMN unfit for surgery. **Patients and Methods** From October 2010 to June 2011, 6 patients (3 male, mean age 53±14.23 years) with IPMN (2 with mixed form: MD + SB-IPMN and 4 with SB-IPMN) diagnosed by MRCP with secretin stimulation underwent PS. Pancreas divisum was diagnosed in 1 patient. In 5 patients IPMN was localized in the head of the pancreas whereas 1 patient was affected by mixed-IPMN head and body. Mean diameter of cystic lesions was 18.8±10.64 mm. All patients were symptomatic for acute pancreatitis: 5 cases mild acute pancreatitis and 1 case severe acute pancreatitis. **Results** In 5 out of six patients, pancreatography showed cystic lesions communicating with main pancreatic duct and confirmed pancreas divisum in one; in one case with mixed type-IPMN visualization of cystic lesion localized in the body was not obtained. Six PS were performed (5 major papilla and 1 minor papilla). Mucus goes out after sphincterotomy in only 2 cases (mixed-IPMN). Mortality of procedure was 0% and morbidity was 16% (one patient presented self-limiting bleeding post-ERCP, 5 days after sphincterotomy). Duration of follow-up was 8 months (range 1-8 months). Two patients presented recurrent pancreatitis and underwent to DCP: one was affected by mixed-IPMN and the other by SB-IPMN (head localization). Conclusion: PS can represent an alternative treatment for symptomatic benign SB-IPMN or MD-IPMN unfit for surgery. Scheduled and regular follow-up with non invasive radiological techniques is mandatory in treated patients.

MiRNAs with a Prognostic Significance in Pancreatic Cancer

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Context MicroRNA (miRNA) altered expression in pancreatic cancer (PC) might pinpoint new diagnostic and prognostic biomarkers. **Objective** To analyze possible associations of miRNAs expression deregulation with clinical-pathological features and to evaluate correlations between miRNAs expression levels in patients with PC. **Methods** After profiling miRNA expression in 17 pairs of tumours and adjacent non-tumours tissues by means of miRNA microarrays, we selected 13 miRNAs for further validation by using qRT-PCR. Relative expression levels of miR-143, miR-21, miR-145, miR-151-5p, miR-155*, miR-199a-5p, miR-23a, miR-31, miR-30a, miR-30c, miR-455-3p, miR-708 and miR-let-7i were analysed in 31 pairs of tissues samples from patients with different histological type of PC. Association analyses were performed using Mann-Whitney U-test and Pearson correlation coefficient. **Results** Compared to adjacent normal tissues, all miRNAs were up-regulated with the only exception of miR-21. Interestingly, expression deregulations of miR-21 and miR-199a-5p were different in ductal adenocarcinoma versus Vater's papilla adenocarcinoma samples. In addition, miR-21 expression was associated with disease progression and survival. Levels of miR-21, miR-199a-5p, miR-145, miR-151-5p, miR-23a, miR-31, miR-708 and miR-let-7i were associated with preoperative serum levels of CA 19-9. Lymph node spreading was negatively correlated to the expression of miR-143, miR-145, miR-155*, miR-199a-5p, miR-23a, miR-31, miR-708 and miR-let7i. Both these associations were regardless of the PC histological type. Furthermore, perivascular invasion was associated with miR-151-5p expression, and perinaural invasion with miR-155* and miR-let-7i levels. Finally, we observed a cancer-specific network between miRNAs expression in PC. **Conclusions** Association data with clinical-pathological features suggest a prognostic significance for these miRNAs in PC. Clarification of the cancer-specific network might highlight new element with a role in regulation of pancreatic tumour biology.

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CASE REPORTS

Cystic Dystrophy of the Duodenal Wall in Heterotopic Pancreas: Is Octreotide Useful?

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Context Cystic dystrophy in heterotopic pancreas (CDHP) is a rare disorder characterized by dilatation of the ectopic pancreatic ducts of heterotopic pancreatic tissue that occurs most often in the second part of the duodenum. This disorder is difficult to diagnose and controversies exist about the optimal management of CDHP, especially in case of associated chronic pancreatitis. We report a case of CDHP of the duodenal wall in a patient with chronic pancreatitis treated with medical therapy. **Case Report** A 58-year-old man presented with recurrent episodes of epigastric pain, vomiting and weight loss (35 kg in 4 years). The patient was alcoholic and smoker. In 2005 he underwent ERCP and cholecystectomy for acute biliary pancreatitis. In 2006, during another episode of pain, a CT-scan showed a mass in the head of the pancreas with thickening of the duodenal wall. An EUS with FNA was negative for tumoral cells. In 2009, for persistent episodes of pain, he underwent a second EUS which revealed substenosis of the second part of the duodenum with thickened wall containing multiple cysts inside and ultrasonographic signs of chronic pancreatitis. On these findings we diagnosed CDHP of the duodenal wall in patient with chronic pancreatitis. Alcohol intake was stopped but patient did not assume suggested therapy with octreotide. Symptoms do not improved, so octreotide was start in hospital during a relapse of acute pancreatitis (octreotide LAR 20 mg every 4 weeks). Five months later control EUS was improved and patient referred only two episodes of mild pain. This treatment was maintained during 9 months without episodes of severe pain, vomiting or pancreatitis. Weight gain was obtained. **Conclusion** Difficult diagnostic and therapeutic dilemmas are raised by CDHP. In our case medical treatment with octreotide along with alcohol abstinence was successful in improving symptoms, weight gain and EUS sign of CDHP for 9 months. A longer follow-up period is required to assume the efficacy of this treatment.

Acinar Cell Cystadenoma of the Pancreas: Case Report of an Unusual Cystic Tumor

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Context Acinar cell tumors of the pancreas are uncommon**.** We report here an unusual case of acinar cell cystadenomas (ACA). **Case Report** A 56-year-old woman was observed for abdominal pain and diarrhoea on April 2009. The physical examination and laboratory tests were normal. US and CT scan showed two hypodense and hypovascular cystic lesions of the pancreas; the first one in the body of 10 mm in diameter with peripheral calcification, the second one was 5 mm in the tail. MRI confirmed the feature and contrast-material enhancement in the pancreatic lesions was not observed. One year after, the patients repeated a US and CT scan revealing increasing size of the cystic lesion of the body (14 mm) and IPMN type II of the tail. EUS revealed that the main pancreatic duct did not communicate with the larger cyst in the body. The diagnosis of mucinous cystic tumour was suggested and in March 2011 a laparoscopic spleen-preserving left pancreatectomy was performed. The postoperative course was uneventful and the patient was discharged in the 7th postoperative day. The pathological characteristics suggested the hypothesis of ACA. The specimen comprised a unilocular cystic lesion of the body that measured 0.8 cm containing clear fluid. The surface of the cyst was smooth and glistening and had no solid areas of papillary projections. At the microscopic examination the unilocular cyst was lined by one to several layers of cytologically bland acinar cells with round, basally oriented nuclei and granular, eosinophilic apical cytoplasm. The cytoplasmic zymogen granules were positive for periodic acid-Schiff and resistant to diastase digestion. Their nuclei were regular and contained small nucleoli without mitosis. The epithelium was not connected to pancreatic ducts or to pancreatic acini and there was no pseudo-ovarian stromal change in underlying

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connective tissue. **Conclusion** ACA is a rare tumour and it has to be included in the differential diagnosis of cystic lesion of the pancreas. This should be the 15th case reported in literature, thus its natural history is not well known and its surgical indication is mandatory for the imaging findings similar to mucinous cystic tumour.

Locally Advanced Unresectable Pancreatic Cancer Become Resectable After Stereotactic Radiotherapy: A Case Report

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Context For patients with exocrine pancreatic cancer, the only curative treatment is complete surgical resection, but about 40% present with localized tumors are unresectable due to involvement of the celiac axis, the superior mesenteric artery, or other major vascular structures. For these patients treatment typically consists of chemoradiation, or initially chemotherapy followed by chemoradiation, if there is no progression. Herein we present the case of a patient with unresectable pancreatic cancer at presentation who obtained good response to radiotherapy to undergo resection. **Case Report** In December 2009 a 56-year-old man had diagnosis of a pancreatic mass by imaging and CA 19-9 equal to 13,000 IU/mL. In other institution he was submitted to explorative laparotomy, biliary, gastric bypass and biopsies (positive for adenocarcinoma) due to involvement of superior mesenteric vein. He was treated with GEMOX for 6 months and subsequently FOLFIRI for lymph nodes progression for other 5 months. In November 2010 a re-evaluation by CT scan showed stable disease. In December 2010 he was treated with stereotactic body radiotherapy (SBRT) delivered with modulated volumetric arc therapy (VMAT) by RapidArc technique. The prescription dose was 45 Gy in 6 consecutive fractions of 7.5 Gy each in preservation of organs at risk (duodenum, spinal cord, liver and kidneys). A subsequent CT scan showed a downstaging of the disease; CA 19-9 was 3,500 IU/mL. In March 2011 the patients was submitted to explorative laparotomy that revealed a pancreatic lesion with a shallow infiltration of transverse mesocolon, with only adhesion to superior mesenteric vein. We realized a PD with gastric resection, maintaining previous gastroenteric anastomosis. Postoperative hospital stay was uneventful and he was dismissed after 7 days. TNM was ypT3pN1. The patient is alive and in good conditions 4 months after surgery. **Conclusion** Stereotactic body radiotherapy seems to obtain downstaging of the disease locally with regression of vascular infiltration, without interfering in surgical dissection by production of tissue oedema and fibrosis.

Incidental, Non-Functioning, Pancreatic Endocrine Tumor. Is Follow-Up a Good Choice?

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Context Even if non-functioning pancreatic endocrine tumours (PET) are usually discovered when they are large and symptomatic, in recent years the frequency of incidental cases increased. The natural history of these tumours is not well known and surgery remains the treatment of choice. We reported a case of an incidental non-functioning PET in a patient who refused surgery. **Case Report** A 64-year-old man admitted to our department for the presence of asymptomatic, solid, pancreatic lesion localized in the head of the pancreas, identified by US on January 2009. All laboratory data, including tumour markers, were normal. CT scan confirmed a round, solid, hypervascular lesion, measuring 23 mm, with early enhancement and delayed washout. EUS-guided fine needle aspiration revealed non functioning PET. PET with 68-Ga-Dotanoc, performed to evaluate the presence of somatostatin receptors and the extension of the disease, was negative. Pancreaticoduodenectomy was recommended to the patient, but he rejected surgery. Follow-up was suggested every three months and medical therapy with somatostatin was begun. On February 2010, a CT revealed an increase in the mass size (35x24 mm) and a suspicious small lesion in the brain. On March 2010, the patient underwent partial temporal lobectomy and pathological examination

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showed a gliosarcoma. The last CT, performed on May 2011, did not reveal any increase of mass size and evidence of distal metastasis. At the present time (29 months after the diagnosis) the patient is well, asymptomatic, in medical therapy, with a PET increase in size from 23 mm to 35 mm but without distal metastasis **Conclusion** Our case showed that a non-functioning, asymptomatic PET increased in size during the time even if they did not present evidence of distal metastasis. It suggests that this type of tumour presents a slowly evolution. Thus, follow-up could not be a good choice in young patients.

A Case of Pancreatic Endometrial Cyst

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Context Pancreatic endometrial cyst is an extremely rare instance of ectopic endometriosis. The surgical mini-invasive approach to the pancreas by the robotic-assisted surgery is becoming the new standard way in many patients affected by pancreatic cystic lesions, such mucinous and serous tumors alone. **Case Report** A 23-year-old woman with a history of recurrent acute upper abdominal pain was found to have a cystic lesion in the tail of the pancreas on abdominal ultrasound. Pre-operative CT scan and MRI findings indicated a mucinous cystadenoma of the pancreas. Both CA 125 and CA 19-9 were increased .For this reason a surgical resection was planned. A robotic-assisted distal splenopancreatectomy was performed. The intraoperative examination of the abdomen did not reveal any pathological findings, except the cystic lesion of the tail of the pancreas. Histopathological examination of the specimen revealed cystic endometriosis, with blood and presence of macrophages with hemosiderin phagocytosis. The patient was discharged on post-operative tenth day. **Conclusion** Pancreatic endometrial cyst is an extremely rare lesion, which is reported seldom in literature, first in 1984. Further, this is the first recorded case of surgical resection by robot-assisted mini-invasive surgery of a pancreatic endometrial cyst.

Synchronous Serous and Mucinous Cystic Tumors of the Pancreas: Case Report

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Context Pancreatic cystic neoplasms are frequently detected due to extended use and better quality of the abdominal imaging. Differential diagnosis is based on typical features indicating with greater probability, a specific neoplasm. Cystic tumors are usually isolated lesions, while IPMN branch duct are often described as multiple cysts. We report a case of coexistent serous cystadenoma and mucinous cystic tumor of the pancreas mimicking at pre-operative imaging IPMN branch-duct. **Case Report** In 2002 a 62-year-old woman, was incidentally diagnosed with a cystic neoformation (20x10 mm) located in the neck of the pancreas. She was also affected by Hashimoto's thyroiditis, osteoporosis and previous phlebitis. Another cystic neoplasm (16x16 mm), in the uncinate process, was detected at the annual follow-up CDT scan in 2007. On February 2010, at the annual follow-up MRI, the size of lesion of the neck had increased (to >30 mm), while the uncinate process cyst was stable. At both CT scan and endoscopic US, either lesions did not appear to be connected to the main pancreatic duct. The laboratory tests showed only slight elevated serum amylase (144 U/L). On August 2010 the patient underwent a mini-invasive full laparoscopic assisted pylorus preserving pancreaticoduodenectomy extended to the body of the pancreas. The operative time was 454 minutes. The post-operative course was uneventful except for delayed gastric emptying (grade B). The patient was discharged on the twentieth post-operative day. Pathological examination concluded for the synchronous presence of serous microcystic adenoma in the neck and mucinous cystic adenoma in the uncinate process. **Conclusion** This case report is intended to increase the awareness of the condition of the synchronous cystic tumors of different nature while alluding to the need for diligent examination by endoscopic US. It also highlights the clinical impact of endosonography on the diagnosis and management of cystic lesions in the pancreas.

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Case Report and Review of the Literature of Mature Cystic Teratomas of the Pancreas

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Context Pancreatic cystic lesions are increasingly recognized and comprise different pathological entities. The management of these lesions is challenging, because of inadequate preoperative histological diagnosis. We report the case of a rare pancreatic cystic lesion. **Case Report** A 61-year-old man was found to have an hypoechogenic lesion of the pancreatic head at abdominal ultrasonography. Serum tumoral markers were normal and abdominal computed tomography showed a 3.2 cm hypodense well-defined lesion in the uncinate process. At endoscopic ultrasound the lesion appeared hypoechogenic, without septations; fine needle aspiration was performed, but cytological examination was unspecific. At explorative laparotomy, a 3 cm soft lesion was found in the uncinate process. Considering the lesion's dimensions, the patient's age, the intraparenchymal location, the presence of mucoid material at intraoperative puncture, the impossibility to have a definitive histologic diagnosis, we performed a pylorus preserving pancreaticoduodenectomy. Histological analysis revealed an intrapancreatic cystic neoplasm with stratified squamous epithelium and skin appendages, surrounded by a lymphoid tissue wall. The presence of sebaceous focal areas supported the diagnosis of benign mature cystic teratoma. The postoperative course was uneventful and the patient is disease free at 8-month follow-up. **Conclusion** Cystic teratomas are congenital developmental abnormalities of germ cell origin and the pancreas is an extremely rare primary site. This one is the 34th reported case of cystic teratoma of the pancreas. The literature analysis shows that median age at diagnosis is 40 years (range 0.3-74 years), without gender preference. The location is pancreatic head in 50% of the cases, body in 36.6% and tail in 13.4%; median dimension of the lesion is 7.5 cm (range 2.2-20 cm). Mature cystic teratomas are strictly benign tumors and theoretically they do not require surgery. Nonetheless, a procedure to assure specific diagnosis of this lesion remains to be determined. Therefore, in case of doubtful dignity, radical resection should be performed.

Case Report: EUS-Assisted Rendezvous ERP for Minor Papilla Endotherapy

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Context Santorinicele and pancreas divisum are pancreatic ductal abnormalities that can be involved in the pathogenesis of acute recurrent pancreatitis (ARP). Endotherapy aims to relieve the true or relative ductal obstruction associated with these abnormalities by improving pancreatic drainage through the minor papilla with benefits on ARP. When cannulation of minor papilla by endoscopic retrograde pancreatography (ERP) failed a EUS-assisted rendezvous ERP has been described in a few case reports as suitable technique. **Case Report** A 54-year-old patient was referred to our center to investigate two recent episodes of pancreatitis and frequent relapses of pancreatic-type pain. She was a previous alcohol abuser and smoker. The pancreas was normal at CT. MRCP detected a pancreas divisum, santorinicele in presence of a not dilated pancreatic duct, hypotrophy of the parenchyma. EUS confirmed pancreas divisum and santorinicele and detected two parenchymal abnormalities. Biochemical tests revealed two CFTR-mutations, normal glycaemia and fecal elastase. Since a first minor papilla cannulation failed, a EUS-assisted rendezvous ERP was performed. Under EUS guidance pancreatic duct was punctured transduodenal using a 22-gauge needle. A 0.018-inch guide wire was introduced into the pancreatic duct and advanced through the minor papilla into the duodenum. The echoendoscope was removed over the guidewire. The distal end of the guidewire exiting through the pancreatic orifice was grasped with a snare and was withdrawn thought the accessory channel of the duodenoscope. Then pancreatic sphincterotomy of the minor papilla was performed and a 7-french nasopancreatic drain was placed. After the procedure the patient developed a mild pancreatitis. The nasopancreatic drain was removed after four days and the patient was discharged from the hospital two days later. **Conclusion** The rendezvous technique, combining EUS-guided transduodenal intervention and ERP, is a complex method that can provide access to the pancreatic duct in patients with failed minor papilla cannulation.

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Stenosis of the Celiac Trunk and Aberrant Branch of Superior Mesenteric Artery Complicating Angiographic Management of Post-Pancreatectomy Hemorrhage: A Case Report

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Context The incidence of post-pancreatectomy haemorrhage (PPH) is between 1% and 8% of all pancreatic resections and accounts for 11% to 38% of overall mortality. Angiographic embolization is a feasible, safe and effective technique to treat grade C PPH. **Case Report** In January 2011 a 72-year-old male patient underwent pancreaticoduodenectomy (PPPD) for a symptomatic mixed type IPMN with moderate grade dysplasia. During surgery a vascular abnormality was found: the first branch of the SMA was very long and with several kinkings, making it a sort of ball located just medially to the uncinate process, into the retroportal tissue; it was carefully preserved during dissection. The postoperative course was complicated by a low-output pancreatic fistula, initially classified as grade A and the patient was discharged 10 days after surgery with a peri-pancreatic drainage still in place. A week later he presented with an abrupt but mild bleeding from the abdominal drainage. In first aid department he underwent an abdominal CT scan that did not show any active bleeding. The patient was admitted to our pancreatic surgery unit and monitored. Four days later, due to continuing blood outflow from drain requiring transfusions, he underwent a new CT scan that revealed a pseudoaneurysm of gastro-duodenal artery. The patient was in stable clinical condition so we decided to perform angiography and selective embolization. The procedure revealed a tight stenosis of the celiac trunk, reperfused by the aberrant first branch of SMA found out during surgery; its presence made pseudoaneurysm embolization unfeasible, despite many efforts. Then the patient underwent surgery achieving successful control of bleeding: a completion pancreatectomy was performed, associated with intra-portal islet-cell auto-transplantation. The postoperative period was uneventful except for the development of a wound infection and the patient was discharged 17 days after surgery. Five months later he is in good clinical condition and free from insulin therapy. **Conclusion** Artery abnormalities are often found during pancreatic surgery; their presence can influence surgical procedure and outcome. In this case, an aberrant artery made the elective conservative treatment for grade C PPH unfeasible.

Management of a Hypervascular Pancreatic Mass: Could We Do Better?

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Context Differential diagnosis of hypervascular pancreatic masses is difficult due to common radiological characteristics of different entities: neuroendocrine tumours, pseudopapillary neoplasms, cystic tumours and distant metastasis from other malignancies (renal cell or breast carcinoma). Surgery is often the last step in the diagnostic process. **Case Report** A 47-year-old woman was referred to our center after discovering, in absence of symptoms, a hypervascular mass of pancreatic tail. No history of previous malignancies was present. Serum markers CEA and CA 19-9 were negative and so were NSE and CrA. CT scan, MRI and CEUS showed a small (10 mm), solid, well defined area, hypervascular in arterial phase with a rapid wash out. Percutaneous cytology was not performed because of size and site (behind the left colonic flessure). Because of suspicion of non functioning endocrine tumour the patient underwent laparoscopy: intraoperative ultrasound supported that hypothesis and therefore a spleen preserving pancreatic tail resection was carried out. In the postoperative course a grade B pancreatic fistula occurred which spontaneously resolved after discharge. Histology examination revealed an intrapancreatic accessory spleen. **Conclusion** Intrapancreatic accessory spleen is a rare cause of pancreatic pseudotumors and is located in the pancreatic tail in approximately 1% to 2%. Accessory spleen itself is found in approximately 7% to 15% of the population. At this stage there is no diagnostic technique which can guarantee a sure diagnosis and cytology is not always technically feasible. With the suspicion of a pancreatic neoplasm, a

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surgical exploration is mandatory and laparoscopy is a minimally invasive approach that should be considered. In conclusion, intrapancreatic accessory spleen is a rare cause of unnecessary laparotomy, but the absence of reliable diagnostics for this entity make histologic ascertainment of a benign tumor indispensable.

Abdominal Wall Metastasis from Pancreatic Carcinoma Treated with Electrochemotherapy (ECT): Report of Two Cases

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Context The standard therapy for many unresectable solid tumors is chemo-radiotherapy (CTRT). The major problem of cytolytic agents with intracellular site of action is the correct penetration of the drug through membrane. ECT is a new ablation modality which provides delivery of the non-permeant drugs into cell by local application of short and intense electric pulse that transiently increases membrane permeability (electroporation). In literature there are few studies regarding its application in case of melanoma, mammarian cancer relapse and other cutaneous carcinomas. We report two cases of abdominal wall metastasis of pancreatic carcinoma treated with ECT. **Case Reports Case #1** A 68-year-old woman previously treated with radiofrequency ablation of stage III pancreatic head carcinoma presented, 8 months after surgery, complaining the onset of a small nodule under the surgical scar. US and FNA showed a 3.2 cm metastatic carcinoma. The patient was treated under sedation with intravenous injection of 24 mg of bleomycin (15,000 U/m^2) followed by 8 applications of electroporation (EP). US in the first post-operative day showed subcutaneous oedema with micro bubbles of air. The post-operative course was uneventful and the patient was discharged after 2 days. **Case #2** A 81-year-old woman previously treated with distal pancreatectomy and splenectomy for stage II pancreatic tail carcinoma (T2N1, G2), complained, 4 months later, the onset of a small subcutaneous nodule in the upper left abdominal wall. US and FNA showed a 2 cm metastatic nodule. The patient was treated under sedation with intravenous injection of 22 mg of bleomycin (15,000 U/m^2) followed by 5 applications of EP. US in first post-operative day showed oedema with micro bubbles of air. The post-operative course was uneventful and she was discharged after 2 days. In both cases one-month follow-up with US and MRI showed partial reduction of the treated nodule. **Conclusions** ECT is an innovative procedure potentially useful for pancreatic cancer. We report the first two cases applied to pancreatic carcinoma metastasis in order to test the sensitivity to bleomycin of pancreatic cancer cells. Further studies are needed to test ECT in unresectable pancreatic cancer.

Intrapancreatic Accessory Spleen

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Context Intrapancreatic accessory spleen (IPAS) is a congenital anomaly due to the fusion failure of primordial mesenchymal tissues of the spleen which can mimic a pancreatic neoplasm. **Case report** We report three cases of IPAS that were resected because misdiagnosed by radiology as pancreatic neoplasms. Two lesions were detected by routine ultrasonography (US) showing respectively a nodular lesion of 3.5 and 1.5 cm in diameter. In the third case there was a 1.9 cm nodule at first observed by US and than studied by magnetic resonance. All the three lesions resulted as well-circumscribed nodules localized within the pancreatic tail characterized by hypervascularization and radiologically diagnosed as pancreatic endocrine neoplasms. After resection the gross examination revealed brick-colored capsulated nodules within the pancreatic parenchyma. Microscopically these lesions resulted to be composed by typical splenic tissue. The surrounding pancreatic parenchyma did not show any fibrotic or inflammatory reaction and the principal pancreatic duct were impinged but not occluded by the nodules. The final diagnosis was intrapancreatic accessory spleen. Curiously, two of the three patients underwent splenectomy for abdominal trauma some years before the finding of the IPAS raising the idea that a compensatory hyperplasia of the accessory splenic tissue can develop these tumor-like lesions. **Conclusion** For this reason, in the case of a hypervascularized well-circumscribed nodule within the pancreatic tail in a patient that previously

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underwent splenectomy is very important to distinguish a possible IPAS from a pancreatic endocrine neoplasm and avoid an unnecessary surgery. Fine needle aspiration cytology in IPAS provides a typical smear, showing polymorphous population of lymphocytes and other inflammatory cells, with red blood cells and thin-walled blood vessels with endothelial cells making possible this differential diagnosis.

Hepatic Metastasis from Gastrinoma and Non-Functioning Pancreatic Head Tumor in MEN I: What Does It Means?

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Context Gastrinomas in MEN I are often multiple, very small (<1 cm), usually located in the duodenum and pancreas, rarely in lymph nodes, gallbladder and biliary tree. In few patients, they could show with distant metastases even if primary localization was not found. Herein, we report a very rare case of a single hepatic metastasis from a non-identified primary gastrinoma associated with a non-functioning pancreatic head tumour in a patient affected by MEN I. **Case Report** A 35-year-old woman was admitted in our hospital on November 2010 for recurrent diarrhea and vomiting. Laboratory tests revealed hyper-gastrinemia (>10,000 pg/mL), hypercalcemia (11 mg/dL) and hyperparathyroidism (PTH 94 pg/mL). Endoscopy showed acute erosive duodenitis and esophageal ulcer. EUS discovered a very small (9x8 mm) lesion of the pancreatic head and a CT confirmed the pancreatic lesion and showed a hepatic metastasis (29x16 mm) of the IV segment. In the suspicion of Zollinger-Ellison syndrome in MEN I, a SPET of parathyroid glands and a RMN of hypophysis were performed. MEN I syndrome was diagnosed. Surgical treatment was planned. First, a pancreatico-duodenectomy with partial gastrectomy and resection of the hepatic metastasis was performed to remove pancreatic tumour with hepatic metastasis. Pathological examination showed: a well-differentiated (G2), non functioning endocrine tumor of the pancreatic head (Ki 67, 3.2%) and multiple associated microadenomas (Ki 67, 7.3%); one lymph node metastasis with IIC positive for gastrin (ln 8a; Ki 67, 0.6%) out of 28 lymph nodes; two hepatic metastases showed a well-differentiated endocrine carcinoma (G2) with IIC positive for gastrin (Ki 67, 2.8%). The postoperative course was uneventful and the patient was discharged 23 days after surgery with gastrinemia returned normal (29 pg/mL; reference value: 13-115 pg/mL). About two months later, the patient underwent surgery to treat hyperpara-thyroidism. Actually, the patient is well and alive, without recurrence of the disease and with normal value of gastrin serum level (33 pg/mL). **Conclusion** In our case, pancreaticoduodenectomy with partial gastrectomy and liver resection, allowed to remove both the identified pancreatic and hepatic lesions and the primary non-identified gastrinoma. It means that wide pancreatic resection are suggested in patients affected by gastrinomas in MEN I.

Solid Pancreatic Hamartoma: Report of Two Cases

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Context Pancreatic hamartoma is an extremely rare tumor-like lesion of the pancreas and its prevalence hamartoma is difficult to establish since a certain amount of cases are likely to be asymptomatic and remain undetected. The examination of almost 1,500 cases of pancreatic surgical specimens in the last 5 years (1994-2011) revealed only two cases of pancreatic hamartoma (0.13%). **Case Report** In the first case, a 57-year-old woman presented with a pancreatic mass, incidentally found by abdominal ultrasonography. The second case was a 50-year-old men with a suspected solid lesion located in the pancreatic body. Radiologic findings suggested the presumptive diagnosis of ductal adenocarcinoma. Intraoperative fine needle aspiration was performed for 3 times in the second case and each time only normal acinar cells were found out. Both patients underwent an intermediate resection of the pancreatic body. In both cases, the lesions presented as solid, well circumscribed, whitish-grey masses, with a

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homogeneous appearance on cut surface and a maximum diameter of 1.5 cm. Microscopically both lesions were composed of well-differentiated acinar and ductal cells, without atypia, disposed in a radial trabecular arrangement. A wide sclerotic paucicellular area was present in the centre of the lesions. Acini and small intralobular and interlobular ducts showed atrophic aspects without any evidence of dysplasia. Rare vascular structures were interspersed between acini and ducts. Discrete islets of Langerhans were lacking while scattered small endocrine cell clusters, detected with immunohistochemistry, were distributed between peripheral acini and ducts. In both cases the surrounding pancreatic parenchyma was regularly lobulated and without evidence of pancreatitis. **Conclusion** In both cases the preoperative diagnosis was that of solid tumour of the pancreas suspicious for malignancy, but only with histology we can demonstrate the benign and non-neoplastic nature of these lesions.

Adenosquamous Carcinoma of the Papilla of Vater Associated with a Small Bowel GIST. A Case Report

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Context Most tumors of the papilla of Vater are adenocarcinomas and other histological types are less frequent. Adenosquamous carcinoma of the papilla is a rare tumor and only three cases have been reported in the literature in the last ten years. **Case Report** We present a case of an adenosquamous carcinoma of the papilla of Vater associated with a small bowel gastrointestinal stromal tumor of the jejunum. An 81-year-old woman presented at a local hospital because of obstructive jaundice. An abdominal CT scan showed a dilatation of the common bile duct and the Wirsung duct down to the papilla of Vater, where an area of thickening and contrast enhancement of about 2 cm was present. A solid lesion of about 5.3 cm adherent to a jejunal loop was also seen. The patient underwent to endoscopic biliary stenting and then she was referred to our hospital. A FDG-positron emission tomography showed an area of hypermetabolism in the pancreatic head and in an area of 5 cm of diameter in the left lower abdomen. The patient underwent to pancreaticoduodenectomy with a Traverso-Longmire reconstruction and resection of a jejunal loop including the gut neoplasm. Histology revealed an adenosquamous carcinoma of the papilla of Vater (size 4 cm in diameter; T4, N1, M0, G2) and a gastrointestinal stromal tumor (size 4x4.5 cm, 1 mitosis/50 HPF, low grade risk according to 2002 Fletcher classification) of the small bowel. Postoperative course was uneventful. The patient is alive with hepatic metastases developed 8 months after surgery. **Conclusion** Adenosquamous carcinoma of the papilla of Vater is a rare tumor and only few cases have been described so far. The association between adenosquamous carcinoma of the papilla of Vater and small bowel GIST has never been reported in the English literature.

Small Asymptomatic Branch Duct Intraductal Papillary Mucinous Neoplasm of the Pancreas with Mural Nodules. Should It Be Resected?

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Context Natural history of branch duct intraductal papillary mucinous neoplasms (BD-IPMNs) remains unclear and the decision whether to treat a patient affected by BD-IPMN with surgical resection or follow-up is challenging. Clinicoradiological findings of the lesions are very important factors in that choice as well as age and general conditions of the patients. **Case Report** A 60-year-old woman came to our attention for the incidental CT finding of a 12 mm BD-IPMN in the head of the pancreas, without radiological signs of malignancy. The past medical history was negative. Since the likelihood of the presence of an invasive cancer was very low due to the small dimension and the absence of symptoms and main

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pancreatic duct dilatation, the patient started a surveillance program. Six months later the patient was still asymptomatic and underwent magnetic resonance cholangiopancreatography (MRCP) that showed the presence of two BD-IPMNs of 14 mm each in the head of the pancreas, without dilatation of main pancreatic duct. Moreover, the proximal lesion was found to contain a antigravitarian contrast-enhancing mural nodule. An ultrasound scan of the abdomen confirmed these findings. To note, the presence of mural nodules was found to be an independent predictive factor for malignancy in a study by Sugiyama *et al*. considering 62 resected IPMNs. Considering the long life expectancy of the patient, her good general conditions and the presence of a feature of invasive neoplasm at imaging, we decided, with patient's agreement, to leave the noninvasive surveillance strategy and perform pancreaticoduodenectomy in order to maximize the overall survival with a good quality of life. **Conclusion** Our surgical indication followed the International Consensus Guidelines released by Tanaka and colleagues. Can be a surgical resection justified in a young patient, without major comorbidities, affected by a small BD-IPMN suspected to be invasive at imaging to grant best overall survival with good quality of life and to avoid a long-term radiological follow-up?

An Intriguing Case of Serum CA 19-9 Elevation

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Context Serum CA 19-9 is the mainstay marker for the diagnosis of biliopancreatic malignancies, even though its diagnostic specificity is limited by elevated serum levels also found in other digestive carcinomas and benign diseases. Autoimmune pancreatitis (AIP) is a rare disorder of presumed autoimmune aetiology which is associated with characteristic clinical, histologic, and morphologic findings. Among patients with AIP, serum IgG4 levels are elevated to more than two times the upper normal limit in most patients. A number of other organs can be involved in patients with AIP. The most common pulmonary involvement is hilar lymphadenopathy occurring in up to 83% of cases. **Case Report** We report the case of a 75-year-old man with a moderate and fluctuating elevation of CA 19-9 (from 47 to 269 U/mL), having a slight elevation of serum IgG4 levels (184 mg/dL) and the presence of a type 2 intraductal papillary-mucinous neoplasm of the pancreas (IPMN) at magnetic resonance cholangio-pancreatography (MRCP). Comorbidities included a pulmonary lymphadenopathy, a cyst of the mediastinum, previous HCV-related hepatitis treated with interferon plus ribavirin in 1995, non erosive reflux disease and uncomplicated diverticular disease of the colon. Since 2010 the patient has been free of any symptoms and, at present, he is in excellent health. IPMN was detected by a routine abdominal US performed in 2009 for the follow-up of hepatitis and confirmed by RMCP. The determinations of serum CA 19-9 and IgG4 were carried out due to the presence of IPMN and parenchymal pancreatic heterogeneity of the pancreas at US. Other imaging investigations such as PET/CT, abdomen and thoracic CT scan, upper GI and colon endoscopy confirmed the findings in the pancreas, thorax and GI tract, but did not show any neoplasm. Other laboratory tests were normal. **Conclusions** Elevation of serum CA 19-9 in this patient can only be accounted for using weak explanations: 1) AIP, whose clinical presentation, however, does not fit with that of the present case (Ig4 levels were moderately increased); 2) IPMN which is type 2 and with no other signs of suspected malignant degeneration; 3) previous HCV-related hepatitis which does not show current cholestatic involvement. Therefore, at present, a careful follow-up and wait and see policy seems the most appropriate strategy in this patient.

The Role of Surgery as Mandatory Strategy to Obtain a Histological Diagnosis for a Solid Peripancreatic Lesion of Uncertain Origin. A Case Report

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Context Solid peripancreatic lesions are part of a small subset of rare pathological entities which may present an uncertain biological behaviour. Standard radiological investigations and non-invasive cytological analyses can often lead the surgeon to obtain a sure diagnosis and avoid unnecessary surgery.

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Case Report A 66-year-old female patient was electively admitted in our department with a peripancreatic mass incidentally diagnosed for a long-standing history of recurrent bibasal chest pain, not associated to any obstructive symptoms, abdominal discomfort or weight loss. Blood tests were unremarkable as well as tumour markers (CEA: 0.8 ng/mL; CA 19-9: 4.3 U/mL). She initially underwent an US-scan which revealed a 3 cm-sized lesion within the pancreatic head. Further investigations such as abdominal contrast-enhanced CT-scan and MRI, raised the strong clinical suspicion of an accessory liver lobe (Riedel's lobe). Finally, an EUS hypothesized the lesion was likely a GIST arising from the posterior wall of descending duodenum (DII) and FNA was also performed at the same time. Curiously, cytological features showed that cell population was made up by few normal epithelial elements and small leukocytes and immunohistochemical analyses were not in keeping with GIST diagnosis. Therefore, after a wide discussion with the patient, a surgical biopsy was warranted in order to reach a definitive diagnosis. Abdominal exploration revealed the presence of a single 3.5 cm-sized lymph node located between DII and the inferior cava vein which was completely removed. No further pathological nodes or other intra-abdominal lesions were found. Histological analysis revealed a grade I follicular non-Hodgkin lymphoma (2008 WHO classification) **Conclusion** Surgery still remains a crucial tool to clarify the biological behaviour of those peripancreatic lesions for which a multidisciplinary approach fails to obtain a firm diagnosis.

Acute Recurrent Pancreatitis in a Young Female After a Hepatico-Digiuno Anastomosis Due to Sludge in the Bile Duct Remnant and an Unrecognised Pancreaticobiliary Maljunction: A Case Report

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Context Pancreatobiliary maljunction (PBM) is defined as an anatomical maljunction of the pancreatic duct and the biliary duct outside of the duodenal wall beyond the influence of the sphincter of Oddi. Children with PBM can present recurrent pancreatitis and PBM is a major risk factor for biliary tract malignancy. **Case Report** A 25-year-old female was hospitalized in our department. When she was 2-year-old underwent cholecysto-digiuno-anastomosis for acute biliary peritonitis due to spontaneous bile duct perforation. From 1998 to 2002 the patient presented multiple attacks of acute pancreatitis and cholangitis due to common bile duct stones; a biliary endoscopic sphincterotomy and 3 sessions of intraendoscopic mechanical lithotripsy were performed. Finally a termino-lateral hepatico-digiuno anastomosis was performed in 2002. In 2006 a celiac disease was diagnosed. From March 2008 the patients suffered from recurrent attacks of acute pancreatic (2 episodes/year). In December 2009 she was hospitalized in our department. Genetic test for pancreatitis associated to genetic mutation was positive for ΔF508 heterozygosis. MRCP and TC showed a chronic pancreatitis with diffuse dilation of the Wirsung duct with little intraductal stones; dilation and stones of residual common bile duct with stones were also diagnosed. ERCP with selective pancreatic sphincterotomy with pancreatic stone extraction was performed. For a new acute pancreatitis attack in March 2010 the patient underwent a new MRCP showing the presence a 10 mm common channel. ERCP was performed. Mucoid whitish material from bile duct remnant and small pancreatic stones from Wirsung duct were extracted. A 7 Fr 5 cm pancreatic stent was inserted to prevent migration of biliary material in the pancreatic duct and new attacks of pancreatitis. Definitive surgical treatment with resection of intrapancreatic common bile duct was performed in May 2010. After 1-year follow-up the patient is asymptomatic and a follow-up MRCP performed 6 months after surgery showed regular pancreatic duct, with a complete regression of chronic pancreatitis signs. **Conclusion** Total resection of the extrahepatic bile duct is recommended in children diagnosed with PBM. Early diagnosis and early surgical treatment provide a good prognosis with few complications. Scheduled radiological follow-up is mandatory for early detection of biliary tract malignancy, especially in patients demonstrating postoperative complications.

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Pancreatic Lymphoepithelial Cyst in a 62-Year-Old Woman

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Context Lymphoepithelial cysts of the pancreas are rare benign lesions which often present as an incidental radiological finding, but may cause symptoms, such as abdominal pain and nausea. It is formed by a stratified squamous epithelial lining atop a dense lymphoid tissue and it can occur at any part of the pancreas. **Case Report** A 62-year-old female was admitted to our hospital with epigastric discomfort and abdominal pain. Blood chemistries were normal. Abdominal ultrasound scan was negative for pancreatic lesions. Abdominal MRI shown a 2 cm exophytic lesion of the pancreatic tail, hypointense both in T1 and T2 weighted images, without significant contrast enhancement. A distal laparoscopic pancreatectomy with total splenectomy was performed and pathology samples were obtained from the whole surgical specimen. Oral feeding was resumed on postoperative day 3 and she was discharged two days later. Histology demonstrated a cystic mass of 2.5 diameter, with hemorrhagic features near to splenic hilus. Microscopic examination revealed spread acute inflammation to the pancreatic parenchyma. The lesion was lined by a flat epithelium with squamous differentiation associated to lymphoid aggregates. **Conclusion** Radiological procedures are very useful in differentiating cysts from other pancreatic lesions. Even if percutaneous or endoscopic aspiration may be helpful in clarifying the diagnosis, in most cases surgical exploration is warranted. For those cysts located in pancreatic tail, laparoscopic distal pancreatectomy with or without splenectomy is indicated to achieve a complete resection and to rule out cancer.

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