MafB Expression in Normal Human Pancreas and Pancreatic Endocrine Tumours

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Context The Maf family is a subgroup of the basic leucine zipper (bZip) transcription factors with homology to the v-Maf oncoprotein, which was originally identified in the genome of the AS42 chicken musculoaponeurotic sarcoma retrovirus. The Maf family members contain a highly conserved extended homology region (EHR), in addition to a typical basic region, and both regions are involved in target DNA sequence recognition. The large Maf proteins form homodimers through their leucine zipper domains and bind to long consensus DNA sequences termed Maf-recognition elements (MAREs) for regulate tissue-specific gene expression and cell-differentiation. In normal developing mice pancreas MafB is a transcriptional regulator of terminal alpha- and beta-cell differentiation. Aim To investigate MafB expression in development of normal fetal and adult human pancreas end in a set of pancreatic endocrine and non-endocrine tumors. Materials and methods Immunohistochemical evaluation was performed in samples from pancreatic head and tail in fetal and adult tissue. Immunohistochemistry for MafB was performed also on tissue microarrays from endocrine pancreatic neoplasms (PEN) defined following WHO classification: 68 well differentiated endocrine tumors with benign behavior (WDET-B); 33 well differentiated endocrine tumors with uncertain behavior (WDET-U); 34 well differentiated endocrine carcinomas (WDEC); and 15 poorly differentiated endocrine carcinomas (PDEC). Immunohistochemical evaluations were also performed in a set of non endocrine neoplasms (N-PEN). Results In early stages of development MafB was expressed with nuclear pattern in endocrine islet cells only, almost in beta-cells; in terminal stage of fetal pancreas development, MafB nuclear immunoreactivity was present in endocrine cells and in some centroacinar cells. In adult human pancreas MafB nuclear expression was evaluable only in endocrine islets. We did not found MafB expression in acinar and ductal cells of fetal and adult pancreas. Results in endocrine tumors are summarized as follows. MafB-immunoreactivity was observed in 78% of WDET-B, in 66% of WDET-U, in 42% of WDEC and only in 13% of PDEC. No MafB expression was observed in N-PEN. Conclusions These findings confirm that MafB is a key regulator in human pancreatic endocrine development, maintaining a role also in adult pancreatic islets. MafB expression correlates with more benign phenotypes, suggesting a possible role in cellular differentiation of endocrine neoplastic growth and a possible use as prognostic tool.
Transcription Factors Islet-1, Pax6, Nkx2.2, Nkx6.1, MafB and Pdx-1 in Pancreatic Endocrine Tumours

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Context Pancreatic endocrine tumors (PET) are a heterogeneous group of neoplasms with variable clinical manifestations and biological behavior. There are not absolute histopathological criteria able to predict an aggressive course. The only reliable features of malignancy are gross infiltration into adjacent organs or metastases. Identification of immunohistochemical markers that predict biological behavior would be extremely helpful in surgical management and adjuvant therapy of disease. Recent works investigated expression and role of transcription factors (TFs) Islet-1, Pax6, Nkx2.2, Nkx6.1, MafB and Pdx-1 in endocrine and exocrine pancreas development, tissue-specific gene expression and cell-differentiation. These nuclear proteins play two critical roles: in earliest stages, they regulate differentiation, later they provide contribution to the commitment of individual cell lineages and maintain a terminally differentiated phenotype. Disruption of these genes results, invariably, in impaired development of pancreatic endocrine structures. Aim To evaluate the immunohistochemical expression of Pax6, Nkx2.2, Nkx6.1, MafB and Pdx-1 in PET. Materials and methods Immunohistochemistry for Islet-1, Pax6, Nkx2.2, Nkx6.1, MafB and Pdx-1 was performed on tissue microarrays from endocrine pancreatic neoplasms (PEN) defined following WHO classification: 68 well differentiated endocrine tumors with benign behavior (WDET-B); 33 well differentiated endocrine tumors with uncertain behavior (WDET-U); 34 well differentiated endocrine carcinomas (WDEC); and 15 poorly differentiated endocrine carcinomas (PDEC). In each case immunoreactivity for all six TFs was evaluated with a positive cut-off of 5% of positive cells. We did also evaluate the immunoreactivity level for each case: the level was low when the case showed immunohistochemical reactivity for 0-3 TFs; the level was high when reactivity was observed for 4-6 TFs. Results The percentage of TFs-immunoreactive cases correlated with WHO categories. Immunoreactivity for 4 or more TFs was observed in 90% of WDET-B, in 69% of WDET-U, in 49% of WDEC; all PDEC showed immunoreactivity for 3 or less TFs. Conclusions Benign and borderline tumor cases showed increased expression of all TFs, whereas well differentiated and poorly differentiated carcinomas displayed a progressive decrease of immunoreactivity. These findings suggest that TFs expression in PET will be informative about biological characteristics of tumors and will define a potential tool for clinicopathological correlations.

Behaviour of CA 19-9 in Patients Suffering from Autoimmune Pancreatitis Before and After Steroid Therapy

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Context Autoimmune pancreatitis (AIP) is an inflammatory disease that may mimic a pancreatic cancer. CA 19-9 may be increased in AIP. Steroid therapy is effective in AIP, both in focal and diffuse forms. Aim Aim of this study was to evaluate the behavior of CA
In patients suffering from AIP before and after steroid therapy. **Patients and methods** We consecutively enrolled patients with a definitive diagnosed of AIP treated with steroids between 2002 and 2007. The diagnosis of AIP was formulated in the presence of all the following criteria: a) associations with other autoimmune disease; b) FNAB or FNCB findings, and c) suggestive radiological findings, as recently published [1]. We investigated the serum levels of CA 19-9, total and direct bilirubin, GGT and smoking habits at the diagnosis of AIP and after 3-4 weeks of steroid therapy. **Results** Thirty AIP patients were studied (20 males and 10 females, mean age 41±15 years), 14 with a focal and 16 with diffuse form. Before steroids, CA 19-9 values above the upper reference limit (25 U/L) were observed in 14 patients (47%) and did not correlate neither with bilirubin levels or GGT nor with smoking habits. CA 19-9 significantly decreased after steroid therapy (before: mean 80 U/L, range 3-581 U/L; vs. after: mean 31 U/L, range 1-398 U/L) (P=0.007), without differences between focal and diffuse form. After steroids, a complete normalization of CA 19-9 after 3-4 weeks was observed in 9 patients (67%). In the remaining 5 patients (33%), the normalization was observed within 3 months. **Conclusions** In AIP patients treated with steroid, a decreased of CA 19-9 may represent a serological marker to rule out a diagnosis of pancreatic cancer.

**Reference**

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**Preliminary Data on Simultaneous Evaluation of HER-2, EGFR and TOPO II alpha in Ductal Pancreatic Adenocarcinoma**

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**Context** In the pancreatic adenocarcinoma, the tumor progression passes through the alteration of the molecular signaling pathways, as studied in a lot of tumors today. Determining few receptors or transducers involved in these processes, we can use this information to hit selectively the neoplastic cells. **Aim** To define for the pancreatic cancer the role of specific molecules studied in other types of tumors, in order to establish if a molecular target therapy will be effective in this pathology. **Methods** In 15 cases of resected pancreatic ductal adenocarcinoma, we simultaneously performed the gene amplification and the determination of related protein for EGFR, TOPO II alpha and HER-2, using respectively FISH and immunohistochemistry. **Results** The pattern of expression we have found has been the following: HER-2 protein and gene was not find on the histological sample. TOPO II alpha was overexpressed in 2/15 cases and there was not correlation with HER-2, while its gene was impossible to amplify. EGFR protein has been overexpressed in 11/15 cases, but the EGFR gene was not amplified, proposing the suspect of a mutational status which make impossible the ligation with the molecular probe. **Conclusions** In these preliminary results we do not find an overexpression of HER-2 as noted in many studies, and so it would be no evidence for chemotherapy based on this target, including anthracycline. On the contrary, EGFR protein is overexpressed in the most part of analyzed pancreatic cancer, opening a possibility of molecular therapy. Obviously other cases are going to be included in the study and further research is needed to clarify the role of this molecular pattern in future therapeutic strategies.
Management of Duodenal Polyps in FAP: Personal Experience from 1986 to 2008
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Context Since the duodenal polyps are a frequent association of FAP and the duodenal cancer is the first cause of death after prophylactic colectomy, a close surveillance of the duodenum is mandatory. The frequency of endoscopical examinations and the modality of treatment are still controversial. 

Aim To study the management of duodenal polyps in FAP according to Spigelman’s classification.

Methods One-hundred and 35 patients affected by FAP were referred to our Surgical Unit (1986-2008) and 58 of them developed duodenal polyps. Periodic (every 12 months) endoscopical (with a lateral vision endoscope) and histological duodenal examinations (when the polyps were more than 5 mm in diameter) were performed. Clinical characteristics, Spigelman’s score of the duodenal polyposis, type of treatment and outcome were evaluated and the results were prospectively analyzed.

Results In our series we had 29 males and 29 females, their median age at last endoscopy was 39 years (range 21-63 years). The mean time of follow-up was 124 months. The Spigelman’s score at last endoscopy was: I stadium, 25 patients (43%); II stadium, 22 patients (38%); and III stadium, 11 patients (19%). A cumulative number of 489 polyps (mean 7.3 polyps/patient) for I or II stadium were endoscopically removed by diathermic coagulation, YAG laser or snare polypectomy. Patients at III stadium underwent surgery: 3 duodenotomies with polypectomies (mean 12 polyps/patient); duodenotomy with ampullectomy in 5 patients and 3 duodenopancreatectomies in case of duodenal cancer (2 patients) or carpeting polyposis (1 patient). Post procedural complications were present in 13% of the I and II stadium patients and in 27% of the III stadium patients.

Conclusion Duodenal polyps in FAP should be considered surgically curable diseases. Surgical resection is preferable to a less radical endoscopical approach in ensuring higher cure rates with limited morbidity also in high stadium of Spigelman’s score. The type of approach (endoscopical or surgical) should be chosen taking in account the relationship of the polyps with the duodenal ampulla. A close endoscopic follow-up is necessary for either an early diagnosis of duodenal polyps and for the evaluation of an eventual recurrence after asportation.

A New Preoperative Work-up for Pancreatic Cancer: Lessons from 110 Cancer-Related Deaths in Resected Patients
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Context One-year survival after resection for pancreatic cancer is about 70-80%. Aim This study examined potential preoperative parameters that would help to avoid unnecessary surgery. 

Patients and methods From 1997 to 2004, 110 resected patients who died of disease were included in the study. Using a survival cut-off of 12-months, 2 subgroups (Gr 1, early death; Gr 2, late death) were identified and compared with a population of 645 patients with advanced disease (ADC) who died during the same period. Preoperative clinical and laboratory data, type and time to recurrence and survival
were analyzed. **Results** In the resected group, 32 patients (29%) died of disease with a recurrence rate similar to that in Gr 2. From recurrence to death, the median survival of Gr 1 was 4.2 months vs. 8.7 months in Gr 2 (P=0.00001). Multivariate analysis selected duration of preoperative symptoms greater than 20 days and CA 19-9 greater than 110 U/mL as independent predictors of early cancer-related death, with a probability of 48%. The addition of pathological grading increased the probability to 66%, with a concordance index of 77% (95% CI: 67-86%; P=0.0001). Survival did not differ between Gr 1 and the ADC group (P=0.51); CA 19-9 serum levels were also similar between Gr 1 and patients in the ADC group with locally advanced disease (P=0.68). **Conclusion** Duration of symptoms greater than 20 days and a CA 19-9 greater than 110 U/mL can be used to identify patients that are not suitable for surgery, even if deemed resectable by high-quality imaging. In high risk, early-death patients, preoperative endoscopic-ultrasound guided-biopsy may be useful to assess pathological grading.

**Therapeutic Perspectives of Patients with Locally Advanced Pancreatic Cancer: An Update**


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**Context** About 30% of patients with pancreatic cancer are not suitable for resection because of invasion of major vessels, in absence of distant metastases. **Aim** To evaluate the effect of a chemotherapeutic regimen (PEFG) to downstage locally advanced pancreatic cancer and to allow laparotomy with curative intent. **Methods** Retrospective evaluation of prospectively collected data. Survival was calculated from the beginning of treatment (Kaplan-Meier method, log-rank test). **Results** From 1997 to 2006, 79 patients with cytologically confirmed locally advanced pancreatic cancer received primary chemotherapy with PEFG regimen (3 cycles, as previously described [1]). All patients were evaluated by a senior surgeon that judged the cancer not resectable during laparotomy, or on the basis of a CT scan (performed at our institution). Patients were restaged by CT scan at the end of treatment. Best response to chemotherapy was partial remission in 38 patients (48%) and stable disease in 32 (41%). Eleven patients (14%) were radically resected yielding two pathologic complete remissions. One patient underwent surgery but was not resected for persistent vessels invasion at laparotomy. Of 11 resected patients, 6 had R0 resection, two R1 (microscopic margin involvement) and three R2 (macroscopic residue). Median survival (OS) was 16.5 months (79 patients); 2-year and 5-year OS was 19% and 5%, respectively. Among 38 partial responders, 11 patients submitted to surgery lived longer than 27 patients who remained not amenable to resection (median OS: 21 years versus 17 years; 2-year OS: 72% versus 12%; P=0.003). Median progression-free (PF) survival was 10.5 months. Pattern of failure was known in 66 of 70 failing patients and consisted of isolated local failure (n=23; 35%); both local and systemic failure (n =13; 20%); isolated systemic failure (n=30; 45%). **Conclusions** Patients with locally advanced pancreatic cancer may benefit of chemotherapy with PEFG regimen. Regression of vessel invasion can be expected in 14% of patients; in these cases a laparotomy with curative intent is indicated.

**Reference**

Endoscopic Ultrasonography in the Follow-up of Intraductal Papillary Mucinous Neoplasia of the Pancreas
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Context Intraductal papillary mucinous neoplasia (IPMN) is a cystic neoplasm of the pancreas that involves main pancreatic ducts, branch ducts or both type ducts. The prognosis of IPMN is favorable compared to pancreatic ductal adenocarcinoma, but during IPMN follow-up ductal carcinoma may develop and so it became crucial the selection of candidate for surgical resection. Aim The aim of this study is to verify the echoendoscopic (EUS) ability to detect the correct timing for surgery. Methods We analyzed 178 consecutive patients that had an echoendoscopic diagnose of IPMN in our centre from April 2003 to May 2008. A linear array echoendoscope (Pentax EG 3630U, EG3830UT) and a Wilson Cook (22 or 25 G) fine needle were used. Results One-hundred and seventy eight patients, 93 men, 85 women, mean age 67 years had an EUS diagnose of IPMN. The mean time of follow-up was 14 months. One-hundred and sixteen patients, 57 men and 59 women, mean age 68 years, underwent an EUS follow-up with a mean of 17.4 months. EUS FNA was performed in 68 patients (58.2%). The lesions are localized in the body in 31% (36 cases), in the head in 27.5% (32 cases), in the genu in 18.9% (22 cases), in the uncinate process in 8.6% (10 cases), in the tail in 6.8% (8 cases) and diffuse to all the gland in 6.8% (8 cases). The EUS presence of murales nodules or mass is scarce in 13.8% and 8.6% cases, respectively. Sixty-two patients (34.8%), 36 men and 26 women, mean age 67 years, underwent surgery after a mean time of 7.6 months. EUS FNA was performed in 51 patients (82.2%). The localization of lesions are in the head in 45.1% (28 cases), in the genu in 30.6% (19 cases), in the body in 16.1% (10 cases), in the uncinate process in 4.8% (3 cases) and in the tail in 3.2% (2 cases). The lesions involve main ducts in 59.6% of cases, both type ducts in 14.5% and branch ducts in 25.8%. The presence of murales nodules or mass is detected in 35.4% and 17.7% cases. Conclusion EUS is a good technique to diagnose IPMN and to select the timing for surgery.

Comparison of Cytology and Histology in Intraductal Papillary Mucinous Neoplasia
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Context Intraductal papillary mucinous neoplasia (IPMN) is a cystic neoplasm of the pancreas that derives from adenomatous proliferation of mucin-producing epithelial cells of the pancreatic duct, with involvement of the main pancreatic duct, branch ducts alone, or both type ducts. Endoscopic ultrasonography (EUS) is an accurate technique to diagnose IPMN and differentiate between IPMN and other pancreatic diseases. Aim The aim of the study is to compare cytology and histology and to detect the presence of differences especially in the type of dysplasia noticed. Methods We considered patients that had an echoendoscopic diagnose of IPMN in our centre from April 2003 to...
May 2008. The cases were analyzed comparing EUS fine needle aspiration (FN) to pathologic finding in those patients who underwent surgery. A linear array echoendoscope (Pentax EG 3630U, EG3830UT) and a Wilson Cook (22 or 25 G) fine needle were used. Results One-hundred and 78 consecutive patients had an EUS diagnose of IPMN. EUS FNA was performed in 51 patients (82.2%) who underwent surgery. Twenty patients had a diagnosis of IPMN with atypias. Seventeen patients had a diagnosis of IPMN-carcinomas, 14 of which confirmed by the surgery. The others were high grade (HG) IPMNs. In 9 patients there was no evidence of CTM but at the surgery one was IPMN carcinoma and 6 were low grade (LG) IPMNs. In 3 samples there are only mucinous cells and at the surgery one was an adenoma, one a LG-IPMN, and one a carcinoma. Two specimens were inadequate because of the lack of cells but at the surgery one was a carcinoma in situ and the other a LG IPMN. Sixty-two patients (34.8%) underwent surgery: 41 had Whipple resection, 17 had distal pancreatectomy and spleenectomy; 3 had total pancreatectomy and one had uncinectomy. In 61 patients (98.3%) surgery confirmed a pattern of IPMN, but 28 (45%) had also an area of carcinoma. One patient had a chronic pancreatitis. The diagnostic accuracy of EUS was 98%. Conclusion EUS is a good technique to diagnose IPMN but EUS features alone are not sufficient to distinguish benign from malignant forms. EUS-FNA seems to improve the diagnostic power.

Pancreatectomies Associated to Vascular Resections: Report of 181 Cases

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Context Pancreatic cancer (PC) involving the main peripancreatic vascular trunks is traditionally considered unresectable. Aim The aim of this study is to analyze the short and long term outcomes of a consecutive series of 181 pancreatectomies associated to vascular resections (PAVR) performed at the First Division of General Surgery of the Pisa University Hospital. Methods From November 1987 to December 2007, 181 patients underwent PAVR at our Institution. There were 99 males (54.7%) and 82 females (45.3%); the mean age was 64.2 years (range 31-84 years). The vascular procedures included an isolated vein resection (IVR) in 134 cases (74%), an isolated arterial resection (IAR) in 19 cases (10.5%) and a combined arterial-venous resection (AVR) in 28 cases (15.5%). Results The mean post-operative hospital stay was 22.9 days. The overall post-operative morbidity and mortality rates were 35.3% and 4.4%, respectively. Final pathologic diagnosis was ductal adenocarcinoma (DA) in 144 patients (79.5%), chronic pancreatitis in 2 (1.1%) and other pancreatic or periampullary lower grade malignancies in 35 (19.4%) cases. One-, 3- and 5-year survival rates of patients diagnosed with DA were significantly worse than in other histologic types (58.8%, 18.0% and 8.6% vs. 87.1%, 59.9% and 49.7%; P<0.0001). In DA group 1-, 3- and 5-year survival rates for patients who underwent IVR, IAR, AVR were 58.4%, 14.9% and 11.8% vs. 69.2%, 40.3% and 0 vs. 12.1%, 11.3% and 0, respectively (P NS). In the DA group a statistically significant advantage in 1-, 3- and 5-year survival rates was found when final pathologic findings showed the lack of vascular infiltration or an infiltration confined to tunica media or adventitia of resected vessels in comparison to patients with infiltration of tunica intima (72.4%, 22.3% and 13.3% vs. 39%, 7.1% and 7.1%;
Conclusions PAVR can be a safe procedure and can be accomplished with morbidity and mortality rates similar to conventional pancreatectomies. In patients diagnosed with DA the histologically proven infiltration of tunica intima seems to be the most significant predictor of a poor oncological prognosis.

Robotic Pancreatectomies: Early Experience in a High Volume Center

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Context Robotic surgery is the actual evolution of traditional laparoscopic surgery. On respect to traditional minimally invasive approach the demolitive and reconstructive phases can be done similar to open surgery, reducing trauma for the patients. Aim The aim of this paper is to report our very preliminary experience in pancreatic robotic surgery. Case report 1 A 60-year-old man was diagnosed with a cystic tumor of the tail of the pancreas 4 cm in diameter. CT scan and US suggested differential diagnosis with serous cystadenoma and neuroendocrine cystic tumor. The patient was candidate for robotic surgery. We proceeded with the section of the neck of the pancreas and with a spleen preserving distal pancreatectomy. The dissection phase of the body and tail of the pancreas from the splenic vessels seems to be very easy by robotic approach due to the 3D vision and the possibility to legate the small vascular splenic branches. The treatment of the pancreatic stump was done by selective ligation of the Wirsung and suture of the pancreatic remnant. Post-operative course was uneventful. Final diagnosis was serous cystadenoma of the pancreas. Case report 2 A 71-year-old woman suffering from an ampullary cancer was treated by robotic Whipple procedure. The en-block lymphadenectomy was easy done thank to the robotic ability of maneuver. Pancreatico-jejunostomy was done by robotic approach. A very small incision was done on right subcostal space to remove the surgical specimen and to perform the biliary and digestive reconstruction. The post-operative course was uneventful. Conclusions Robotic surgery seems to be safe and effective for pancreatic surgery. On respect to traditionally laparoscopic surgery a more accurate radical approach is possible and the reconstructive phase seems to be easier and safer. More data will be necessary to demonstrate if a robotic approach will have a role in pancreatic surgery.

Are Atypical Resections of the Pancreas Safe and Effective in Treating Small Pancreatic Endocrine Tumors?

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Context Atypical resections of the pancreas (ARs), including enucleation (E) and middle pancreatectomy (MP), are parenchymasparing techniques aimed to reduce the risk of postoperative pancreatic insufficiency. While ARs are safely performed for treating insulinomas, their role in the management of non-functioning pancreatic endocrine tumors...
(NF-PETs) is debated. **Aim** To evaluate perioperative and long-term outcomes of 127 patients (53 male, 74 female, median age 46 years) who underwent AR for insulinomas and NF-PETs at two academic, tertiary centers for pancreatic surgery. **Methods** The outcomes after AR for NF-PETs (n=52) were compared with those of patients who underwent AR for insulinomas (n=75). **Results** Overall, 91 enucleations and 36 MPs were performed. Enucleation was carried out in 63 patients with insulinomas (84%) and in 28 patients (54%) with NF-PETs, MP in 12 insulinomas (16%) and 24 NF-PETs (46%) (P=0.001). Mortality was zero and overall morbidity was 55%. A clinically significant pancreatic fistula was reported in 21 patients (16%), and nine patients (7%) required reoperation. Median length of stay was 9 days. Overall and abdominal complications were higher for patients who underwent MP than enucleations (P=0.01). Median size of the tumors was 16 mm (range 6-50 mm) with no significant differences between insulinomas and NF-PETs and between E and MP groups. At pathology there were 58 (76%) benign lesions, 17 (24%) neoplasms of uncertain behavior in the insulinoma group and 34 (65%) benign lesions, 16 (31%) neoplasms of uncertain behavior and 2 well-differentiated carcinomas (4%) in the NF-PET group (P NS). After a median follow-up of 59 months (range 12-188 months), no patient died of disease. Overall three patients (2.5%) experienced tumor recurrence after a mean of 79 months (three NF-PETs who underwent two MP and one enucleation). The incidence of exocrine and endocrine insufficiency was low (6%). **Conclusion** ARs are safe and effective procedures for treatment of pancreatic endocrine tumors. However, given the recurrence rate in NF-PETs, better selection criteria must be identified.

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**Urokinase Plasminogen Activator Receptor: A New Useful Marker for Diagnosis and Prognosis in Pancreatic Cancer?**

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**Context** According to recent report of high expression of urokinase plasminogen activator receptor (uPAR) in various types of cancer, we demonstrated elevated plasmatic and urinary uPAR levels in pancreatic carcinoma compared to overall benign and malignant pancreatic disease and healthy control group. **Aim** We further investigated to assess whether: uPAR could be useful when the differential diagnosis between PDC and chronic pancreatitis (CP) appears a matter of difficulty; uPAR might be likely related to survival in PDC. **Methods** We collected serum and urine from 60 patients (28 males, 32 females; mean age 52.8 years, range 18-77 years) suffering from CP (20 patients) and PDC (40 patients). The latter group was composed by 10 patients in stage 3, 15 in stage 4A and 15 in stage 4B. Then plasmatic and urinary levels of uPAR were measured after correlation with creatinine levels. **Results** Plasmatic uPAR values appeared to be significantly higher (P<0.03) in PDC compared to CP group, while mean urinary levels showed an increasing trend for PDC (15.6 pmol/L vs. 12.2 pmol/L) but did not reach a statistical difference. In PDC group 3 patients are still alive with a median follow-up of 23 months. The median overall survival in the other 37 patients was 10.5 months (range 0.8-36 months). Mean survival amounted to 22.8 months in stage 3 and 10.3 months in stage 4. In order to stress a possible relationship with survival, we divided these
patients in short (<13 months) and long (>13 months) survivors and we found significantly higher (P<0.003) urinary uPAR levels in the former group. Moreover, median survival reached 15 months in patients with urinary uPAR values <15 pmol/L, while came down to 7.6 months in patients with >15 pmol/L (P<0.02; ratio: 1.98). **Conclusion** These data suggest that uPAR could represent an useful diagnostic markers in patients suffering from PDC and might have a likely relationship with prognosis and survival.

**Pancreas Transplantation Inside Emilia-Romagna, Italy: Referral Pattern, Demand Forecasting and Organ Availability**


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**Context** In Italy, referral of diabetes patients to pancreas transplantations (PT) is an unstructured process, resulting in a low-rate activity and in late referrals, often when the patient has already undergone dialysis. In addition, the continuous improvement in pancreas transplant alone, offering the opportunity to reduce cardio-vascular risk due to proteinuria and reduced GFR, is rarely appreciated. **Aim** To evaluate the pipeline of PT in Emilia-Romagna (4 millions inhabitants) as for factors affecting demand and offer. **Methods** We analyzed: 1) referral activity to PT during the time frame 2001-2005, by collecting ICD 9 CM codes (55.69+52.80; 52.86 and 52.80 alone) by residence of the patient; 2) demand of PT by a sample population of 1,670 diabetes patients, whose charts were reviewed as for type of diabetes and presence of overt diabetic nephropathy (DN) (proteinuria >300 mg/24 hours and/or GFR <60 mL/min); 3) potential pancreas availability as the ratio between pancreas and hearts utilized (UP/HR) in different areas of our country. **Results** 1) Referral activity reached 8.4 PT/pmp in five years in the whole region, ranging from 2.6 in the province where a PT program is active, to a maximum value of 20.7 in the province where a devoted out-patient clinic is operated by nephrologists. 2) Prevalence of overt DN was 6% in our cohort, corresponding to 510 D1 patients worth of information and evaluation for PT inside Emilia-Romagna region. 3) During 2006 UP/HR was 0.58 in AIRT agency, 1.16 in Tuscany, 0.30 in Piedmont and 0.26 in our region. **Conclusions** Taken together, our data suggest that: 1) the referral of D1 to PT has to be empowered, aimed to keep in touch with all patients suffering from diabetic nephropathy; 2) the out-patient clinic devoted to evaluation and recruitment of D1 with DN plays the key role in this program of timely and widespread referral; 3) the availability of pancreases can be increased by utilizing larger criteria for harvesting, increasing the consent rate to donation and increasing the demand of PT (recipients pool). Pancreas grafts still have a large room for increase, since the current low demand gives to under-utilization of the pancreas resource, due to the frequent lack of a suitable recipient.
Idiopathic Pancreatitis

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Context Patients in whom this initial evaluation does not reveal underlying etiology are classified as having idiopathic acute pancreatitis. It is in these patients where one can consider a more extensive evaluation. In most analyses, the most common explanations which are identified with a more extensive evaluation include microlithiasis, SOD dysfunction, pancreas divisum, and other congenital abnormalities, pancreatic neoplasm and genetic causes. Case report A 34-year-old previous health woman was seen in the Emergency Department with epigastric pain associated with nausea and vomiting. Initially pancreatitis in not suspected due to no elevation in lipase and amylase. The patient takes no medication and has no family history of pancreatitis or trauma. Right upper quadrant ultrasound is normal. The day after admission, elevation in lipase and amylase. Abdominal CT scan shows mild enlargement of the pancreas with stranding into the peripancreatic fat. In this moment we made a diagnosis of acute idiopathic pancreatitis; 5 days after “empiric” cholecystectomy without total or partial recovery; 10 days after cholecystectomy ERCP whit only partial recovery. After demission one month late the magnetic resonance cholangiopancreatography (MRCP) is negative. Conclusion Based on local expertise MRCP or EUS should be considered for the initial step in the specialized evaluation for the pancreatitis but if the MRCP or EUS is negative then either empiric cholecystectomy or ERCP and bile analysis for crystals should be considered.

Pancreatic Tuberculosis vs. Cystic Pancreatic Tumor: A Case Report

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Context Pancreatic tuberculosis (PT) is a rare clinical entity, even if recently tuberculosis’ incidence is increased following immigration from endemic geographical areas and immunocompromized patients’ prevalence. The PT’s clinical and the radiological findings could be a-specifics and mime a pancreatic malignancy. Frequently definitive diagnosis is histological during laparotomy, whereas a suspicion of PT can be support by endoscopic ultrasound, guided fine needle aspiration (EUS-FNA) or biopsy using computer tomography (CTMD) or ultrasound guidance. In PT the role of resection is very limited, whereas the response to the anti-tubercular therapy is excellent. Case report We report a case of a 45-year-old Italian man with acquired immune deficiency syndrome (AIDS) since 1991 and systemic micobacteriosis atypical (avium) diagnosed in 2007. Recently he has developed epigastric pain with dorsal irradiation. Initial laboratory evaluation was normal. Chest X-ray is normal. Ultrasonography reveals two pancreatic lesions and a peripancreatic mass defined-such as first hypothesis-pancreatic cystic tumor. After few days the patient, has been subject to a CTMD and a CPMR which showed two simil-cystic pancreatic masses not in communication with the main pancreatic duct and peripancreatic lymph nodes enlarged with a central necrosis. Considering the patient’s history and the imaging findings, we made diagnosis of PT confirmed by biopsy CTMD guidance. The patient was put on anti-tubercular therapy.
with a regression of the pancreatic lesions at the first follow-up CT. **Conclusion** The PT’s clinical and radiological findings are non-specific and PT may mime malignancy or focal pancreatitis; despite that it should be suspected in young patients, human immunodeficiency virus positive, tuberculin skin test positive, or coming from areas where tuberculosis is endemic, with heterogeneous or cystic pancreatic mass and peripancreatic lymph nodes with a rim enhancement at imaging. Tuberculous HIV positive patients have a higher mortality risk: a right diagnosis and a proper therapy could improve surviving possibilities.

**Adenocarcinoma of the Pancreas and Autoimmune Pancreatitis: A Challenge for the Diagnostic Imaging**

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**Context** The role of imaging in autoimmune pancreatitis (AIP) is relevant both for the diagnosis and the therapy. AIP is generally characterized by focal or diffuse enlargement of the pancreas with dilatation of the common bile duct (CBD) and irregular narrowing of the main pancreatic duct (MPD), elevation of serum IgG and lymphoplasmacytic infiltration; these findings usually regressing after steroid therapy. The clinical and radiological features of the AIP may mimic a pancreatic malignancy. **Case report** We report a case of a 59-year-old man with weight loss, abdominal pain, dark urine, pale stools and jaundice; a suspicion of pancreatic malignancy was posed. Laboratory evaluation revealed an elevation of serum concentrations of bilirubin (total bilirubin: 2.03 mg/dL; direct bilirubin: 1.18 mg/dL) and AST (52 IU/L, reference value <37 IU/L), ALT (104 IU/L, reference value <40 IU/L); GGT (268 IU/L, reference value <30 IU/L). Multidetector computer tomography (MDCT) showed a diffuse edematous pancreas, with a hypodense lesion of 4 cm in diameter in the head of the gland and involvement of celiac trunk and mesenteric vessels. It was present dilatation of the common bile duct and a slight dilatation of main pancreatic duct (3.5 mm). It was performed a biopsy of the pancreatic lesion and the histological examination showed fibrosis, lymphoplasmacytic infiltration (CD45++; CD3++; CD8+), eosinophilic infiltration and vasculitis. The multidetector computed tomography (MDCT) follow-up performed after steroid therapy and a progressive reduction of the pancreatic lesion and of the pancreatic edema was observed. **Conclusions** The absence of dilatation of the main pancreatic duct and the histological findings may help to reach a diagnosis of AIP. MDCT is the preferred imaging technique for the follow-up of AIP during and after steroid therapy.

**Focus on Options in Pancreatic Surgery**

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**Context** From 01/01/1994 to 01/01/2008, 98 patients in our institution underwent radical pancreatic surgery for malignant and benign pancreatic disease. **Aim** To evaluate surgical
results, mortality and morbidity focusing on controversies in pancreatic surgery (preoperative biliary drainage, postoperative biliary and pancreatic drainage, methods of reconstruction, lymphadenectomy extension, adjuvant chemo-radiotherapy and IORT. **Methods** We have conducted a retrospective study on 85 patients who underwent pancreaticoduodenectomy; preoperative diagnosis and staging included ultrasonography and CT-scan; CT-PET total body has been recently introduced and utilized for preoperative staging. Preoperative biliary drainage was used in 7 cases (8.2%); no postoperative biliary and pancreatic drainage was used; lymphadenectomy was extended in 30 cases (35.3%); we conducted 23 Wirsung-gastric anastomoses, 61 Wirsung-jejunal anastomosis, 5 vascular reconstructions. Five patients affected by advanced pancreatic cancer underwent IORT. **Results** Morbidity rates have been higher in patients treated with preoperative biliary drainage (wound infection, gastrointestinal bleeding). No difference in survival rate has been observed after extended lymphadenectomy. No differences in terms of morbidity have been shown after Wirsung-gastric and Wirsung-jejunal anastomosis; pancreatic atrophy is more frequent in long survivor patients with Wirsung-gastric anastomosis (33.3% vs. 5.9%). **Conclusions** Preoperative biliary drainage could be useful in patients with severe jaundice; anyway, we found increased postoperative stay, morbidity and technical intraoperative difficulty. We found no survival rates differences in patients treated with extended lymphadenectomy. Wirsung-gastric and Wirsung-jejunal anastomosis are both safe methods of reconstruction; long survivor patients treated with Wirsung-gastric anastomosis shows more frequently pancreatic atrophy. In our recent experience, IORT showed good results, in particular for advanced neoplasms.

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68-Ga-DOTATOC-PET, EUS and CT in Diagnosis of Pancreatic Neuroendocrine Tumors

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**Context** EUS was shown to be the most accurate method for detection of primary pancreatic neuroendocrine tumors (NET). EUS-guided FNA allows a preoperative cytologic diagnosis. In a recent study comparing 68Ga-DOTATOC-PET with conventional somatostatin receptor scintigraphy and multidetector CT in diagnosis, staging and follow-up of patients affected by NET, 68Ga-DOTATOC-PET showed a higher detection rate, than other methods. **Aim** This retrospective study compares results of EUS, 68Ga-DOTATOC-PET and CT in our patients with suspected NET. **Methods** Eight consecutive patients (4 female; mean age 50 years; range: 21-79 years) who underwent both EUS-FNA and PET, since March 2007 to March 2008 were retrospectively included in the study. Dual phase multidetector CT was performed in 7 patients. Five patients underwent surgery. Analysis of data was performed for lesions. Detection rates of EUS, 68-Ga-DOTATOC-PET and CT were computed. **Results** Fifteen lesions (mean diameter 26 mm; range 5-80 mm) were detected in 8 patients. EUS and PET both detected 12/15 lesions (80%). CT detected 8/12 lesions (66%) in 7 patients. Median diameter of lesions detected by CT, EUS and PET was respectively 15 mm
(range: 5-84 mm), 10 mm (range: 5-80 mm) and 10 mm (range: 5-80 mm); differences were not significant. A lesion was diagnosed only by CT. PET detected 2 lesions not identified by other methods, but 2 lesions not identified by PET, were visualized by both EUS and CT. EUS-FNA could be performed in 11/12 lesions visualized by EUS and was informative in 9/12; in 8/12 lesions the diagnosis of NET was confirmed. A conclusive diagnosis was available after surgery or FNA for 10/15 lesions. According to this diagnosis, true positive, true negative, false positive, false negative findings were respectively: 7, 1, 0, 2 for CT; 8, 0, 1, 1 for EUS; 7, 0, 1, 2 for PET. **Conclusions** EUS, 68Ga-DOTATOC-PET and also CT seem to have comparable accuracy in diagnosis of NET and we believe that the combination of these techniques can afford an optimal preoperative diagnosis.

**UICC-R Classification and Distance of the Tumour from Resection Margin Are Inadequate to Predict Local Recurrence After Pancreatic Cancer Resection**

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**Context** According to the UICC-R classification, if a tumor is 1 mm or less from the resection margin, it must be coded R0 (no residual tumor); only if a tumor is transected must be coded R1 (microscopic residual tumor). The high rate of margin invasion and nodal metastases could explain the frequent occurrence of local failure after surgery. No data are available on the recurrence rate of the few patients in which surgery achieved an apparent radicality, namely R0-N0 patients.

**Aim** To assess the relationship between the distance of the tumor from surgical resection margin and risk of local recurrence and long term survival.

**Methods** Between 1995 and 2005, 384 resections for ductal adenocarcinoma were performed. Pathologic evaluation of margins was made by multiple axial sections after specimen inking. Margin invasion was found in 168 patients (44%); 309 patients (80%) had positive lymphnodes. We retrospectively reviewed 34 R0-N0 patients. At pathologic re-evaluation, 2 of them resulted biliary duct carcinoma, 1 ampullary carcinoma and 3 were R1 pancreatic cancer. The remaining 28 cases were considered for the analysis (12 of them resulted invasive IPM carcinoma): we re-evaluate minimal distance of the tumor from resection margin at the pathologic specimen. Median follow-up was 68 months (range 24-135 months); two patients were lost at the follow-up; disease failure was assessed by CT scan every 3-4 months after surgery.

**Results** Minimal distance of the tumor from resection margin was less than 4mm in 19 patients (group A; average distance: 1.3 mm) and equal to, or greater than, 4mm in 9 patients (group B; average distance: 6 mm). During the follow-up a recurrence was detected in 53.5% of patients: 8 patients (28.5%) had only distant metastases, 3 (11%) had only local relapse and 4 (14%) had both. Five patients of group A (26%) and 2 of group B (22%) presented a local relapse. Median recurrence of disease was 15 months and median local recurrence was 23 months. Median overall survival was 34 months; in group A median survival was 21 months, in group B it was 44.5 months. Seven patients are alive in absence of recurrence of disease: 6 of them are affected by invasive IPM carcinoma; 3 invasive IPM carcinomas locally relapsed.

**Conclusions** The distance of the tumor from resection margin seems to be a prognostic factor but it is inadequate to
predict local recurrence. Among R0N0 patients those affected by invasive IPM carcinoma are more likely to be cured.

Circulating Markers of Angiogenesis in the Pancreas Carcinoma: An Evaluation of Prognostic Roles
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Context Researching for new antitumoral therapeutical strategies, many authors focused on the angiogenetic process. Neoangiogenetic factors (assessed directly on the surgical specimen) are overexpressed in the tumoral cells and can be dosed in patient’s serum. The extent of this over-expression directly correlates with the biological tumoral behavior and the patient life expectancy. Available data, for pancreatic carcinoma, come only from histological specimen, and are then related to patients undergoing a surgical resection. Aim In our study we tried to figure out if the tumoral neoangiogenetic factors, researched in the patient serum, showed the same prognostic ability of those found in the tumoral cells. Methods Blood concentration of Angiopoietin2, EGF, bFGF, PDGF and VEGF were evaluated by SearchLight technology in two different cohorts of patients. The first one was a retrospective cross-sectional study of 177 patients in which neoangiogenetic factors were analyzed at the time of diagnosis. The second one was a prospective longitudinal study of 28 patients with advanced disease resistant to conventional chemotherapeutic regimen treated with combination of raltitrexed and oxaliplatin. Results In retrospective cross-sectional study a significant higher blood concentration of Angiopoietin2 (Mann-Whitney test, P=0.004) was observed in metastatic patients. Cox regression analysis showed that patients’ overall survival rate was inversely associated with levels of Angiopoietin2 (P=0.005, odds ratio: 1.086) and EGF (P=0.005, odds ratio: 1.032). Multivariate analysis showed that only Angiopoietin2 was an independent prognostic marker for overall survival (P=0.037, odds ratio: 1.088). Angiopoietin2 showed also a correlation (Cox regression; P=0.025, odds ratio 1.268) with the early onset of metastatic relapse. The prospective longitudinal study confirmed pre-treatment serum Angiopoietin2 circulating level as an independent significant prognostic factor for the survival, while no significant temporal correspondence between neoangiogenetic factors level and tumoral progression was evident during chemotherapy. Conclusions Angiopoietin2 serum circulating level at the time of the diagnosis is an independent prognostic factor for pancreas adenocarcinoma.

Risk Factors for Pancreatic Endocrine Tumours: A Multicenter Case-Control Study
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Context Pancreatic endocrine tumors (PETs) are rare neoplasms with an incidence of some 0.1/100,000. Apart from genetic disorders, risk factors for the occurrence of PETs have
never been specifically investigated. Smoking, drinking and obesity have been found to be risk factors both for GI carcinoids and pancreatic ductal adenocarcinoma (PDAC). The possible role of family history has seldom been evaluated in GI endocrine tumors before. **Aim** We aimed at determining risk factors for the occurrence of PETs. **Methods** Multicenter case-control study. Patients with either new diagnosis of sporadic PET or in follow-up seen during a 12-month period were administered a specific questionnaire registering data on possible risk factors (smoking, alcohol intake, BMI, medical history 1 year before PET diagnosis) and family history of cancer. Controls were patients with non-neoplastic, non-chronic disorders. Differences between groups were calculated by means of Fisher or Wilcoxon tests, and odds ratios by multiple logistic regression, through a dedicated software. **Results** One-hundred and 59 patients (50% males) and 559 controls (47.4% males) were enrolled. Mean age: 52.9 years for PETs and 52.5 years for controls. Forty-two percent of PETs and 33% of controls were ever smokers (P NS). A pack x year (No. of daily packs x years of smoking) ≥ 20 was more frequent amongst PETs (22% vs 15%; P=0.03). Drinking alcohol recorded in 35% of PETs and 25.5% of controls (P NS), while drinking ≥ 21 units/week was significantly more frequent in PETs (14% vs .3%; P<0.0005). Median BMI was 24.8 kg/m^2 in PETs and 24.9 kg/m^2 in controls (P NS), with obesity similarly distributed, while both diabetes (10.6% of PETs vs. 2.6% of controls; P<0.0005) and chronic pancreatitis (3.1% vs. 0.3%; P=0.007) were more frequent in PETs. 52.8% of PETs had at least one 1st degree family member with a neoplasm vs. 32.3% of controls (P NS). PDAC 1st degree family history was found in 7 PETs (4.4%) and 6 (1.1%) controls (P=0.011). All 7 PETs with PDAC 1st degree family history were NF and 1 PET kindred met criteria for familial PDAC. No other site specific neoplasm family history significantly different. At a univariate logistic regression analysis, smoking ≥ 20 pack year (OR 1.6), drinking ≥21 units/week (OR 4.7), past history of diabetes (OR 4) and chronic pancreatitis (OR 9), 1st degree family history of any cancer (OR 2.3), and PDAC 1st degree family history (OR 4.2) were significant risk factors. All these factors were confirmed to be significant in different multivariate analysis models, but smoking which was close to significance. **Conclusions** Drinking alcohol at high doses is an important risk factor for PETs, while the role of smoking seems less clear. Past history of diabetes and chronic pancreatitis are also associated with an increased risk of PETs. Analysis of time of onset of diabetes and its course after treatment deserve further investigation. Family history of cancer, particularly of PDAC is a risk factor for PETs. This is interesting as occurrence of PETs has been reported in kindreds with familial pancreatic cancer. Overall, our findings suggest similar risk factors for PETs and PDAC, with interesting possible speculations on the molecular aspects of carcinogenesis in the pancreas.

Pancreatoduodenectomy with Enucleation of Liver Nodules for Neoplasia of Uncertain Origin: A Case Report

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**Context** A patient with severe jaundice, vomiting and back pain due to a voluminous mass of the head of the pancreas of uncertain origin underwent a pancreatoduodenectomy with removal of two nodules of the liver. In our Institution 13 pancreaticoduodenectomies have been performed in the last year for lesions within
the head of the pancreas with excellent peri-operative and long term results in a median follow-up of 7 months. **Case report** We report the case of a 73-year-old patient who in April 2007 referred to our hospital for jaundice (12 mg/dL), vomiting, back pain and weight loss. Neoplastic markers were normal. In the history were a radical prostatectomy (10 years before) and a left lung lobectomy followed by chemo-radiotherapy (2 years before) both for carcinomas. A total-body CT scan revealed a 6 cm solid lesion of the head of the pancreas associated with two sub-centimetric suspected lesions of the right liver, no other lesions elsewhere. Laparoscopy showed no carcinosis and frozen sections of a small superficial nodule of the right liver showed unusual malignant cells not referable to ductal or carcinoma. Considering a possible less aggressive disease, shifting to laparotomy a pylorus preserving pancreaticoduodenectomy with tangential resection of portal vein and removal of the hepatic lesions was performed. The patient recovered quickly with oral alimentation after six days from operation and was discharged in the 10th post-operative day. The histological study revealed the metastatic origin of the neoplasms from lung carcinoma. The patient more than one year from intervention is still asymptomatic although with small multiple metastasis recurring in the liver. **Conclusions** Better prognosis is reported in the literature, about 25% of survival rate at 5 years, after pancreatic resection for metastatic lesions compared to those for ductal adenocarcinoma (5-10%). We can consider the feasibility of major pancreatic resections also for metastatic lesions in Centre with adequate results with the purpose of achieving a better quality of life for a longer period.

**Pancreatoduodenectomies in a Not Referring Centre:**

**Early Experience After 15 Months**

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**Context** Team been trained in a referring centre for the treatment of pancreatic diseases, introducing new surgical skills in a peripheral hospital. **Aim** To evaluate the feasibility of major pancreatic resections in a peripheral unit. **Methods** Fourteen pancreaticoduodenectomies have been performed in our institution from March 2007 to May 2008. Almost all patients referred to our unit for jaundice. Mean age was 68 years (range: 48-85 years) and total bilirubin level 13 mg/dL (range: 4-25 mg/dL). In a third of patients vomiting was associated and in 15% abdominal pain irradiated to the back. Three patients received a pre-operative biliary drainage (two external and one endoprosthesis positioned elsewhere before our observation). In three cases CA 19-9 was negative. Radiological examinations (US, CT or MRI) revealed a lesion within the head of the pancreas in all cases showing no involvement of major arteries or distant metastasis. Post-operative histological examinations revealed six ductal adenocarcinomas, five ampullary carcinomas, one a mucinous cystadenoma, one a carcinoma of distal choledochus and one a metastasis from lung carcinoma. In all cases a pylorus preserving pancreaticoduodenectomy with pancreatico-jejunal anastomosis and a wide lymphadenectomy was performed. In three cases a vascular resection (two portal and one caval) has been necessary. Adequate training of nurses and doctors was specifically performed at the beginning of the experience. **Results** The median intervention time was 6.5 hours (range: 5.30-11 hours). No peri-operative mortality was observed. Short post-operative course was uneventful in all cases. Oral re-intake was completed after a mean...
time of eight days (range 5-18 days) and the abdominal drainages were removed in a mean time of eleven days (range 6-18 days). Fifty percent of patients received a mean of 2 units of concentrated red blood cells. The mean hospital staying was 14 days (range: 7-26 days). Two patients developed a glycemic instability that required insulin therapy. One patient required re-intervention for a small wound hernia. Actual mean follow-up is eight months. All patients are still alive and in a very good performance status. **Conclusions** Major pancreatic resections can be feasible with good results by an expert team also in a peripheral centre.

**Complication Rate After EUS-Guided Fine Needle Aspiration of Pancreatic Lesions: A Large Single Center Experience**

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**Context**
EUS-guided FNA is effective for establishing tissue diagnosis in suspected pancreatic cancer, for collecting fluid in cystic tumors, and it is useful to select the most appropriate management of the patients. **Aim**
The aim of our study was to determine the frequency and severity of complications after EUS-FNA of solid and cystic pancreatic lesions in a large series of patients consecutively recruited in our tertiary care University Center. **Methods**
EUS database entries (EUS-HSR database, Excel Microsoft Corp) between March 2001 and May 2007 were reviewed searching for all complications (hemorrhage, acute pancreatitis, perforation, etc.) related to EUS-FNA of solid and cystic pancreatic lesions. EUS examinations were performed with the patients placed in left lateral decubitus and under deep sedation with intravenous Propofol. The procedures were performed by 3 experienced endosonographers with a linear array echoendoscope (FG36UX or EG3830UT, Pentax, Hamburg). Either 22 or 25 Gauge needles (Wilson Cook, Ireland) were used for biopsies. Antibiotics were prophylactically administered before the aspiration of cystic lesions. A complication was defined as any deviation from expected clinical course during or after EUS-FNA. **Results**
A total of 2,797 pancreatic EUS were performed over about 6 years, of which 1,019 (36.4%; 750 solid masses, 269 cystic lesions) with FNA. Over 1,019 pancreatic EUS-FNA, we observed 7 (0.69%) hemorrhages (4 intra-cystic, 2 in the pancreatic duct, and one in a small carcinoma), 2 (0.20%) acute severe pancreatitis and one (0.10%) duodenal perforation followed by complicated postsurgical hospitalization and death of the patient. Overall, major complications occurred in less than 1% of pancreatic EUS-FNA. **Conclusion**
EUS-FNA is safe with a low risk of hemorrhage. In our study population, this complication was self-limited, without any need of interventional therapy. Although rare, acute pancreatitis is generally severe requiring prolonged hospitalization. One fatal complication occurred after duodenal perforation in a patient with duodenal neuroendocrine tumor and pancreatic infiltration.
Endoscopic Ultrasound-Guided Fine Needle Aspiration Biopsy in Patients with Obstructive Jaundice: Does a Biliary Stent Interfere with the Final Diagnosis?
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Context EUS-FNA has a high accuracy but in patients with obstructive jaundice, if a stent has been previously placed in the CBD, the accuracy and the NPV seems to decrease because of fibrosis and artifacts. Aim To assess the yield of EUS-FNA in the diagnosis of pancreatobiliary malignancy in two groups of patients with obstructive jaundice treated or not with biliary stent. Methods Group A: 49 patients, previously admitted to other hospitals and treated with ERCP and stent placement, referred to our unit to undergo EUS-FNA. Group B: 49 patients admitted to our hospital with a suspected pancreatic mass. Pentax echoendoscopes and Wilson Cook 22 or 25 G needles were used. A cytopathologist was present in the endoscopic room during FNA. The final diagnosis was given by surgical specimens or clinical follow-up of patients. Results Pancreatic adenocarcinoma and CBD cholangiocarcinoma were diagnosed in 79 (81%) and 6 (6%) patients respectively without a significant difference between the two groups. Other diagnoses were: NET (2; 2%); focal mass in chronic pancreatitis (8; 8%); IPMN or serous cystic adenoma (3; 3%). The size of the lesion ranged from 15 to 60 mm with no significant difference between the two groups. An average of 2.7 needle passes was made to reach the cytological adequacy. The two groups did not show any significant difference when needle size or number of passes were considered. A cytological diagnosis of malignancy was reached in 87% of patients. In the 13 patients no malignancy was detected however the clinical course revealed that in 4 patients with carcinoma a false negative result occurred. In our study population with a cancer prevalence of 89%, the sensitivity, specificity, PPV, and NPV of EUS-FNA were 95%, 100%, 100% and 69%, respectively. Overall accuracy was 96%. When the diagnostic accuracy of EUS-FNA was evaluated separately in each patient group, no significant difference was elicited. Conclusion The accuracy of EUS-FNA in pancreatobiliary malignancy in patients with obstructive jaundice is very high and is unaffected by the presence of biliary stents.

Diagnosis of Hemorrhagic Complications in Patients Submitted to Pancreatic Surgery: Role of Multidetector CT (MDCT)
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Context MDCT imaging in association with clinical data and laboratory values is needed to diagnose hemorrhagic complications after pancreatic surgery. Aim To assess the role of MDCT in diagnosing hemorrhagic complications in patients submitted to pancreatic surgery. Materials and methods Retrospective analysis of 13,800 patients (12 men, 1 woman; age range 41-70 years, mean 60 years) who underwent pancreatic resection
(9 pancreaticoduodenectomy; 1 spleno-pancreatectomy; 2 intermediate pancreatic resection; 1 total pancreatectomy) from April 2006 to May 2008. Inclusion criteria: laparotomic/laparoscopic treatment, clinical and laboratory data for hemorrhage, abdomen MDCT within 1 week after treatment. Exclusion criteria: pancreatic resection for non neoplastic diseases. All patients underwent quadruphasic MDCT examination (6 slices from April 2006 to March 2008 and 64 from April 2008 to May 2008), and received medical therapy or second treatment (surgical or angiographic embolization). Two radiologists analyzed MDCT images in a double blinded trial with final consensus. The qualitative analysis included: abdominal hyperdense collection, active bleeding during contrastographic phase, abdominal liquid film. The quantitative analysis included: hyperdense collection’s mean maximum diameter. Results Qualitative analysis: abdominal hyperdense collection was found in 11/13 patients, active bleeding during contrastographic examination in 7/13 and abdominal liquid film in 5/13. Quantitative analysis: 55 mm was fluid collection’s mean maximum diameter. Five out of 7 patients with MDCT diagnosis of active bleeding needed second surgery: hemostatic treatment and drainage of hyperdense collections were made, 1/7 angiographic embolization, 1/7 both treatments. Patients with MDCT diagnosis of abdominal hyperdense collection or abdominal liquid film but not active bleeding had follow-up imaging and medical therapy until complication’s resolution. Conclusions MDCT is the most useful imaging modality for the evaluation of hemorrhagic complications in patients submitted to pancreatic surgery.

A Prospective Study Comparing Ultrasound, Contrast Enhanced Ultrasound and Diagnostic Laparoscopy in Achieving the Correct Staging in Advanced Pancreatic Cancer Patient

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Context Most of patients suffering from ductal adenocarcinoma of the pancreas are unresectable at diagnosis and despite the pre-operative work-up with non-invasive imaging techniques; there is still a good proportion of them clearly understaged because of millimetric nodules in the liver or on the peritoneal surface. Aim The aim of this paper is to demonstrate the usefulness of contrast enhanced ultrasound in correctly staging pancreatic cancer patients compared to conventional ultrasound and laparoscopy. Methods Nineteen patients considered unresectable at preoperative staging or without successfully pathological diagnosis underwent laparoscopic procedures in order to obtain cytohistological definition of their disease or to confirm metastases. All of them underwent also contrast enhanced ultrasound. They were compared with a control group previously studied with laparoscopy which did not perform contrast enhanced ultrasound. Results Laparoscopy was able to confirm unresectable disease and to achieve cytohistological characterization in all patients. The re-staging rate was 21% (4/19) in the study group compared to 31.5% (6/19) in the control group (P=0.7). Conclusion Contrast enhanced ultrasound is mandatory in patients suffering from ductal adenocarcinoma of the pancreas in order to achieve the best pre-operative staging. Laparoscopy still maintains the highest sensitivity and specificity as all in one procedure to stage and to characterize these patients.
PEXG (P: Cisplatin, E: Epirubicin, X: Capecitabine, G: Gemcitabine) versus PDXG (D: Docetaxel) Regimen in Advanced Pancreatic Cancer: A Randomized Phase II Trial

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Context PEFG regimen (P: cisplatin, E: epirubicin, F:5-fluorouracil, G: gemcitabine) significantly prolonged progression-free (PFS) and overall survival (OS) of patients with advanced pancreatic adenocarcinoma (PA) with respect to standard gemcitabine [1].

Aim The current single institution phase II randomized trial was aimed to further prolong PFS by replacing E with docetaxel (D).

Methods Patients with stage III or metastatic PA, age 18-75 years, Karnofsky performance status (PS) >50 were randomized to receive either D (arm A: 25 mg/m2 days 1 and 14) or E (arm B: 30 mg/m2 days 1 and 14) while P (30 mg/m2 days 1 and 14), G (800 mg/m2 days 1 and 14) and capecitabine (X) (1,250 mg/m2/day days 1 to 28) were administered in both arms. Cycles were repeated every 28 days. The sample size was calculated on the probability of being PF at 6 months (PFS6) from treatment start. Assuming P0=25% and P1=45%, with alpha P=0.05 and beta P=0.20, the study was to enroll 32 patients per arm.

Results Between July 2005 and January 2007, 64 patients were enrolled, stratified by stage and randomized (32 per arm). Main patient characteristics were balanced (A/B): median age 61/58, PS >80 50%/47%, metastatic disease 69%/69%. Treatment is ongoing in 1/5 patients; 18/16 patients concluded at least 6 cycles of chemotherapy while 13/11 interrupted treatment due to progressive disease (PD; 10/9), consent withdrawal (2/0) and toxicity (1/2). To date, 58 patients are assessable for response and 54 for PFS6: 18 of 31 (58%) arm A patients and 12 of 27 (44%) arm B achieved a partial response. PFS6 was 57%/46%. Final results will be available at time of meeting.

Conclusion PEXG regimen yielded similar results when compared to historical series treated by PEFG regimen, suggesting that X may replace F without compromising the outcome. The inclusion of D instead of E seems to be promising. The present trial further confirms the role of four-drug regimens in advanced PA.

Reference

“Bull’s Eye Calculi” in Diagnosis of Gene Mutation Associated Chronic Pancreatitis (GMAP): the Role of MDCT. Final Results

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Context In patients with chronic pancreatitis “bull’s eye” calculi are highly associated with GMAP. Aim To evaluate MDCT findings of ductal calculi useful allow to detect GMAP from obstructive pancreatitis. Materials and methods From May 2006 to June 2008, 50 patients affected by chronic pancreatitis with ductal calculi were prospectively enrolled in
this study (32 males, 19 females). Inclusion criteria were: clinical, laboratory and imaging (US, ERCP, RM) findings of pancreatitis, presence of ductal calculi, genetic test, and MDCT study examination. Exclusion criteria were: patients with autoimmune pancreatitis, with intraductal papillary mucinous tumors, who underwent ERCP, lithotripsy or surgery treatment. Clinical symptoms at presentation included, abdominal pain, diabetes, steatorrhea and jaundice. Images analysis was performed by two independent radiologists. Qualitative criteria were: structure of the endoductal calculi (homogeneous/heterogeneous: non-calcified central core (“bull’s eye”), pancreatic parenchyma contrast-enhancement in pancreatic phase compared to renal cortex (hypo-/iso-/hyper-vascular). Quantitative criteria were: number and diameter of endoductal calculi, size of pancreatic parenchyma (head, body, tail), size of main pancreatic duct (MPD).

Results
Qualitative analysis: heterogeneous calculi with non-calcified central core (“bull’s eye”) in 12/51, homogeneous calculi in 38/50; pancreatic parenchyma was hypovascular in 35/51, isovascular in 16/51. Quantitative analysis: mean number of calculi was 22 (range 5-45), mean diameter of calculi 15 mm (range 3-40 mm), median thickness of the pancreatic parenchyma in head, body and tail was respectively 14 mm (range 2-40 mm), 10 mm (range 2-40 mm) and 10 mm (range 2-40 mm); mean size of MPD was 11 mm (range 3-25 mm). Gene mutation was CFTR 9/51, SPINK1 5/51 and 2/51 both CFTR and SPINK mutation. Nine out of 16 (56%) patients with GMAP have “bull’s eye” calculi; 2/34 (6%) patients with chronic pancreatitis have “bull’s eye” calculi, in particular one have an idiopathic pancreatitis and the other have alcoholic pancreatitis.

Conclusions
In our conclusive study MDCT can identify “bull’s eye” and have a good correlation with GMAP.

Lymphoepithelial Cyst of the Pancreas
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Context
Lymphoepithelial cyst of the pancreas (LCP) is a rare, benign cyst that mimics pseudocyst or cystic neoplasm. It is a true cyst filled with pasty, keratinous material. Histologically, the wall of the cyst consists of a keratinizing squamous epithelium surrounded by lymphoid tissue. The interest of surgeons for LCP is related to the differential diagnosis with pancreatic cystic mucinous neoplasms (PCMN), that allows to avoid an unnecessary radical surgery. Aim We update the literature to assess clinical and pathological characteristics of this uncommon pancreatic disease. Methods We searched MEDLINE and PubMed for all articles using the key-words “lymphoepithelial cyst” and “pancreas”. For each article, the following data were recorded and included in a data base: age and sex of patient(s); size of LCP; site of the lesion (head, body or tail of the pancreas); presenting symptoms; relevant laboratory findings; diagnostic means used and preoperative diagnosis; performed treatment and outcome. Results In the last twenty years, from November 1987 to June 2007, fifty-seven works concerning sixty-five cases of LCP were published in the literature. LCP is usually localized in the tail of the pancreas, but it can be found also in the head or in the body, with a size ranging from 2 to 10 cm in greatest dimension. It usually occurs between 41 and 70 years of age with a male:female ratio of 6.3:1. LCP is asymptomatic in the

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majority of cases, but it can be occasionally responsible for aspecific abdominal pain or other symptoms as diarrhea, weight loss, and back pain. The diagnosis is occasional or consequent to symptoms and it is usually made by US or CT. Nevertheless, there are no specific radiologic characteristics of this disease. The level of tumoral markers in the serum, as in the cystic fluid, fails to aid the diagnosis. Only an EUS-guided or CT-guided FNA cytology could allow a correct diagnosis when the pathologist has familiarity with cytologic features of the disease. Fifty patients underwent surgical resection: 28 left pancreatectomies, in 6 cases with spleen preservation, 19 local excisions and 3 Whipple’s procedures were performed. **Conclusion** LCP represents a rare lesion: consequently, the knowledge of the disease is essential to achieve a correct diagnosis. When a certain diagnosis of LCP is achieved preoperatively, a conservative treatment is possible: in fact, there has never been a report of degeneration of LCP into a malignancy or local recurrence after resection. Otherwise, a pancreatic resection is justified to exclude the diagnosis of PCMN.

**Role of Multidetector CT (MDCT) in Diagnosing Complications in Patients Submitted to Pancreatic Surgery**

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**Context** MDCT imaging associated with clinical and laboratory data is highly reliable to assess complications in patients after pancreatic surgery. **Aim** To evaluate the role of MDCT in diagnosing complications in patients submitted to pancreatic surgery. **Materials and methods** Retrospective analysis of 45/800 who underwent pancreatic or palliative surgery from April 2006 to May 2008. Inclusion criteria: laparotomic/laparoscopic treatment, fever, increase of inflammatory laboratory values, abdomen MDCT within 1 month after treatment. Exclusion criteria: pancreatic surgery for non neoplastic diseases. All patients underwent quadriphasic MDCT examination (6 slices from April 2006 to March 2008 and 64 from April 2008 to May 2008); in 11/45 diluted contrast medium was administrated by abdominal drainage. All of them received medical therapy or second treatment (surgical or percutaneous). Two radiologists analyzed MDCT images in a double blinded trial with final consensus. Qualitative analysis: abdominal fluid collection, leakage of anastomosis after contrast medium introduction in abdominal drainage, hypodense areas of residual pancreatic parenchyma, abdominal liquid film, intra/extrahepatic biliary tree dilatation. Quantitative analysis: fluid collection’s mean maximum diameter. **Results** Qualitative analysis: abdominal fluid collection was found in 34/45, leakage of anastomosis after contrast medium introduction in abdominal drainage in 5/11, hypodense areas of residual pancreatic parenchyma in 5/45, abdominal liquid film in 18/45, dilatation of intrahepatic biliary tree in 1/45 patients. Quantitative analysis: 67 mm was fluid collection’s mean maximum diameter. Seven out of 45 patients needed US/CT-guided drainage: all of them had an abdominal fluid collection. Eight out of 45 were submitted to second surgery: MDTC diagnosis of leakage of anastomosis was confirmed in 4/8 patients, severe pancreatitis in 2/8 and abdominal fluid collection in 2/8. Thirty out of 45 had follow-up imaging and medical therapy until complication’s resolution. **Conclusions**
MDCT is very helpful in diagnosing and following complications in patients submitted to pancreatic surgery.

**Prognostic Relevance of Lymph Node Ratio and Number of Resected Nodes After Curative Resection of Invasive Ampullary Carcinoma**

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**Context** Nodal metastasis is considered a major prognostic factor in patients with invasive carcinoma of the ampulla of Vater. Recent studies of gastric and colon cancer have shown a prognostic significance of lymph node ratio (number of positive nodes divided by total number harvested, LNR) and of number of resected nodes. However no study has investigated the prognostic role of these factors in ampullary invasive carcinoma. **Aim** Our aim was to determine whether LNR and the number of resected nodes would predict survival and tumor recurrence in a cohort of patients who underwent pancreaticoduodenectomy with radical intent for invasive carcinoma of the ampulla of Vater from 1990 to 2005 in a tertiary academic center. **Methods** Demographic, operative and pathology data (including number of resected nodes and LNR) were collected. Survival rates and recurrence patterns were evaluated and predictors were identified. **Results** In 90 evaluable patients (51 males, 39 females; median age of 62.5 years), 5-year disease-specific survival (DSS) was 61%. The median number of resected nodes was 16 (range: 5-47); fifty percent of the patients had nodal metastases. The 5-year DSS according to LNR was 75%, 49%, 38% and 0% for LNR=0, LNR >0 and ≤0.2, LNR >0.2 and ≤0.4, and LNR >0.4, respectively (P=0.002). The 5-year DSS was 81% in patients with >16 resected nodes compared to 45% in those with ≤16 resected nodes (P=0.001). At multivariate analysis LNR and a number of resected nodes >16 were significant predictors of survival; a number of resected nodes >16 was also the only independent predictor of recurrence. **Conclusion** After R0 resection for ampulla of Vater carcinoma, LNR and a cut-off of 16 resected nodes are powerful prognostic factors. LNR might represent a major parameter for patient stratification in adjuvant treatment trials.

**Conservative Treatment and Surgical Timing of Severe Acute Pancreatitis (SAP) in a Casistic’s Review**

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**Context** According to Atlanta 1992, severe acute pancreatitis (SAP) is defined as an acute pancreatitis (AP) associated with local and/or systemic complications inducing single and/or multi-organ dysfunction. Several problems concerning intensive treatment, surgical timing and operative strategies are still unsolved now. **Methods** From February 1995 to January 2008, 156 patients were consecutively admitted to our division with diagnosis of AP. SAP occurred in 35.2% with these characteristics: serum level of amylase...
>350 IU; PCR >35 mg/dL; Ranson score >3; Apache II score >8. CECT of the abdomen showed pancreatic necrosis involving 50% of the pancreas and peri-pancreatic tissues in 70% of cases. Conservative treatment includes: constant monitoring of vital parameters; fluid resuscitation; parenteral/enteral nutrition; antibiotic therapy. Operative strategies adopted in emergencies were: necrosectomy and wide debridement of the peripancreatic spaces, positioning of drainage tubes in association with continuous washing or VAC therapy, cholecystectomy and intraoperative cholangiography. Results SAP occurred in 55 patients (35.2%). Conservative treatment was successful in 37 patients (67.3%). 18 patients (37.2%) underwent surgery: 5 cases (28.4%) within 48 h after onset due to surgical acute abdomen with increased abdominal pressure (≥30 mmHg), 13 cases (70.6%) between 14 and 21 days after onset for incoming sepsis or unsuccessful conservative treatment. In 6 patients a continuous washing of the abdomen was set on; in 3 cases a VAC therapy system was associated (surgical re-look every 48 h was necessary to renew the system). Overall mortality was 7.2% (4 cases). Mean hospital stay was over 60 days. Conclusion AP’s treatment represents a real problem for surgeons as far as discrimination between mild acute and severe acute pancreatitis in the first 48 hours is concerned. In our experience conservative treatment is successful in most cases. Surgical treatment should be avoided if possible due to mortality, high rate co-morbidity and long hospital stay.

Gemcitabine Based Chemoradiation in Unresectable Locally Advanced Pancreatic Cancer: A Long Term Analysis

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Context Prognosis of pancreatic cancer patients in the advanced stage remains poor despite advances in therapy and diagnosis. Aim To evaluate efficacy of gemcitabine (Gem) based chemoradiation (CT-RT) in treating patients affected by locally advanced pancreatic cancers (LAPC). Methods Weekly Gem (100 mg/m²) was given as a 24-hour infusion during the course of 3D radiation therapy (39.6 Gy to the nodal drainage areas; 50.4 Gy to the tumor). After CT-RT patients with an ECOG PS <3 received further 5 cycles of sequential chemotherapy with Gem (1000 mg/m²; 1-8, q21). Response rate was assessed according to WHO radiological criteria 6 weeks after the end of CT-RT. Local control (LC), time to progression (TTP), metastases free survival (MFS) and overall survival (OS) were analyzed by the Kaplan Meier method. Cox proportional-hazards regression was used in multivariate analysis. Results Forty patients (M/F: 22/18; median age 62 years, range 36-76 years) were treated from 2000 to 2005. The majority of patients were T4 (n=34; 85%), 6 patients (15%) were T3. Sixteen patients (40%) were node positive at diagnosis. Thirty-three patients (82.5%) completed radiotherapy (dose range 27.9-50.4 Gy). The median Gem dose administered was 76% (range 32-100%). Thirty patients (76.3%) received sequential gemcitabine. A clinical remission either complete (n=4; 10%) or partial (n=8; 20%) was achieved in 12 patients (30%). Stable disease was observed in 18 patients (45%). Ten patients (25%) had disease progression. With a median follow-up of 76 months (range: 32-98 months), 3- and 5-year LC was 38% (median: 11 months), 3- and 5-year TTP was 23% (median: 10 months), 3- and 5-year MFS were 30%
(median: 10 months). Three- and five-year OS were 22.5% (median: 15.5 months). Univariate analysis was used to identify factors impacting on LC, TTP, MFS and OS. Complete delivery of prescribed RT dose and clinical remission were significantly related to all the outcomes analyzed (P<0.04). Sequential chemotherapy and the concurrently Gem rate administered were significantly associated with improved TTP, MFS and OS (P<0.02). Otherwise node-involvement had a significant impact only on MFS (P=0.025). The prognostic significance of clinical remission on all the variables was strengthened on multivariate analysis. **Conclusions** Gemcitabine based CT-RT may be effective in treatment of unresectable pancreatic cancer. The outcome of these patients seems to be strongly influenced by treatment response.

### The Clinical Management and Outcome of Hemorrhage after Pancreaticoduodenectomy: Results in a Continuous Series of 755 Patients

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**Context** Hemorrhage after pancreaticoduodenectomy (PD) may be a dramatic complication and a standardized management is still unavailable. **Aim** To assess the possible risk factors involved in the development of hemorrhage, the outcome of surgical or conservative approach or the combined use of both techniques, the impact of hemorrhage in favors further complications. **Methods** We reviewed all the patients who underwent PD in our institution from 1996 to 2006. Perioperative features of each patient were prospectively collected. We focused on the clinical presentation of hemorrhage, defining mild and severe, early and delayed forms. Success rate of interventional angiography and surgery in arresting the hemorrhage were analyzed as well as hemorrhage-related overall outcome. **Results** Postoperative hemorrhage occurred in 48 out of 755 patients (6.3%), 18 patients had a mild bleeding, 30 had a severe bleeding. In this group of patients 16 had an early bleeding, 14 a delayed form. Hemorrhage was closely related to the occurrence of pancreatic fistula, but did not show any significant correlation with the softness of the pancreatic remnant. Surgical reintervention, which was performed in all patients with severe early bleeding, was able to stop hemorrhage in all cases but one patient who died of fulminant sepsis. All cases of delayed hemorrhage (14 patients and 2 drop out) were treated with surgical re-exploration. Interventional angiography was used in 6 of these patients, but a subsequent surgical procedure was necessary to stop a recurrence or to evacuate an infected collection. Overall mortality rate of PD was 1.3%, but the mortality rate among the hemorrhagic group of patients rises to 10%. Both early and delayed forms prolonged the duration of the hospital stay, compared to non-hemorrhagic patients (median 20.5 and 33 days, respectively vs. 12 days). **Conclusion** Prognosis of hemorrhage after PD depends on a prompt diagnostic device such as CT scan and an aggressive therapeutical strategy with interventional angiography and surgery combined. Even if successfully treated, they are often productive of further complications and a prolonged in-hospital stay.
Pancreas Paraganglioma: A Surgical Challenge
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**Context** Pancreas paraganglioma is extremely rare and only 11 cases are reported worldwide. There is not a gold standard strategy in surgical management. We report our case in a critical point of view. **Case report** A 58-year-old female was admitted to our institution for abdominal pain since few months. Abdomen ecochography revealed a solid mass of pancreatic body. Blood specimens showed only an elevation at chromogranin A levels (193.4 ng/mL). Perfusion ultrasonography and CT scan demonstrated a 3.0x3.4 cm mass behind the pancreatic gland, with perfusional pattern compatible with neuroendocrine neoplasia. The patient was operated on distal spleno-pancreatectomy. Postoperative course was uneventful and the patient discharged on 10th postoperative day. At follow-up patient developed insulin-dependent diabetes mellitus requiring 14 IU insulin a day. Histopathologic specimen showed the diagnosis of paraganglioma arising from retropancreatic plexus. Immunohistochemical staining revealed positivity for chromogranin A and synaptophysin. **Conclusion** Paraganglioma of the pancreas is a rare disease, often mimicking a pancreatic neoplasia. In our case history, blood markers and morphological and perfusional appearances at CT scan and ultrasonography were suspicious for neuroendocrine non functioning neoplasia. We proceeded to distal pancreatic resection and lymphadenectomy since there was not clear evidence to exclude malignancy. The patient anyway became diabetic and this should be a point of discussion and challenging. In fact, it would be probably better to perform a simple tumor excision instead of pancreatic resection, allowing to the patient to be free from glycemic abnormalities. In case of doubt about malignancy tumor-bed biopsies can be obtained intraoperatively in order to choose the optimal surgical strategy.

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Pancreatic Fistula After Pancreaticoduodenectomy: Effectiveness of the International Study Group of Pancreatic Fistula Definition: Results in 147 Consecutive Patients
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**Context** Postoperative pancreatic fistula (POPF) is a common major complication after pancreaticoduodenectomy (PD). The reported rates of POPF largely vary, since one common definition is still unavailable. **Aim** The aim of this study is to affirm the validness of the International Study Group of Pancreatic Fistula (ISGPF) definition applied in a retrospective consecutive series. **Methods** A retrospective study of a prospectively collected database of 755 patients who underwent a PD for various indications at the Surgical and Gastroenterological Department of the University of Verona, between November 1996 and October 2006. One-hundred and 47 patients (19.5%) have developed a POPF according to a previously applied definition. ISGPF definition was retrospectively used in order to define the complication’s grading. **Results** According to the ISGPF definition, 19% of all POPFs (grade A), have no clinical
impact on the patient; most POPFs (70.7%), (grade B), can be successfully managed with conservative therapy or mini-invasive procedures; the remaining patients (8.8%), (grade C), present severe complications associated to the fistula, with invasive therapy being required, and high mortality rate (30.7%). Patients with carcinoma of the ampullary region have a higher incidence of POPF when compared to patients with other
types of tumor, nonetheless there is a predominance of grade A fistulas (P=0.036).

Conclusions Even if pancreatic fistula is frequent after PD it does not always determine a substantial change of the postoperative management. The grading system proposed by the ISGPF allows a correct stratification of the complicated patients, based on the real clinical impact of the POPF.

The Role of Intraoperative Ultrasonography (IOUS) in Pancreatic Surgery for Multifocal Intraductal Papillary Mucinous Neoplasms (IPMNs)
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Context IPMNs are neoplasms of the pancreatic duct epithelium characterized by papillary proliferations of mucin-producing epithelial cells and cystic dilatation of the pancreatic ducts. IPMNs have malignant potential, a broad histologic spectrum ranging from dysplasia to invasive carcinoma, sometimes coexisting within the same tumor, and can be multifocal. Aim The aim of the study was to define the role of IOUS in planning and guiding the surgeon in patients with multifocal IPMNs undergoing surgery. Methods Four patients with multifocal IPMNs candidate to surgery were included in the study. All underwent pre-operative CT scan and MRCP for staging. Patient #1 was a 70-year-old male with an invasive carcinoma of the head of the pancreas and 2 branch duct (BD) IPMNs ≤15 mm of the body and the tail, respectively. Patient #2 was a 77-year-old male with a colorectal cancer in whom the preoperative CT scan revealed a BD IPMN of 30 mm with mural nodules of the head of the pancreas and multiple small BD IPMNs of the body and the tail. Patient #3 was a 84-year-old female with an invasive carcinoma of the tail of the pancreas, multiple BD IPMNs, up to 20 mm, of the body and multiple BD IPMNs ≤10 mm of the head. Patient #4 was a 68-year-old female with a main duct type IPMN of the head of the pancreas and multiple BD IPMNs ≤10 mm of the body and the tail. Results IOUS confirmed the preoperative staging of the multifocal tumor and the planned pancreaticoduodenectomy in patient #1 and #2, respectively. Patient #3 underwent distal pancreatectomy: IOUS showed a 20 mm cystic neoplasm near the mesenteric vein which was included in the resected specimen and resulted to be an IPMN with focus of carcinoma at histology. Patient #4 underwent the planned pancreaticoduodenectomy: the IOUS clearly showed the extension of the cystic dilatation of the main pancreatic duct and was determinant in obtaining a free resection margin. Conclusion IOUS is of clinical utility in selected patients with IPMNs undergoing pancreatic surgery. IOUS should be routinely used in planning and guiding the surgeon in the resection of pancreatic multifocal neoplasms.
Wait and See: the Actual Clinical Approach to Branch Duct IPMN
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Context IPMN of the pancreas are traditionally considered potentially malignant lesions, for which surgical therapy is advocated; nevertheless branch duct IPMN (BD-IPMN) seem to often pursue a more indolent course and consequently to allow a conservative management. Aim To analyze a consecutive series of 35 patients diagnosed with BD-IPMN who underwent a clinical and radiological follow-up at our Institution. Methods According to the International Association of Pancreatologist guidelines, we recommended a follow-up in case of cysts less than 30 mm in diameter in absence of mural nodules. Between October 2004 and January 2008 35 patients with these characteristics were enrolled in a follow-up protocol: there were 17 males (49.6%) and 18 females (51.4%); mean age at diagnosis was 64.3 years (range 33-84 years); in 5 cases (14.2%) there was a familial history of pancreatic cancer. Mean time interval between first diagnosis and our evaluation was 9.7 months (range 1-60 months). Cysts were incidentally discovered in all but 3 patients, who showed mild abdominal or back pain and increased serum amylase level, respectively. The evaluation protocol included serum CA 19-9, CT scan, MRCP, and PET. Results Cysts were located in the pancreatic head in 7 cases (20%), in the body-tail in 10 cases (28.6%) and involved the entire gland in the remaining 18 cases (51.4%); cysts were multiple in all but 2 patients. PET and CA 19-9 were negative in all cases; the cysts did not exceed 30 mm in diameter except than in 2 patients, showing lesions until 40 mm: in one case we recommended surgery but the patient refused the operation, the other patient had a significant comorbidity (liver cirrhosis) entailing an increased surgical risk so we suggested a strict follow-up. After a mean follow-up of 22.7 months (range 6-60 months) all lesions were stable except than in 5 cases who showed a mild evolution: there was an increasing in the number of cysts in 3 and in their diameter in other 2 cases, but at the longest follow-up all patients still embraced criteria for conservative management. Conclusions A conservative approach seems to be justified in clinical management of carefully selected patients diagnosed with BD-IPMN; however a longer follow-up is required to confirm the safety of this protocol.

Surgically Treated IPMN of the Pancreas: A Single Institution Experience
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Context The incidence of IPMNs has dramatically increased over the past 10 years; nevertheless the clinical management of these diseases remains controversial. Aim To retrospectively analyze the results of pancreatectomies performed for IPMN of the pancreas at our Institution. Methods From 2000 to 2007, 44 patients underwent pancreatectomy for IPMN at our Institution. Twenty-two patients (50%) were males; mean age was 68.2 years. Seventeen patients (38.6%) were referred at our center after a mean time of 8.5 months from a previous misdiagnosis, most commonly with acute...
pancreatitis (4 patients; 23.5%) and chronic pancreatitis (4 patients; 23.5%). All patients diagnosed with main duct (MD-IPMN) or combined variant of IPMN with a reasonable surgical risk were evaluated for surgery. The indication for patients diagnosed with branch duct IPMN (BD-IPMN) were: clinically relevant symptoms (66.6%), elevated CA 19-9 blood levels (28.6%), lesions larger than 3 cm (14.3%) and radiologic signs of malignancy (61.9%). Nine patients (20.5%) received a pancreaticoduodenectomy, 8 (18.2%) a distal pancreatectomy, 1 (2.3%) a middle pancreatectomy, and 26 (59%) a total pancreatectomy. One patient (2.3%) required an en-bloc resection of SMV.

**Results** Cystic lesions included: 11 (25%) MD-IPMN, 12 (27.3%) combined variant IPMN, 21 (47.7%) BD-IPMN. Final pathological diagnosis was positive for adenoma in 6 (13.6%) patients, border line lesion in 11 (25%) and carcinoma in 27 (61.4%). In the carcinoma group, 13 patients (48.1%) showed positive lymph nodes and 8 (29.6%) microscopic residual disease. In the BD-IPMN group a cancer was found in 10 cases (47.6%), a border line lesion in 8 (38.1%) and an adenoma in 3 (14.3%). In 4 patients (9%) other types of tumors were synchronously present in the specimen: a neuroendocrine tumor in 3 patients (2 in carcinoma and 1 in borderline group) and a distal bile duct cancer (in borderline group). One patient died postoperatively (2.2%) and 9 (20.4%) developed post-operative complications. One patient (2.2%) required a relaparotomy for bleeding. Mean post-operative stay was 17 days. One-, 3- and 5-years survival rates for patients treated for adenoma, border line IPMN and carcinoma was 100%, 100%, and 100% vs. 100%, 85.7%, and 85.7% vs. 87.8%, 37.1% and 37.1%, respectively (P=0.02). In the carcinoma group a statistically significant advantage in survival rates was found in N0 patients on respect to N1 patients (P=0.02).

**Conclusions** The conventional sign of malignancies in IPMN branch duct seem to be useful to identify patients candidate for surgery. Even when malignant, IPMN seem to have a better prognosis than pancreatic cancer.

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**Surgical Treatment of Neuroendocrine Tumors of the Pancreas: Results and Prognostic Factors**

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**Context** Neuroendocrine tumors of the pancreas (NETP) are a rare disease usually associated with a better prognosis on respect to ductal adenocarcinoma. **Aim** To retrospectively analyze the outcome of surgically treated NETP at a single Institution. **Methods** From 2003 to 2007, 59 patients were surgically treated for NETP at our Institution. Twenty-eight (47.5%) were males; mean age was 56 years. A pancreaticoduodenectomy was performed in 11 patients, a distal pancreatectomy in 35, a total pancreatectomy in 9, an enucleation in 2 and a middle pancreatectomy in 2. Seven patients (11.8%) required a simultaneous enucleation of liver metastases and 3 patients (5.1%) a vascular resection. **Results** Mean post-operative stay was 22.8 days. Overall post-operative mortality and morbidity rates were 0 and 23.7%, respectively. Final diagnosis was insulinoma in 8 patients (13.6%), endocrine tumor in 12 patients (20.3%) and neuroendocrine carcinoma (NEC) in 39 patients (66.1%). In the NEC group 24 patients (61.5%) had lymph-nodes metastases, 3 (7.7%) microscopic margin infiltration and 13 (33.3%) liver metastases. All patients treated for insulinoma were still alive 5 years
after intervention. When comparing the group of NEC with other types of NETP we did not find any statistically significant difference in 1-, 3- and 5-year survival rates (100%, 100% and 100% vs. 94.1%, 80.6% and 80.6%; P NS); on the other hand, disease free survival (DFS) rates at the same time points were significantly different between the two groups (P=0.01). In NEC group we evaluated the prognostic implication on survival time and DFS of the following factors: residual disease, lymph nodes or hepatic metastases, gross invasion of adjacent organs, tumor diameter, angioinvasion, perineural invasion, mitoses, proliferative index, and necrosis. A significant survival advantage was found in non metastatic vs. metastatic patients (P=0.02) and in case of lack of perineural infiltration vs. infiltration (P<0.0001). In the non metastatic group a significant better survival was found comparing the absence vs. presence of perineural infiltration (P=0.008). **Conclusions** Synchronous liver metastases remain, together with perineural infiltration, a leading prognostic factor for survival in NE carcinoma of the pancreas.

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**Preliminary Experience with Intraoperative Ultrasound and Contrast Enhanced Intraoperative Ultrasound During Resective Pancreatic Surgery**

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**Context** Previous studies showed that intraoperative ultrasonography (IOUS) and contrast-enhanced intraoperative ultrasonography (CEIOUS) are useful during surgery for primary or metastatic liver tumors. **Aim** The aim of this study is to prospectively evaluate the role of IOUS and CEIOUS during resective pancreatic surgery as a tool for characterization and definition of the primary lesion and for possible detection of new liver lesions. **Methods** Twenty-one consecutive patients planned for pancreatic resection were enrolled. Seventeen patients underwent pancreaticoduodenectomy (PD), two patients central pancreatectomy and one patient distal pancreatectomy while one patient with pancreatic adenocarcinoma underwent surgical palliation for the presence of preoperatively undetected liver metastases. Thirteen patients had pancreatic ductal adenocarcinoma (13/21), three had neuroendocrine carcinoma (3/21), two had carcinoma of Vater’s papilla (2/21), one had pancreatic cystadenoma (1/21), one had carcinoma of extrahepatic bile ducts (1/21) and one had focal chronic pancreatitis (1/21).

All patients underwent IOUS and CEIOUS with intravenous injection of 4.8 mL sulphur-hexafluoride microbubbles. Size and location of primary tumor, relation to the main vessels, presence of liver metastases and multifocal pancreatic involvement were evaluated. **Results** In one patient (4.7%) with neuroendocrine carcinoma located in the pancreatic body, IOUS found a small, non palpable neoplastic nodule close to the primary tumor and resection line was extended to the left. In two patients (9.5%) three focal liver lesions were discovered at IOUS; in one case (4.7%) CEIOUS confirmed the IOUS diagnosis of liver metastasis (subsequently, no resection was performed) and in the second case IOUS suggested the diagnosis of hepatic hemangioma (confirmed by CEIOUS and histology). IOUS and CEIOUS modified the operative decision making in 9.5% of the patients in our series. In comparison to preoperative investigations, no further data were added about vascular involvement by IOUS and CEIOUS. **Conclusions** From this preliminary report, IOUS and CEIOUS seem to provide...
additional findings useful for optimizing patients’ management during surgery for pancreatic neoplasm. Our data suggest the need for further larger confirmatory studies.

**GemOx in Combination with Erlotinib (E) in Pancreatic Cancer (PC)**

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**Context** We report a case of clinical benefit and metabolic response to GemOx and E.

**Case report** In November 2007 a 48-year-old woman was admitted to the our Oncology Unit for a suspected PC with a doubtful lung lesion on the basis of a CT carried out following the appearance of the abdominal pain and alteration of CA 19-9 (1,719 U/mL). A biopsy of pancreatic lesion documented an infiltrating pancreatic ductal adenocarcinoma. In December, the patient underwent exploratory laparotomy but due to the infiltration of the main vascular structures only a diagnostic laparotomy was possible. The clinical conditions were compromised (ECOG 2). CA 19-9 was 21,890 U/mL. The patient started on a chemotherapy (CHT) with gemcitabine 1,000 mg/m\(^2\)/d1 and oxaliplatin 100 mg/m\(^2\)/d2 every 2 weeks (GemOx). After 3 cycles of CHT a CT showed a reduction in size of the pancreatic lesion (from 4.4x3.3 cm to 2.8x2.6 cm), a doubtful liver lesion, a stable lung lesion and multiple bone thickening lesions. CA 19-9 was 8,942 U/mL. In February a PET showed a hyperfixation of tracer in pancreatic head, left lung and at the level of multiple segments of bone compatible with secondary lesions. The clinical conditions worsened. Therefore, the patient started on GemOx combined with E 100 mg daily and also zoledronic acid. After 6 cycles of CHT, a CT showed an important reduction of the lung lesion, compatible with a primary neoplasm; the bone lesions were stable and the pancreatic lesion was further reduced. A subsequent PET showed a minimal residual disease at the bone level only. The clinical conditions improved significantly (ECOG 0). CA 19-9 was 1,382 U/mL. **Conclusion** This is the first case reported in literature in which the combination of GemOx and E was used.

**Src Family Kinases Regulate the mTOR Pathway in Pancreatic Endocrine Cells**

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**Context** The regulation of protein synthesis, and in particular the activation of the PI3K/AKT/mTOR pathway, is important for cell proliferation and survival and it is frequently deregulated in many types of cancers, including pancreatic cancers. Moreover, a regulated increase in cap-dependent mRNA translation also occurs during cell adhesion to the extracellular matrix (ECM). **Aim** Given the important role played by Src kinase family in pancreatic endocrine tumor (PET) cell adhesion and spreading, we set out to investigate whether these kinases modulate the activation of mTOR pathway and cap-dependent translation during cell adhesion. **Methods** We have used two PET cell lines as model systems (QGP-1 and BON). To avoid
interference by serum, we performed all the adhesion experiments on pre-coated dishes in the presence or absence of Src inhibitors. 

**Results** We observed that the rate of protein synthesis during adhesion of QGP-1 cell on FBS-precoated plates line was dramatically reduced in the presence of the Src kinase inhibitor PP2. Moreover, both PP2 and Src-inhibitor I, but not the inactive analogue PP3, strongly reduced activation of PI3K/mTOR pathway during QGP-1 adhesion on FBS-precoated plates, as monitored by phosphorylation status of the ribosomal protein S6 and 4EBP1. Similar results were also obtained on fibronectin-precoated plate, ruling out any interference of residual growth factors on serum-precoated dishes, and on poly-lysine pre-coated dishes, a Src-independent adhesion system, indicating that Src activity is required also downstream of adhesion to stimulate the mTOR pathway. Inhibition of Src-related kinases reduced also the formation of the mRNA translation initiation complex eIF4F in QGP-1 cells. On the basis of these results, we performed a microarray analysis on mRNAs purified from polysomal fraction from QGP-1 treated or not with PP2. We observed a strong reduction of the polysomal profile in cells treated with PP2. We spotlighted a group of genes whose translation was regulated by Src activity. Further experiments are ongoing to elucidate the mechanism by which Src kinases modulate the activation of TOR.

**Conclusions** The evidence that Src kinases modulate the mTOR activation and regulate the translation of a subset of mRNAs, points out a novel mechanism of regulation of translation, but it also suggests a new approach for therapies to overcome the activation of AKT caused by mTOR inhibitors. As mTOR inhibition is effective only in few types of tumors, likely because it often causes an unexpected activation of AKT, our findings may have interesting clinical consequences.

**GemOx in Advanced Pancreatic Cancer (APC): Experience in 31 Patients**

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**Context** To date, gemcitabine (GEM) remains the cornerstone of chemotherapy (CHT) for APC. According to a phase III trial the combination of GEM and oxaliplatin (OHP) (GemOx) has proven superior to GEM alone in terms of response rate (RR), time to progression (TTP) and clinical benefit (CB).

**Methods** We retrospectively analyzed a series of 31 patients affected by APC, in order to determine the impact of GemOx as first-line chemotherapy in terms of objective responses (OR) and TTP, using the Kaplan-Meier method. Among the 31 patients considered there were 20 males and 11 females (median age at diagnosis of 59.8 years; ECOG 0-2). The staging, according to AJCC criteria, was: IIB in 5 cases, III in 8 cases and IV in the 18 remaining cases. The metastatic sites were liver and lung. Six of the 31 patients underwent surgical treatment prior to CHT: 4 radically resected (R0) subsequently treated with GEM as adjuvant, and with GemOx after recurrence, and two with positive margins (R1). Twelve patients received a II line CHT after disease progression. All patients received GEM 1000 mg/m² d1 + OHP 100 mg/m² d2 every 2 weeks. **Results** Among the 31 patients, 2 had a partial response (PR, 6.5%); 7 had stable disease (SD, 22.6%); 22 patients had progressive disease (PD, 71.0%). The overall disease control rate (DCR: PR + SD) was 22.6% while the OR were 12.9%. The median survival observed was 10.8 months (95% C.I. 9.68-11.91 months) and the
median TTP was 3.46 months (95% C.I. 2.65-4.28 months). The main toxicities were: leuco-piastrinopenia, diarrhea, nausea, fever and peripheral neuropathy; 4 patients discontinued the treatment due to grade 3-4 neurotoxicity. **Conclusions** In our experience GemOx gives an improved control of APC in terms of OR and TTP, with acceptable toxicity.

**Evaluation of Intraductal Papillary Mucinous Tumors with Secretin-Stimulated MR Pancreatography**

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**Context** Intraductal papillary mucinous tumor (IPMT) is a pancreatic neoplasm with characteristic histology and distinctive clinico-biologic behavior, which is characterized by proliferation of ductal epithelium associated with ductal dilation and variable mucin production. This tumor is usually classified into 3 types: main duct, branch duct, and mixed, according to the site and extent of involvement. **Aim** Our study is aimed to assess the usefulness of secretin-stimulated MR pancreatography (SSMRP) for evaluating IPMTs. **Methods** We retrospectively analyzed 38 patients who had been diagnosed with IPMTs based on surgery or on a combination of diagnostic imaging findings (ERCP, endoscopic US, CT, and MRCP). All patients underwent MR imaging at 1.5 T (Signa EXCITE, GE Healthcare) with high performance gradients. The phased-array 8-channel body coil was used for both excitation and signal reception. A super-paramagnetic suspension (Lumirem®, Guerbet) was orally administered ten minutes before the MR examination. The MRI findings identified 30 cases of the branch duct type (14 monofocal, 16 multifocal), four of the main duct type, and four of the combined type. After secretin administration, in 25 patients a normal duodenal filling (grade 3) was observed, while in 13 patients (4 cases of the main duct type, 4 of the combined type, and 5 of the markedly diffuse branch duct type), the pancreatic fluid outflow appeared reduced, limited into the duodenal bulb (grade 1), or partially filling the duodenum up to the genu inferior (grade 2). **Conclusion** Our results show that secretin-stimulation increases the diagnostic value of MR pancreatography both in the morphological and functional evaluation of IPMTs.

**Pancreatic Fistula after Pancreaticoduodenectomy: Role of Fistulography**

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**Context** Pancreatic fistula (PF) is the most frequent complication of PD. To our knowledge, no studies in the radiology literature have ever focused attention on the
value of fistulography on patients after pancreatic surgery. **Aim** To prospectively evaluate with fistulography the radiological features of post-operative pancreatic fistula (PF) after pancreaticoduodenectomy (PD) in correlation with the clinical findings. **Methods** A prospective study was performed on the fistulograms carried out for clinical suspicion of PF after PD. Out of a total of 427 PDs performed from 2001 to 2007, 84 fistulograms were carried out. PF was clinically defined according to the international study group (ISGPF). Fistulographies permitted to determine: the site of the distal portion of the drainage, the presence or absence of connection with jejunal loop or stomach, the presence or absence of fistulous tract or fluid collections, the presence or absence of connection with the main pancreatic duct, and or the biliary tree. **Results** Forty-nine out of 84 patients (58.3%) had PF confirmed by fistulography. In 35 patients (41.6%) the drainage was abnormally placed inside the jejunal loop or stomach: in all these cases, once the drainage was mobilized, the complication resolved within 72 hours. The most important factor to distinguish the two pathological entities was the presence or absence of fistulous tract. **Conclusion** Fistulography helps in the confirmation of clinical suspect of PF decreasing post-operative morbidity and re-operation rate, and is crucial in distinguishing PF from fistulas due to the migration of the drainage into an intestinal structure.

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**Analogues of Vitamin E Epitomised by Alpha-Tochopherol Succinate (alpha-TOS) for Pancreatic Cancer Treatment: “In Vitro” Results Induce Caution for “In Vivo” Applications**

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**Context** “Mitocans” destabilise mitochondria, causing apoptogenic factors’ release. “Mitocans” include alpha-TOS, thought to be toxic only for cancer cells. **Aims** 1) To verify alpha-TOS effects on pancreatic cancer (PC) and normal cell growth; 2) to ascertain whether the combination of non toxic alpha-TOS and 5-FU dosages causes cancer cell death; 3) to obtain insights into caspase3 activation. **Methods** Five PC cell lines and normal monocytes were cultured in 1% and 10% FCS, without or with alpha-TOS (5, 10, 20, 50, 100, 200 and 500 µM), for three days. Two cell lines were treated with 5-FU (0.0001 mM) and alpha-TOS (20 and 50 µM) alone or in combination. Cell growth (XTT) and caspase3 activity (colorimetric method) were measured. **Results** In 1% FCS, 20 µM or more alpha-TOS inhibited PC cell growth (F=57.9, P<0.001, BxPC3; F=91.8, P<0.001, Panc1; F=54.4, P<0.001, SeCa2; F=48.9, P<0.001, PANC1; F=110.6, P<0.001, PSN1). In 10% FCS the same effect was obtained with higher alpha-TOS dosages (100, 200 and 500 µM). Alpha-TOS dose dependently inhibited monocytes’ growth in 1% FCS (F=110.5, P<0.001); 100 µM or more were effective in 10% FCS (F=83.8, P<0.001). PSN1 growth (F=658, P<0.001), not Capan1 (F=63, P<0.001), was delayed after non toxic 5-FU and alpha-TOS combination. PSN1 and monocytes caspase3 activity doubled after 5-FU, alpha-TOS or their combination (0.036 to 0.066 pmol/min/µg protein). **Conclusion** PC cells are sensitive to high alpha-TOS dosages, not safe for normal cells. Treatment with safe alpha-TOS and 5-FU dosages caused only a transient PC cell growth inhibition. Alpha-TOS activated caspase3 both in neoplastic
and normal cells. Our findings highlight the limitations of this molecule for “in vivo” applications and the need for searching new compounds.

**Neuroendocrine Pancreatic Tumors in MEN-1 Syndrome with Intraductal Growth into the Main Pancreatic Duct**

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**Context** The intraductal growth of a non-functioning neuroendocrine pancreatic tumor is thought to be very rare, with only other six cases described in the literature. **Case report** A 38-year-old man was referred to our institution for evaluation and treatment of an asymptomatic persistent hyperparathyroidism. The patient had a family history for MEN-1 syndrome, which was confirmed by our laboratory with the identification of a missense mutation in the MEN-1 gene (W423R). In the screening, abdominal computed tomography (CT) demonstrated multiple well-enhanced masses (the main of 1.6 mm in diameter) in the tail of the pancreas, with an interruption of the main pancreatic duct (MDP). A distal pancreatectomy (7 cm) was performed. Macroscopically, multiple hard, whitish tumors were located in the pancreatic tail. The largest one (1.1 cm of diameter and 1.8 cm of length) was restricted into the MPD, which was completely obstructed by the tumor. Histologically, thirty others major tumors, ranging from 0.2 to 1.0 cm, were observed. Immunohistochemistry showed the tumor cells to be patchy positive for glucagon, and negative for insulin, gastrin, somatostatin and pancreatic peptide. Positive immunoreactions for synaptophysin, NSE and chromogranin indicated neuroendocrine differentiation of the tumors. The postoperative course was complicated with a grade A pancreatic fistula. The patient is well and alive 6 months after surgery. **Conclusion** Intraductal growth is not peculiar of intraductal papillary mucinous neoplasms but may occur occasionally in neuroendocrine pancreatic tumors, even in patients affected by MEN-1 syndrome, causing pancreatic main duct obstruction.

**A Surgical Navigator for Laparoscopic Pancreatic Interventions**

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**Context** Surgical navigators are leading a revolution in the surgical scenario. Virtual reality reconstruction of patient anatomy, extracted from preoperative images (CT or MRI), can be fully integrated in the surgical workflow to assist the surgeon during the planning and the execution of the surgical procedure. Bringing all the diagnostic information available for a patient inside the operative room, surgical navigators improve the safety and the efficiency of surgical procedure, especially in minimally invasive interventions, and introduce big advantages for patients, surgeons and healthcare system. **Aim** In this work we present the EndoCAS Navigator, consisting in a surgical navigator we developed for laparoscopic interventions. Specific problems, related to: processing of radiologic images, intra-operative registration of virtual models with real patient position, and the integration of the system in the operative room, have been solved using an
interdisciplinary approach (engineering, radiology, surgery). **Methods** We designed and implemented a software for 3D reconstruction of abdominal structures. Taking into account anatomical and technical aspects of the whole surgical workflow (from the acquisition of radiological images up to the surgical room), we defined a procedure that allows precise intra-operative rigid registration of patient’s abdomen. **Results** EndoCAS Navigator has been used for preoperative dataset visualization and surgical planning in more than 10 interventions and it has been used to perform a laparoscopic distal pancreatectomy. **Conclusion** The use of surgical navigators significantly improves surgical performance: the 3D reconstruction of the anatomical structures is a very useful aid for preoperative surgical planning providing the surgeon a complete knowledge of the patient’s anatomy, the intra-operative assistance drastically improves orientation during intervention allowing overlay of hidden anatomies (mixed-reality) and visualization of the entire surgical scenario from several viewpoints (virtual-reality).

**Imaging of Intraductal Papillary Mucinous Tumors of the Pancreas: A Single Center Experience**

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**Context** The intraductal papillary mucinous tumors of the pancreas (IPMT) represent a challenge for the diagnostic imaging. **Aim** To prospectively assess the type and the frequency of imaging techniques for diagnosis and follow-up of IPMT. **Methods** All consecutive patients with clinical suspicion of IPMT from January 2005 to December 2007 were enrolled. The type and the results of imaging techniques were recorded at the initial study as well as in the follow-up period. The Fisher’s exact, Mann-Whitney and Pearson’s chi-squared tests were applied. **Results** Ninety-seven patients (39 males, 58 females; mean age 69.7 years) were studied. Five patients (5.2%) had IPMT type I, 67 (69.1%) IPMT type II and 25 (25.8%) had IPMT type III. The tumor was localized in the head in 32 patients (33.0%), in the body in 15 (15.5%), in the tail in 6 (6.2%), in the head-body in 8 (8.2%), in the body-tail in 10 (10.3%) and it was diffuse throughout the gland in 26 (26.8%). The size of the lesions was (mean±SD) 2.0±1.5 cm. A difference was found between the type of the lesion and the size (P=0.197). The tumors caused an atrophy of the pancreatic gland in 12 patients (12.4%), an aspect compatible with chronic pancreatitis in 7 patients (7.2%) and pancreatic calcifications were present in 7 patients (7.2%). Presence of parietal nodules was observed in 7 cases (7.2%) and wall thickness in 9 (9.3%). The imaging technique used for the initial diagnosis was the multidetector computed tomography (MDCT) in 68 cases (70.1%), colangio-Wirsung magnetic resonance (CWRM) in 27 (27.8%) and ultrasonography (US) in 2 (2.1%). Mean duration of follow-up was 12 months. Eleven patients were operated: 6 cases of IPMTs type II with morphological findings suggestive to malignancy, 4 cases of the IPMTs type III and 1 case of IPMT type I. The preferred imaging technique used in the follow-up period was CWRM (54.8% of the imaging techniques performed). **Conclusion** In our experience the MDCT is the technique of choice for the diagnosis of the IPMT, whereas the CWRM is the preferred imaging technique for the follow-up.
Pancreaticoduodenectomy Is a Feasible Procedure in Octogenarians
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Context Pancreaticoduodenectomy is still a challenging surgical procedure, because of its technical difficulties, its high morbidity and mortality rate (about 20% in low-volume centers). Therefore, in many centers, the indication to perform pancreaticoduodenectomy is on principle excluded in elderly patients, depriving them of a chance for cure. Aim To assess the short-term outcome after pancreaticoduodenectomy in elderly patients. Methods In our department, from January 2000 to December 2007, 529 patients underwent pancreaticoduodenectomy, either for benign or malign disease. The following data were collected prospectively in the departmental database: age, gender, weight loss, preoperative serum albumin, tibc and hemoglobin concentration, disease, intraoperative blood loss, transfusions, length of stay, complications, re-operation, and mortality. According to age, patients were then divided in three different groups: <70 year-old (Group A, n=345), 70-80 year-old (Group B, n=156), ≥80 year-old (Group C, n=28). Results The mean±SD age of patients in the different groups was: group A: 57.7±9.7 years; group B: 73.3±2.4 years; group C: 81.8±1.8 years. The three groups were homogeneous according to gender (P=0.2) and preoperative nutritional status (minimum P=0.34). In the group A there was a significant lower rate of patients with malignant disease (73.3% vs. 88.4% in the group B and 100% in the group C; P<0.0005). Intraoperative blood loss and transfusion rate were not significantly different in the three groups. In groups A, B and C, the morbidity rate was 54.8%, 62.8% and 57.1%, respectively, without any significant difference (P=0.24). Considering the singular complications, we found a significant higher UTI and pneumonia rate in the elderly patients (P=0.02 and P<0.0001, respectively). Moreover, mortality and re-operation rate did not vary among the different groups. Finally, postoperative stay was not significantly longer in elderly patients (group A: 17.0 days, group B: 18.1 days, group C: 18.9 days; P=0.37). Conclusion Pancreaticoduodenectomy is a feasible procedure in elderly patients and must be considered a curative option even in octogenarians. Selection of the patients should be based on the presence of co-morbidity factors, not on age.

The Unaspected Outcome of a Locally Advanced Pancreatic Cancer Treated with RFA and …
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Context Patients affected from locally advanced pancreatic carcinoma have a very poor prognosis. Till now the association of chemo and radiotherapy (CT/RT) is the only option for stage III and IVa. The need for a challenging solution is strong. Applying radiofrequency (RFA) to obtain a cytoreductive effect on a primitive pancreatic cancer could represent the first step of a multidisciplinary new approach. Case report A 77-year-old man with diagnosis of 4 cm ductal carcinoma of the uncinate process involving the superior mesenteric vessels (SMVs) and the duodenal wall underwent explorative laparotomy confirming the preoperative staging. RFA of the lesion was
done under US guide. Severe pancreatitis occurred after surgery and thrombosis of portal vein was incidentally detected by CT scan. Duodenal bleeding due to RFA induced necrosis of the tumor occurred and it was completely treated by endoscopy. One month later the patient underwent to re-laparotomy because of stenosis of the duodenum: the same surgeon who performed RFA observed a significant downstaging of the pancreatic tumor and a duodenopancreatectomy was carried out. Histology of the surgical specimens describes very few neoplastic cells in a 2 cm hard area of the uncinate process with a minimal involvement of the resection margins. Then the patient received CT/RT. He is now in good condition; one year follow-up is negative for local recurrence or metastasis. **Conclusion** Radiofrequency ablation (RFA) of locally advanced pancreatic carcinoma is a new application of a standardized technique. Too high temperature can lead to thermal injury of duodenum and pancreas itself other than thrombosis of portal vein. The procedure, because of its cytoreductive intent, has to be associated to CT/RT to be complete. This is the only existing histology of a pancreatic cancer treated with RFA.

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**3D In Vitro Model of Pancreatic Ductal Adenocarcinoma: New Strategy to Study Pancreatic Ductal Carcinoma**

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**Context** 2D monolayer has been the most popular *in vitro* model for pancreas cancer research. 2D monolayer model are easy and convenient to setup, however it lacks 3D co-localization. This fact could affect data reliability *in vitro* studies. **Aim** The purpose of this works has been to begin to build a model *in vitro* using a primary cellular culture of PDAC. **Methods** A 3D model of PDAC was obtained by culturing PP244 cells inside 3D porous scaffolds based on poly-vynil alcohol (PVA) and gelatin (G). PVA/G (80/20, wt/wt) sponges were fabricated via emulsion-freeze drying, cut into discs (8 mm diameter, 1.5 mm thickness) and sterilized with ethanol washing. Such scaffolds offer a highly porous and hydrophilic environment allowing cell 3D colonization and survival *in vitro*. Then PP244 cells were seeded both on the scaffolds and on 24 well plates as (as standard 2D models) at a seeding density of 250,000 cells/sample and cultured with RPMI medium for one week. At the end-point, cell growth of both 3D and 2D samples was quantitatively evaluated and compared using the Alamar Blue (AM) (Serotec Ltd, UK), a cellular metabolism-based assay. Samples were incubated for 3 h in culture medium containing AM dye and the supernatants were read with a spectrophotometer (at both 600 and 570 nm). Measurements were performed in triplicate and quantitative data were obtained following the manufacturer’s protocol. Afterwards, 3D constructs were washed in PBS, fixed with 10% formalin and paraffin embedded following standard tissue protocols to detect the features of cancer cells by hematoxylin and eosin coloration into slices of sponge. **Results** we found many cancer cells attached in the sponge. The findings of the cellular metabolic growth assay resulted in a metabolic ratio of 1.38±0.004 (3D/2D models). This can be caused by a rise in either cell metabolism or cell number in the 3D model. **Conclusion** After these preliminary results we think that it...
is possible to build a 3D model of PDAC in vitro. This new scaffold could present better information than 2D monolayer model. In the next future we will investigate different biological and molecular aspects in PDAC cells grown in this scaffold and compare it with traditional cell cultures.

Detection of Pancreatic Islet and Beta-Cell Surfaces in Diabetic Mouse Model: A Quantitative Computerized Approach
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Context The quantitative analysis of immunohistochemical data is still largely difficult and uncertain. In particular, the evaluation of the percentage of endocrine immunoreactive cells in pancreatic tissue appears to be troublesome and often misleading, because the count of positive cells is very time-consuming and the variability in staining intensity is not usually taken into account. Aim To improve the current methods of morphometric analysis applied to the immunohistochemical evaluation of functional beta cell mass in a murine model of type 2 diabetes and to test the effect of the treatment with a new antioxidant agent (IAC, Medestea). Methods Total neuroendocrine surface (TNS), total beta cell surface (TBCS) and islet number (IN) were determined by a morphometric analysis (MA) program (Analysis b, Olympus) on paraffined pancreas tissue sections stained with hematoxylin (blue) and conjugated anti-insulin antibody (brown) (Histomouse kit, Zymed) from four groups of mice: controls (C), diabetics (D), diabetics treated with low IAC dose (T2) and diabetics treated with high IAC dose (T3) (n=4 for each group). By using this program, it was possible to calculate all surfaces (µm²) on the basis of the color (blue or brown). The statistical analysis was performed by GraphPad program (n=4, paired Student’s t test, 95%CI, P<0.05). Results MA revealed that T2 and T3 mice had significantly higher values with respect to D mice in terms of IN, TNS and TBCS. No statistical differences were found when C vs. T2, C vs. T3 and T2 vs. T3 were compared. The mean number of islets/mm² (MI) was as follows: C=0.64, D=0.35, T2=0.79 and T3=1.05. To assess accurately the functional beta cell mass, we calculated a neuroendocrine functional index (NFI) as the product MIxTBCS. In the different mice groups, NFI was: C=0.46, D=0.19, T2=0.55 and T3=0.65. We also considered the number of duct-associated islets (i.e. islets located at a distance of less than 100 µm from the pancreatic ducts), on the basis of the hypothesis that neo-formed islets might originate from duct cells. We observed indeed a greater number of duct-associated islets in T2 and T3 mice than in D or C mice (C=4.0, D=2.75, T2=8.25, and T3=12.0). Conclusion By using such methodological approach, it has been possible to calculate the real neuroendocrine and beta-cell surfaces present in this experimental model and to document statistically significant differences between treated and untreated mice. Altogether our data point out that the IAC is able to preserve the integrity of neuroendocrine tissue.
Laser Microdissection (LMD) and Primary Cell Cultures Improve Pharmacogenetic Analysis in Pancreatic Adenocarcinoma, Allowing the Use of Gene Expression Levels and WHO Grading as Prognostic Markers

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Context Research on pancreatic adenocarcinoma (PDAC) is focusing on new techniques to tailor gemcitabine and 5-fluorouracil treatments. Availability of tumor tissue is critical for the accurate assessment of gene expression and LMD and primary cell cultures may be useful tools to separate tumor cells from the stromal reaction. Aim The purposes of this study were: 1) to address the genetic profile relevant to drug activity; and 2) to evaluate differences between microdissected and non-microdissected tumors, normal tissues, and primary cell cultures. Methods Quantitative-PCR of 7 key genes was performed on mRNA from 113 microdissected, 28 non-microdissected tumors, a pool of normal tissues and 4 established primary cell lines. Protein expression was evaluated by western blot and immunocytochemistry, cytoxicity by MTT. Results LMD allowed the analysis of 110 samples and revealed significant differences in mRNA levels between microdissected tumors and normal tissues, as well as between non-microdissected and relative microdissected tumors. In contrast, the cells showed similar expression profiles with respect to their respective microdissected tumors. Gene expression profile differed significantly between WHO grade 1/2 (n=48) and grade 3 (n=33) tumor samples. Indeed, human equilibrative nucleoside transporter-1 (hENT1) mRNA levels in WHO grade 3 specimens re significantly lower with respect to those measured in grade 1/2 PDAC. Several studies demonstrated that histopathological grading could be useful for predicting prognosis in PDAC patients, and, in view of the relevant role of hENT1 in the response to gemcitabine, these results suggest that drug sensitivity profile may change with respect to histological grade of neoplasms. The multivariate analysis performed showed that both disease grading and hENT1 expression are significant independent prognostic factors of PDAC. Furthermore, expression levels of hENT1 and thymydilate synthase were significantly related to gemcitabine and 5-fluorouracil cytotoxicity. Conclusions LMD is a reliable technique for mRNA extraction, and allows the detection of significant differences in the expression of target genes with respect to non-microdissected specimens and normal tissues. Expression levels in microdissected tumors are similar to those observed in primary cell cultures, both at mRNA and protein level, and are related to chemosensitivity, suggesting the use of these ex vivo models for molecular analysis to implement the clinical management of PDAC.

Duplications of PRSS1 Gene in Italian Patients Affected by Idiopathic Chronic Pancreatitis

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Context We can have duplications of chromosomal tracts that generate an increase of gene dosage. These copy number mutations have been described in PRSS1 gene (cationic trypsinogen gene) in French families affected by hereditary pancreatitis (with absence of gene PRSS1, SPINK1 and CFTR mutations) and in 6% of French patients affected by idiopathic pancreatitis. Aims To determine the number of PRSS1 gene copies in Italian subjects with idiopathic chronic pancreatitis and in healthy control subjects. Methods We analyzed 123 DNA samples of idiopathic chronic pancreatitis and 110 healthy control subjects. The study of PRSS1 gene was performed by spectrophotometry, electrophoresis and direct sequency. In order to evaluate PRSS1 duplications or triplications we performed quantitative PCR real time with SYBR green. The difference between control gene and PRSS1 dosage has been evaluated by ΔΔct (cycle threshold) method. Results have been evaluated by allelic frequency calculation (Hardy-Weinberg law). Results Only in one patient with idiopathic chronic pancreatitis we found a PRSS1 duplication. No copy number mutation is present in the control group. Conclusions The PRSS1 copy number increase causes a gain of gene dosage with a consequent imbalance of pancreatic proteases. This gain dosage can explicate the onset of pancreatitis also in presence of normal trypsinogen protein. These genic aberrations have to be tested in all familial pancreatitis negative for PRSS1, CFRT, SPINK1 mutations and in idiopathic pancreatitis.

Functional Results After Pancreatectoduodenectomy
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Context From 01/01/1994 to 01/01/2008, 85 patients in our institution underwent radical pancreatic-duodenectomy for malignant and benign pancreatic disease. Aim To evaluate the pancreatic remnant exocrine function in terms of elastase digestion and alpha tocopherol metabolism in long survivors. Methods Thirty-two long survivor patients (15 reconstructed by Wirsung-gastric anastomosis and 17 by Wirsung-jejunal anastomosis) underwent fecal elastase dosing. Results have been compared to a 10-patient control group. We also evaluate the seric lipidic antioxidants, tissutal concentration of alpha tocopherol and the efficacy of alpha tocopherol supplementation. Results The fecal elastase was higher in long survivor patients reconstructed by Wirsung-jejunal anastomosis. Antioxidant dosing before and after supplementation showed no differences between the two groups. Conclusions Exocrine function is better preserved by Wirsung-jejunal reconstruction. Antioxidant absorption after pancreatoduodenectomy is reduced, particularly for carotenoids. Tissutal antioxidant concentration is reduced. Even after supplementation antioxidant increasing is less than expected. Functional damage is not related to the method of reconstruction.
PPP-Syndrome (Panniculitis-Polyarthritis-Pancreatitis): A Case Report

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**Context**
Steatonecrotic (lobular or nodular) panniculitis and polyarthritis may rarely complicate a pancreatic disease; this association is defined PPP-syndrome and is characterized by relevant morbidity and mortality. Panniculitis is related to subcutaneous (liquefactive) fat necrosis with secondary skin changes due to the local activity of pancreatic enzymes released during different pancreatic diseases (inflammatory, acute and chronic, and neoplastic). The reported incidence of association of panniculitis and pancreatitis is 2-3% of all pancreatic diseases while the complete PPP-syndrome is reported in very few cases. Polyarthritis is preferentially symmetric with more frequent involvement of legs and arms and negativity of serum rheumatoid-factor.

**Case report**
A 48-year-old female was admitted in hospital because of a dull upper quadrant abdominal pain, nausea and vomiting. Few days before she suffered from articular pain localized at shoulders, radiocarpic and metacarpo-phalangeal joints with functional impairment and nodular slight painful cutaneous nodular dyscromic lesions at legs level. Past history showed polycystic kidney disease with arterial hypertension and progressive renal failure requiring dialysis during the last 14 months. She also suffered from recurrent abdominal pain radiated to the back from several years, partially responder to analgesic treatment. Two years before she underwent cholecystectomy because of gallstones; pancreatic calcifications were discovered at this time by CT scan. After cholecystectomy, abdominal pain recurred with the same characteristics. The patient was teetotaler. During hospitalization the patient underwent an extensive diagnostic work-up, including full laboratory and instrumental exams and cutaneous biopsy. Treatment consisted of nutritional support together with oral anti-inflammatory drugs (coxibs). The patient was discharged at the 25th day of hospitalization without abdominal and joints symptoms. Final diagnosis was “recurrence of chronic calcifying idiopathic pancreatitis with tail pseudocyst, steatonecrotic nodular panniculitis and polyarthritis (PPP syndrome)”.

Quality of Life in Long-Term Survivors After Pancreaticoduodenectomy

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**Context**
Few data are available in literature about quality of life (QoL) in long-term survivors after pancreaticoduodenectomy (PD).

**Aim**
To evaluate QoL and long-term outcomes in patients who underwent PD for any reason between 1990 and 2003 at the Department of Surgery of the University of Verona with a minimum follow-up of 48 months.

**Methods**
Among 268 patients identified, 168 were still alive. One-hundred and nine (65% of them) agreed to participate (median FU of 7.5 years) and were interviewed with the EORTC QLQ-C30 Questionnaire, and with an institutional questionnaire on long-term complications.

**Results**
Pylorus-preserving pancreaticoduodenectomy (PPPD) was performed in 75% of cases. 56 patients (51.5%) had malignant
neoplasms, 23 (21%) borderline tumors, and 30 (27.5%) benign neoplasms. Intraductal papillary mucinous neoplasms (IPMNs) was the most common indication for surgical resection (27.5%) followed by ductal adenocarcinoma (12%). Postoperative complications were found in 63 patients (58%). Overall, 75% of patients reported good scores in their perception of QoL. A significant decrease in QoL was found in four categories of patients: patients with malignancy, with IPMNs, in survivors >10 years, and in those who experienced postoperative complications (P<0.05). Despite no significant differences in overall QoL perception, Whipple resection was more frequently associated with alterations of functional and symptomatic domains than PPPD. Overall, the 55% of patients complained steatorrhea, the 40% dumping syndrome, the 54% weight loss. Dumping syndrome was not significantly associated with Whipple procedure, while weight loss was more frequently observed after pancreate-gastrostomy than pancreate-jejunostomy. New endocrine insufficiency was found in 17% of cases. Recurrent abdominal pain was found in 41% of patients; these patients reported also a significant impairment of QoL. Conclusions PD is associated with acceptable QoL over time. However, a careful long-term follow-up is necessary given to the significant rate of exocrine insufficiency rate and impairments in digestive function. Patients with complicated postoperative course, malignancies, IPMNs and who underwent PD with pancreategastric anastomosis are at higher risk of long-term complications and QoL impairments.

Diagnostic Role of [18F]-FDG-PET/CT in the Preoperative Evaluation of Pancreatic Lesions
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Aim The aim of this study was to preoperatively evaluate the usefulness of PET/CT with [18F]-FDG, in patients with pancreatic masses suspicious for malignancy, after conventional imaging investigation. Methods We consecutively studied 27 patients which were referred to our PET centre, in order to metabolically characterize pancreatic masses suspicious for malignancy. All patients underwent a whole-body PET/CT scan followed by biopsy, surgery and/or clinical follow-up. PET images were qualitatively evaluated by two independent nuclear medicine physicians; PET findings were compared with biopsy, surgery and/or clinical follow-up. Results Out of the 27 included patients we had 12 benign and 15 malignant masses (12 adenocarcinomas, 2 lymphomas, 1 carcinoid). PET study correctly identified 11 out of 15 malignant masses (10 adenocarcinomas and 1 lymphoma), while it was negative in the other 4 cases (2 adenocarcinomas, 1 lymphoma and 1 carcinoid; sensitivity 73.3%). PET study was negative in the 12 patients with pancreatic benign lesions (specificity 100%). PET accuracy was 88.4%. Conclusion: according to our findings, [18F]-FDG PET/CT study shows high accuracy in the preoperative metabolic characterization of suspected pancreatic lesions.
Asymptomatic Pseudocyst of Pancreas: A Strange Case of Undifferentiated Carcinoma
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Context Pancreatic pseudocysts are usually identified by radiological findings such as pseudo-wall and necrosis according to anamnesis of severe acute pancreatitis. We present a case of large pseudocyst of pancreas in an asymptomatic 61-year-old man with diabetes and weight loss. Case report We report a case of a 61-year Caucasian male admitted to our Department with diagnosis of asymptomatic 8 cm pseudocyst. His medical history is negative for surgical operations, cardiopulmonary and previous metabolic diseases or alcohol abuse. The patient presented weight loss (10 kg in 3 months) and decompensated diabetes. He underwent ultrasound, CT scan and MRI who showed 8 cm pseudocyst of pancreatic body-tail involving the posterior gastric wall and splenic vessels with necrosis inside. CEA and CA 19-9 serum level were negative. We performed endoscopy who revealed gastric ulcer. Because of poor symptoms we performed endoscopic ultrasound and oral contrast-enhanced CT scan who revealed little increase of wall thickness and migration of oral contrast from stomach to pseudocyst. Endoscopic FNA of ulcer margins revealed the presence of undifferentiated carcinoma. The patient underwent surgery and submitted to distal pancreatectomy, splenectomy, total gastrectomy and also right adrenalectomy because of suspect of neoplastic involvement. The postoperative course was characterized by acute pancreatitis with peritoneal abscess treated with endoscopic drainage and broad-spectrum antibiotics. The patient was discharged after 24 days. The pathological findings showed undifferentiated carcinoma involving pancreatic body-tail and gastric body with unknown origin. Conclusion We reported a case of asymptomatic undifferentiated carcinoma hidden by large pseudocyst. In case of asymptomatic pseudocyst further investigations are mandatory in order to evaluate eventual neoplastic etiology.

Pancreatic Carinoma Disappeared After Radiofrequency Ablation: A Case Report
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Context Radiofrequency ablation (RFTA) is a standard procedure in unresectable liver tumors. In literature there is only few experiences related to RFTA in pancreatic solid tumor. We reported a case of complete treatment of unresectable pancreatic carcinoma after radiofrequency ablation associated to adjuvant therapy. Case report We report a case of 56-year Caucasian female admitted to our Department with diagnosis of unresectable pancreatic carcinoma. Medical history was negative for surgical operations, cardiopulmonary and previous metabolic diseases. The clinical course started with epigastric pain associated to hyperglycemia initially treated with diet and hypoglycemic drugs. She underwent ultrasound and abdominal CT-scan who showed a 5.5 cm mass of pancreatic body-tail involving celiac axis and mesenteric superior artery. FNA was
positive for pancreatic carcinoma. CA 19-9 serum level was 343 U/mL. The patient underwent explorative laparotomy who confirmed the unresectability. She was submitted to RFTA (105°C for 12 minutes) of the mass with final good sonographic effect. The clinical course was uneventful and she was discharged after 9 days. Radiology before discharge revealed necrosis of pancreatic site of ablation without peritoneal fluid or splenoportal thrombosis. After treatment she was referred to oncologist for chemotherapy and radiotherapy. After the treatment MRI and CT scan did not reveal tumor residual. After 6 months of follow-up she is free of disease also confirmed with PET. **Conclusion**

Standard approach of unresectable pancreatic tumors is relied to oncological approach with chemotherapy and radiotherapy with poor prognosis. Radiofrequency ablation is usually performed in primitives or metastatic hepatic tumors with good results in terms of survival. In literature radiofrequency ablation of pancreatic mass is uninvestigated. We have reported one of our clinical cases of experimental use of RFTA in unresectable cancers. RFTA must be considered one step in multimodal treatment. Further studies are mandatory to assess prognostic impact and timing of association with standard palliative approach.

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**Pancreaticoduodenectomy with Mesentericoportal Vein Resection: Safe and Worthwhile?**


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**Context** Malignancies of the peri-ampullary region are characterized by early local extension to contiguous structures, so the mesentericoportal vein is early involved. Historically, the inability to separate the tumor from the portal vein (PV) during surgery has been considered a contraindication to resection. Frequently, isolated local invasion of the PV is the only obstacle to curative resection. Experienced centers have suggested that combined resection of the pancreas and PV could be performed with acceptable mortality and survival results comparatively to PD without mesentericoportal vein resection (MVR). **Aim**

In the present report we investigated morbidity and mortality after PD with or without MVR in patients with malignancies of the pancreas and peri-ampullary region at the General Surgery III - Liver and Lung Transplant Unit of Ospedali Riuniti of Bergamo. **Methods** From October 1997 to May 2008, 144 patients underwent a laparotomy for tumors of the pancreas or peri-ampullary region. Total obstruction of the mesentericoportal vein shown in the preoperative imaging was considered as a contraindication for curative surgery. The decision to do a PD with MVR was made intraoperatively. **Results** During surgery, the involvement of the mesentericoportal vein was observed in 21 patients (14.6%). Ten of them (47.6%) underwent a PD with MVR. In 6 patients we did a complete resection of the mesentericoportal vein and the reconstruction was done using an homograft (in one of them the resection and reconstruction of the superior mesenteric artery was also performed). Four patients had a partial resection of the PV which was reconstructed without an homograft. The resected endothelia or margins of blood vessels were tumor free in 8 cases. The postoperative mortality was 0%. The morbidity rate was high (75%) but with no significant difference with the group underwent PD without MVR. The 3-year survival was significantly higher in the PD with MVR group than that in
palliative surgery for vascular invasion group (45% versus 0%, log rank P=0.02). **Conclusions** Mesentericoporal vein resection is safe and worthwhile: no increase in mortality and better 3-year survival rate.

**Duct-to-Mucosa Pancreaticojejunostomy**


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**Context** Pancreaticoduodenectomy (PD) is the only potential cure for peri-ampullary tumors. Whereas, in the last two decades, the mortality rate associated with PD has dramatically decreased and is approaching zero at high volume centers, the morbidity rate remains high (30% to 50%). Pancreatic anastomotic leakage is the most important technique-related complication after PD its incidence, ranging from 2% to 51% and may be a significant cause of operative mortality. In recent years, the “duct to mucosa” (DM) technique of pancreatico jejunostomy (PJ) is reported to effectively prevent this complication. **Aim** In this study we retrospectively compared the outcomes of PD performed with two different techniques of PJ at our institution. **Methods** From October 1997 through May 2008, 91 patients underwent PD. The PJ was performed with the conventional invagination technique in all cases performed until December 2005 (Group A) and with DM in all cases performed afterwards (Group B). Demographics, clinical and surgical details were collected from the medical charts. **Results** There were 62 males and 29 females with a median age of 66 years. In 84 (92.3%) of them the indication for the procedure was a malignancy (54 pancreatic, 21 ampullar and 9 distal bile duct adenocarcinomas). In 70 cases (76.9%) the pylorus was preserved. Seventy-two patients were in Group A (57 end to end, 15 end to side) and 19 in Group B (20.8%). Pancreatic anastomotic leakage was reported in 16 patients (17.6%), all of them were in patients in group A (22.2%) whereas none was reported in Group B (P<0.01). There were 8 postoperative deaths (6.6%); all of them were in group A (8.8%), no postoperative mortality was observed in Group B (P NS). The overall survival for patients with a malignancy was 84.6%, 44.1% and 28.7% at 1, 3 and 5 years, respectively with a median follow-up of 17.6 months (range: from 6 days to 10 years) and with no significant difference between the two groups. **Conclusions** Although retrospective and on a limited series, our results confirm the superiority of the DM technique. In our experience its introduction was related with the disappearance of leakages and postoperative mortality. DM technique can be used with ducts of any size duct and any consistency of pancreas.

**Insulinomas in Multiple Endocrine Neoplasia Type 1 (MEN-1): Up-Dated Surgical Approach**

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**Context** Insulinoma is a frequent functioning pancreatic endocrine neoplasia (PENs) in MEN-1, occurring in about 15-20% of all affected patients. Since in these cases multiple
pancreatic lesions are often present, which diagnostic procedure and which surgical approach are hotly debated. **Aim** To evaluate the efficacy of pre- and intra-operative diagnostic tools in MEN-1 associated insulinomas and the strategy for complete resection of pancreatic lesions. **Methods** Seven MEN-1 patients were referred to our Surgical Unit (1992-2008) and were operated for hypoglycemic crisis along with hypergastrinism in 3 patients, and/or with non-functioning PENs in 6 patients. Preoperative tumor localization was carried out using ultrasonography, computed tomography, endoscopic ultrasonography (EUS) and somatostatin receptor scintigraphy. Intraoperative ultrasonography (IOUS) and intraoperative insulin measurement by rapid assay were also employed. **Results** All pancreatic lesions larger than 0.5 cm were removed by resection of the most affected pancreatic regions and in least affected regions by enucleation of nodules (4 patients). Two pancreaticoduodenectomies and 5 distal pancreatectomies were performed, with no postoperative mortality. EUS was the most sensitive preoperative imaging technique (sensitivity 71%), while IOUS proved to be the most sensitive overall (86%). Intraoperative insulin assay predicted outcome in all patients. At a mean follow-up of 66 months, all patients were normoglycemic with no evidence of disease recurrence. **Conclusion** MEN-1 insulinomas should be considered surgically curable diseases. Pancreatic resection is preferable to a less radical surgical approach in ensuring higher cure rates with limited morbidity. The type of pancreatic resection should be chosen depending on the localization of the PENs, their relationship with the Wirsung duct and the presence of other duodeno-pancreatic lesions. IOUS and intraoperative insulin assay may be of value both in surgical decision-making and in the evaluation of the surgical cure.

**Early and Late Complications in Spleen Preserving Distal Pancreatectomy with Splenic Vessels Sacrifice. A Single Centre Experience**

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**Context** Spleen preservation during distal pancreatectomy for benign tumors is considered the gold standard operation to surgically cure the patients. In order to keep the spleen vascularized it is possible to resect the pancreatic tail with splenic vessels preservation (SVP) or to sacrifice the splenic vessels (SVS) using the circulation of the short gastric vessels (Warshaw’s technique). Early and late complications of SVS are not well known yet. **Aim** The aim of this study was to review our experience with SVS spleen preserving distal pancreatectomy. **Methods** A retrospective analysis of all patients undergone to spleen preserving distal pancreatectomy with SVS was performed. All data regarding operative procedures and outcome were prospectively recorded since 2002. All patients were directly contacted and invited to clinical visit with follow-up ended on June 2008 with execution of contrast enhanced MSCT or MRI and blood examination. **Results** Eight patients undergone to SVS spleen preserving distal pancreatectomy. One patient had undergone to splenectomy for splenic infarction on 3rd post-operative day, one patient with a regular postoperative course died for lung cancer during the follow-up and no data are available regard late complications. Among 6 patients
still alive only 3 run the follow-up. Their blood examination revealed thrombocytopenia in 2 of them and at radiological imaging all 3 had gastric varices. All patients are still working with 100% PS and completely asymptomatic. Conclusion In our experience, SVS spleen preserving distal pancreatectomy had determined early complication such as spleen infarction and as late finding perigastric varices associated to thrombocytopenia without clinical symptoms. This technique should not be applied as routine procedure. A case control study involving SVP spleen preserving distal pancreatectomy is warranted.

Cystic Lesions of the Pancreas: Preliminary Evaluation of the Appropriateness of $^{18}$F-FDG PET Imaging in Surgical Decision Making


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Context Positron emission tomography with $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG PET) is extensively employed in oncologic field. However, surgical treatment for pancreatic solid lesions is recommended based on long-validated criteria, which do not include this diagnostic tool, while clear indications for excising cystic lesions remain elusive. Aim Our aim was to conduct a preliminary evaluation of the appropriateness of $^{18}$F-FDG-PET in the surgical decision making on pancreatic cystic lesions. Methods We analyzed images from 34 consecutive patients, undergoing whole-body PET scan, one hour after injection of about 370 MBq of $^{18}$F-FDG. Standardized uptake values (SUV) were calculated as ratios of radioactivity in the lesion of interest to the injected dose normalized by body weight. Eleven patients had solid lesions together with a cystic component. Two of them died before surgery. They had undergone PET with positive findings (SUV=6.5-16.0). Nine patients underwent surgical excision. Six had carcinoma, two had low-grade neuroendocrine lesions, and one had a pseudo-papillary tumor. Results PET was positive in four carcinoma, and negative in all other cases. Twenty-three patients showed cystic lesions of benign or unclear nature on anatomic imaging. Based on the overall clinical evidence, ten of these lesions were not operated, and are undergoing follow-up. $^{18}$F-FDG-PET was negative in all of them. Thirteen lesions underwent surgical removal. Histology was malignant in 2, uncertain in 2, and benign in 9 cystic lesions. PET was positive in one of the two carcinomas (SUV=7.3), and in 3 of the 9 benign lesions (SUV=4.7-7.0). It was negative in 6 of 9 benign, in 2 uncertain, and in 1 malignant lesion. Thus, in all 23 cystic lesions, the false positive and false negative rates of $^{18}$F-FDG-PET were 75% and 5-16%, respectively. Conclusion Our preliminary collection indicates that $^{18}$F-FDG-PET has poor positive, and acceptable negative predictive values in cystic lesions. Our data confirm the inappropriateness of $^{18}$F-FDG-PET in the detection of low-grade neuroendocrine neoplasms.
Role of Radiation Dose in Unresectable Pancreatic Cancer
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Context In pancreatic cancer treatment, the role of radiation dose is controversial owing to the risk of GI toxicities. Aim To investigate the impact of radiation dose on local control (LC), time to progression (TTP) and overall survival (OS), in treatment of locally advanced pancreatic carcinoma (LAPC). Methods Patients with LAPC treated in our institution were considered in this retrospective analysis. All patients underwent external radiotherapy (dose range: 40-60 Gy) associated with either 5-FU or gemcitabine. A group of patients also received an additional radiation boost using brachitherapy low dose rate (dose: 20-50 Gy), brachitherapy high dose rate (dose: 20 Gy), extracranial stereotactic radiotherapy (range dose: 20-25 Gy) and intraoperative radiotherapy (dose: 10 Gy). The total radiation dose delivered was calculated in terms of equivalent dose in 2-Gy fraction (EQD2). Two groups of patients were considered according to EQD2 received: group A (EQD2 equal or major than 60 Gy) and group B (EQD2 inferior than 60 Gy). The prognostic impact of EQD2 on LC, TTP and OS was investigated at the univariate and multivariate analysis. Results Between 1991 and 2007, 90 patients (median age: 63 years, range 34-76 years) with LAPC (cT4, n=33; cT3, n=57; N1, n=50) were treated in our institution. Group A was made of 36 (40%) patients, group B of 54 patients (60%). Among group A, 17 (18.8%) patients received a radiation boost using special techniques. Three patients (3.3%), treated only with external radiotherapy up to 60 Gy, developed late toxicity. No late toxicities were observed in patients who received the boost with special techniques. Median OS was 11 months (range 2-52 months); median TTP was 6 months (range 1-51 months); median LC was 9 months (range 1-51 months). Statistically significant differences were observed between the two different groups in terms of LC (P=0.026), TTP (P=0.001) and OS (P=0.003) at the univariate analysis. At multivariate analysis, T stage, N stage, concomitant chemotherapy, ECOG PS and EQD2 were evaluated. Concomitant chemotherapy and EQD2 showed to be significantly related to OS (P<0.05). Also the total EQD2 showed a trend of significance on LC (P=0.09). Conclusions The total radiation dose evaluated in terms of EQD2 seems to be effective in treatment of LAPC. To deliver higher radiation dose, special techniques could be safely employed.

Problem in Diagnosis and Intraoperative Treatment in Case of Rare Peripancreatic Tumors

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Context Surgical resection of pancreatic tumors is still related with relevant risk of morbidity and mortality so that it is to perform only if really needed. The rate of blind resection should be minimized. Both intraoperative surgical evaluation and biopsy sometimes does not clear the doubts concerning diagnosis and true origin of the tumor. In rare situations, like the presented one, extremely rare tumors could be resected.
without performing unnecessary pancreatectomy. **Case report** A 62-year-old man was admitted at our department for head trauma due to motor bike fall. Brain CT scan and blood exams were normal, but abdominal ultrasound revealed a 11x14 cm large mass in the upper abdomen, pressing and shifting the neighboring organs. Thoraco-abdominal CT scan confirmed the mass suggesting its from the head of the pancreas but with unclear borders and with involvement of the retroperitoneum. No invasion of organs or the portal vein was apparent but more caudally mesenteric veins were displaced suggesting the presence of a capsule. Distant metastases were excluded. Serum tumoral markers, esophagogastroduodenoscopy and colonoscopy were normal. Elective surgery was performed and a round tumor 15 cm in diameter was found in the upper abdomen showing an evident capsule. The entire tumor accurately prepared following the plane of the capsule and could curatively resected with oncological criteria leaving intact the entire pancreas. The mass was hardly stuck to the origin of the mesenteric vein and hepatic artery so it was needed to resect the artery and tangentially the vein. The histopathological evaluation was extremely difficult and interdepartmental second opinion, finally conclusive diagnosis was: well differentiated neuroendocrine tumor of the retroperitoneum with unclear malignancy. **Conclusion** The diagnosis of a retroperitoneal mass involves several problems about the origin especially if it seems to develop from the pancreas. In these cases pancreatic resection could be the best surgical option, but in some case a planned pancreatico-duodenectomy could result an over treatment. In pancreatic surgery intraoperative decision can result challenging and related also to unknown difficult histopathological diagnosis.

**Early Fractalkine Receptor (CX3CR1) Activation in Pancreatic Ductal Adenocarcinoma Is Associated with Local Neural Invasion**

**Context** Ductal pancreatic adenocarcinoma (PAD) expresses chemokine receptors, which can promote migration, invasion and metastasis. The fractalkine receptor CX3CR1, involved in vascular and neural adhesion, is a candidate mediator for PAD neural and vascular invasion (NI and VI, respectively) which contributes to its poor outcome. In addition, as CX3CR1 allelic variants exhibit different adhesive properties, individual genotypes (T280M, V249I) might confer different chemotactic drive to PAD. **Aims** To assess whether: 1) PAD expresses CX3CR1; and 2) neural and/or vascular invasion correlates with CX3CR1 expression and genotypes. **Materials and methods** The study series included 85 consecutive pancreatic cancers (65 PAD, 14 ampullary, and 6 endocrine), of known stage (TNM classification), grade, VI (29 PAD+), and NI (27 PAD+). Fifteen PAD specimens also contained early ductal neoplastic lesions (pancreatic intraductal neoplasia, PanIN). CX3CR1 expression, assessed by immunohistochemistry, was scored as negative/low (L) and high (H), and CX3CR1 was genotyped at codons 249 and 280. **Results** Thirty (46%) PAD showed H-CX3CR1, but 2 (14%) ampullary (P=0.02), and 0 endocrine (P=0.03) cancers did. In the 15 PAD with PanIN (13 H-CX3CR1), the H-expression rate increased from normal ducts and PanIN1 (19/66, 29%), to PanIN2 (27/41, 66%) and PanIN3 (29/38, 76%) (P<0.001). NI
was seen in 15 (50%) H- and in 12 (34%) L-
CX3CR1 PAD (P=0.02), while no difference
was observed as to VI and CX3CR1
expression. Among 25 PAD with no lymph
node metastasis (N0), NI was present in 8 of
12 (75%) high- but in 3 of 13 (23%) L-
CX3CR1 (P=0.03). Out of 36 non-VI PAD,
only 4/18 (22%) L-CX3CR1 had NI, vs. 12/18
(67%) H-CX3CR1 (P=0.007). In 15 N0, non-
VI PAD, 6 of 7 (86%) H-CX3CR1 cancers
showed NI, vs. 0/8 L-CX3CR1 ones
(P=0.001). CX3CR1 variants at codon 249
(hetero/homozygous) were associated with a
lower frequency of NI, which occurred in
only 2/14 (14%) PAD patients with such
genotypes, as compared to 16/35 patients
(46%; P=0.03) with no variants. **Conclusions**
With respect to pancreatic tumors, CX3CR1
expression increases selectively in PAD, and
anticipates malignant transformation and
invasion, potentially contributing to
neoplastic progression. Our data also suggest
that H-CX3CR1 participates to PAD NI early,
before lymph node and VI. CX3CR1
contribution to local PAD progression and NI,
possibly depending upon specific genotypes,
deserves further attention in the light of its
pharmacological blockade as a potential tool
in this disease marked by a doom prognosis.

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**Subcellular Immunohistochemical Localization of Somatostatin Receptor SSTR2A in Endocrine Pancreatic Tumors: A Critical Methodological Approach**

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**Context** Neuroendocrine tumor of the pancreas (NET-P) are rare and with elusive
clinical behavior. There are several therapeutic options for NET-P: surgery,
chemotherapy, and biotherapy. The latter includes somatostatin analogue
administration, both in medical treatment and as radio-labeled agents. The rationale for
somatostatin analogue treatment is the presence of somatostatin receptors (SSTR) on
the surface of tumor cells. Of the six SSTR subtypes, SSTR 2A is the most important for
its high overexpression in tumors and its high affinity for the clinically available
somatostatin analogues. Specific anti-SSTR antibodies for immunohistochemistry (IHC)
have been recently developed and some are now commercially available. Previous reports
on IHC-SSTRs in NE are limited and generally there is a lack of standardization.
Recently, a scoring system has been proposed in the analysis of IHC-SSTR 2A
interpretation. Until now, limited data exists on the distribution of SSTR 2A in NET-P as
well as on their correlation with clinic-pathologic findings. **Aim** to define in a
routine series of NET-P the feasibility of IHC SSTR2A evaluation and the immunostaining
pattern comparing the results with the main clinical-pathologic parameters and outcome.

**Method** After methodological setting by
testing SSTR-2A-Ab, 20 consecutive cases of
surgically treated NET-P (functioning and
non functioning) were analyzed for
immunohistochemical expression and
distribution. **Result** All cases, except one,
were SSTR2A positive, characterized
simultaneously by both membranous and
cytoplasmatic staining. No cases showed only
cytoplasmatic pattern. The positivity was
heterogeneous. Major IHC disadvantages
were related to the lack of standardization of
the method (from both technical and
interpretation viewpoints), difficult to applied
scoring system, as well as, interpretation of
heterogeneous pattern of reactivity.
Conclusion IHC represents a reliable and useful method to characterize SSTR 2A expression in NE-P tumors; accurate methodological conditions and standardized IHC methods are needed; a membranous as well as cytoplasmic pattern are obtained; the use of a standardized scoring system for IHC is encouraged in order to better predict clinical response to somatostatin analogue therapy, although further validation on large series is needed.

Laparoscopic Approach for Treatment of Distal Pancreatic Tumors
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Context The role of minimally invasive techniques in pancreatic surgery remains controversial although laparoscopic resection of the distal pancreas for benign or endocrine lesions has become routine in expert centers.

Aim Aim of this study is to evaluate the results of the laparoscopic approach for the treatment of distal pancreatic tumors.

Methods From January 1993 to June 2008, 18 patients underwent laparoscopic enucleation (EN) in 8 patients (2 males, 6 females; median age 40.8 years, range 25-54 years) and distal pancreatectomy (DP) with spleen preservation in 10 patients (3 males, 10 females; median age 47.4 years, range 20-70 years) in our Department. Tumor pathology in all patients who underwent enucleation was insulinoma, with a median diameter of 1.2 cm (range 0.5-2 cm). Patients who underwent distal pancreatectomy with spleen preservation had a mucinous cystic neoplasm (5 patients) and a serous cystadenoma (4 patients). The histological examination of the last patient is on going. Results Mean operative time from skin incision to skin closure was 94.3 min (range 80-110 min) in the EN and 164 min (range 90-240 min) in DP. Intraoperative bleeding occurred in 4 cases and was effectively dealt with by laparoscopy. No conversions to open surgery occurred. Minor morbidity was observed in 2 patients (25%) who underwent enucleation, including pancreatic fistula (n=1) and abdominal collection (n=1). Mean hospital stay was 6.8 days (EN) and 6.5 days (DP), respectively. Mortality was nil. At a median follow-up of 53 months (range 93-14 months) no recurrences were observed. Conclusions The laparoscopic approach to distal pancreatic tumors is feasible and safe, provided the necessary experience and technology are available, and it allows to reduce the hospital stay with excellent cosmetic results.

Magnetic Resonance Cholangiopancreatography in Asymptomatic Pancreatic Hyperenzymemia
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Context It has been reported that most of the subjects with asymptomatic pancreatic hyperenzymemia (APH) have pancreatic lesions at magnetic resonance (MR) [1, 2].

Aims The aim of this study is to compare the type and frequency of pancreatic lesions detected by MR in our study group with those of these two earlier studies. In addition, we
also attempted to establish whether there is a relationship between the pancreatic lesions and the hyperenzymemia by measuring serum pancreatic enzymes for five consecutive days. Our rationale was that if enzyme levels vary widely and normalize from day to day, the enzyme elevations are not likely related to pancreatic lesions. **Methods** During the period from January 2005 to May 2008, 62 healthy subjects with chronic APH (40 M, 22 F; mean age 45 years, range 22-70 years) were studied. All underwent MR of the abdomen including the pancreas. In addition, serum amylase, pancreatic isoamylase, and lipase were determined for five consecutive days. **Results** In the vast majority of cases (n=56, 90.3%) MR showed a normal pancreatic parenchyma and a normal Wirsung duct. In the remaining 6 cases (9.7%) the following alterations were found: pancreas divisum in 2 subjects, aspecific Wirsung alterations in 3, and a small (5 mm) intrapancreatic cyst as a solitary finding in one. In these 6 last subjects, as in the others with no pancreatic lesions, pancreatic hyperenzymemia was highly variable from day to day, with frequent normalizations. **Conclusions** The results of this study indicate that most of the subjects with APH seen by us do not have pancreatic lesions detectable by MR. In the few cases in whom a lesion was found, as in the other cases without lesions, the great variability and the frequent normalization of serum enzyme levels tend to exclude that there is a relation between the pancreatic lesions found and the hyperenzymemia.

**References**


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**Beneficial Effect of a Non-Peptidyl Low Molecular Weight Radical Scavenger on Cultured Human Islets Function**


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**Context** During the isolation and culture processes, islets are subjected to severe adverse conditions that impair survival and ultimately contribute, in case of transplant, to graft failure. **Aim** The aim of this study was to culture the islets for 7 days from isolation, with or without a new antioxidant called Iacvita (IAC), to reduce oxidative stress and ameliorate islet function. **Materials and methods** For this study eight pancreases from multiorgan donors (age: 49±16 years; 4M/4F; BMI: 25.6±2.5 kg/m²) were used. Islets were cultured in M199 culture medium containing, or not, 10 µmol/L IAC. Then, islet function, viability and redox balance were determined. **Results** Apoptosis increased significantly in islets cultured for 7 days (0.78±0.07 OD au, by ELISA technique) respect to fresh islets (Ctrl, 0.14±0.01 OD au, P<0.05). In IAC exposed islets, apoptosis was lower in respect to islets cultured for 7 days without IAC (0.58±0.02 OD au, P<0.05). The EPR technique evidenced a significant increase of oxidative stress after 7 days of culture (nitroxide levels: 8.53±2.18 OD au), respect to Ctrl (5.32±6.22 OD au). Seven days incubation with IAC determined a reduction of oxidative stress, as evaluated by nitrotyrosine concentration, respect to non-treated islets (1.71±0.62 and 5.96±2.1 nmol/L, P<0.01). In Ctrl, expression of scavenger genes was: Mn-SOD: 4.5±0.7; Catalase:
1.5±0.6; Cu/Zn-SOD: 24.9±3.8; and GSH-px: 3.5±1.1. Following 7 days IAC exposure, there was a significant increase in mRNA expression for all genes studied: Mn-SOD: 7.8±1.4; Catalase: 4.3±1.1; Cu/Zn-SOD: 48.1±6.7; and GSH-px, 37.2±13.9 (all P<0.01). This was paralleled by the significant increase of intracellular GSH in islets exposed to IAC (6.4±0.8 µM/mg protein), respect to Ctrl (2.1±0.1 µM/mg protein) (P<0.01). Oxidative stress reduction was associated with a significant amelioration of glucose-stimulated insulin secretion in islets exposed to IAC (Simulation Index, SI: 2.2±0.27), respect to Ctrl (SI: 1.8±0.25) (P<0.01). Conclusions IAC, for its antioxidant properties, could represent a potential therapeutic tool for the pre-transplant culture of human islets in human islet trials.

A Prospective Randomized Study on the Safety of Precut Papillotomy with Analysis of the Factors Associated to the Development of Complications During ERCP

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Context Needle knife precut papillotomy is employed as a rescue technique when conventional methods fail to gain biliary access at ERCP. Precut is often regarded as an unsafe procedure carrying increased complications rates, mainly pancreatitis. Many authors suggest, however, that the high complications rate is likely to be determined not by precut per se, but by the several attempts to cannulate the papilla that precede precutting. Aim This is a prospective randomized study aiming at evaluating the safety of precut papillotomy and the factors associated to the development of complications. Methods Patients undergoing ERCP, in which after 10 minutes the cannulation in the conventional methods failed, were prospectively randomized in two groups: group A (n=27) that immediately underwent precut, and group B (n=26) in which cannulation was attempted for at least 10 further minutes before the endoscopist was free to decide to perform precut or to continue in the conventional method. Incidence and severity of pancreatitis, hyperamylasemia and other complications were recorded, as well as factors associated with their development. Results The two study groups were similar in term of age, sex, and indication to ERCP, and risk factors for pancreatitis. Cannulation was successful in all patients but 3 (94%). Precut was performed in all patients of group A and in 17/26 (65%) of B. Incidence of pancreatitis was 0/27 in group A and 4/26 (15%) in group B (P<0.05). Amylase levels increased of 309.2±516.5 in group A and 1,106.7±2,076.3 in group B (P<0.05). No differences were observed for the other complications (abdominal pain: 4 vs 2; hemorrhage 1 vs 0; perforation 0 vs 1). Number of attempts to cannulate the papilla and number of pancreatic duct injections were significantly higher in group B. Conclusions Precut papillotomy is a safe procedure which does not bring an adjunctive risk of developing pancreatitis and other complications. Pancreatitis is likely to develop as a consequence of the many attempts to cannulate the papilla and of pancreatic duct injection, while does not seem to be correlated to precutting per se.
Evaluation of VEGF-A, IL-6 and TNF-alpha Polymorphism Frequencies in Patients with Pancreatic Cancer

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Context Pancreatic adenocarcinoma (PK) is characterized by a wide variety of molecular alterations such as mytogen and angiogenic growth factors and their receptors over-expression. VEGF-A is an important angiogenesis and vessels permeability regulator. Several studies on mice models showed that suppression of its expression reduced pancreatic cancer cells tumorigenicity. VEGF was found to be over-expressed in various cancers and this was associated with a worse prognosis. Other molecules play a key role in neo-angiogenesis and in the maintenance of an inflammatory status which is associated to a higher probability of cancer development and a worse evolution; they are IL-6 and TNF-alpha. Elevated serum levels of these molecules were found in various cancers with high rates of metastatization, PK included. Genetic polymorphisms consisting of a single nucleotide substitution in the promoter or coding region, can influence the expression or function of these molecules. They have been associated also to susceptibility and development of various diseases, cancer included. Aim We wanted to evaluate the possible association between functional polymorphisms of VEGF-A, IL-6 and TNF-alpha and the susceptibility to the development of PK and the aggressiveness of the tumor. We considered VEGF polymorphisms in the position C-460T of the promoter region and in the position G+405C and C+936T in the 5'UTR and 3'UTR regions of the gene which regulate the cytokine production and its function, respectively. We also evaluated the polymorphism in the position C-174G of the promoter region of IL-6 and in the position G-308A of the promoter region of TNF-alpha. Methods VEGF-A, IL-6 and TNF-alpha were evaluated using ARMS-PCR (refractory mutational system) and RFLP (restriction fragment length polymorphism) methods on DNA extracted from whole blood from 48 subjects suffering from PK and from 20 slices of paraffin embedded tissue samples from subjects with PK. Results Preliminary results due to the construction of apolotypes formed considering the different polymorphisms studied, do not show a statistically significant association with grading and susceptibility to cancer development when compared to a control group (120 normal subjects). Immuno-histochemical analysis revealed positivity for VEGF-A, indicating a strong inclination to tumoral neo-angiogenesis of PK. Conclusion The enrollment in the study of a higher number of patients could modify the trend observed until now, and this is suggested by a P value close to significant. Of certain interest will be to consider also genetic polymorphisms on genes coding for VEGF-A, IL-6 and TNF-alpha receptors.

In Dubiis Abstine. Protease-Activated Receptor 2 in Macrophage-Monocyte During the Progression of Acute Pancreatitis:
Hints From Two Different Experimental Models

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Context Proteinase-activated receptor-2 (PAR-2) belongs to a family of G protein-coupled receptors activated by tethered ligand sequences within the N-terminal. It is known that one of the pancreatic enzymes, trypsin, modulates many biological processes by acting on specific PAR-2. PAR-2 is distributed throughout the gastrointestinal system including the pancreas and may be involved in the inflammatory process of acute pancreatitis (AP). It is uncertain whether pancreatic PAR-2 plays a protective or an injurious role in acute pancreatitis. Aim The aim of this study is to attempt further insights into the role of PAR-2 in acute pancreatitis in two different experimental AP rat model. Methods We induced mild pancreatitis by using cerulein to induce acute edematous pancreatitis (AEP) and severe pancreatitis by using DL-ethionine and a protein-deficient meal to induce acute necrotizing pancreatitis (ANP). Gabexate mesilate (GM) (10 or 30 mg/kg) was injected intraperitoneally to the AEP rats every 12 hours to investigate the effects of protease inhibitor on pancreatitis and PAR-2 activation. Camostat mesilate (CM) (200 mg/kg) was orally administered to ANP rats every 24 hours. Results Immunoreactive PAR-2 was most prominent in ED1-positive macrophages/monocytes in ANP and infiltration of PAR-2-positive macrophages was significantly inhibited by CM (200 mg). PAR-2-positive macrophages/monocytes were observed in AEP. Plasma IL-8 levels increased in ANP and were inhibited by CM. Amylase secretion from acinar cells was elicited in a dose-dependant manner by SLIGRL-NH2, an amino-terminal residue of PAR-2-tethered ligand, indicating that PAR-2 may exist in acinar cells and may mediate amylase secretion. Conclusion Contrary to very recent findings in PAR-2 knockout mice, our present studies in vivo would suggest that the PAR-2 system of macrophages/monocytes is indeed activated and involved in the exacerbation of acute pancreatitis, presumably via release of cytokines such as IL-8.

Autoimmune Pancreatitis: A Case Report
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Context Autoimmune pancreatitis (AIP) is characterized by some clinical (the clinical picture of autoimmune pancreatitis is not characteristic: obstructive jaundice, abdominal pain, and weight loss are frequently observed), serologic (elevated serum IgG4 immunoglobulin concentrations), morphologic (association of diffuse enlargement of the pancreas and irregular narrowing of the main pancreatic duct), and histopathologic features (lymphoplasmacytic infiltration with high level of IgG4, interstitial fibrosis, periductal inflammation and periphlebitis). Apart from pancreatic manifestations, other organs may also be affected, thus associations with sclerotising cholangitis, sialoadenitis, retroperitoneal fibrosis, Riedel thyroiditis and inflammatory bowel diseases have been described. Based on these findings, autoimmune pancreatitis should be regarded as a manifestation of systemic IgG4-related sclerosing disease. AIP responds dramatically to steroid therapy. It is important not to misdiagnose pancreatic cancer as AIP, and not to misdiagnose AIP as pancreatic cancer. Case report A 48-year-old male patient came to our attention for obstructive jaundice and abdominal pain. The patient had no history of alcoholism or gallbladder lithiasis. The CT showed a small pancreatic mass involving and stenotizing the bile duct. The endoscopic retrograde cholangiopancreatography cytological brushing has not shown signs of malignancy.
No other organs were involved. The intraoperative histology did not reveal signs of cancer. The patient was treated with biliary derivation for the stenosis. The postoperative course was regular, and 8 days after the intervention he was discharged. The histology reveals lymphoplasmacytic infiltration with high level of IgG4, interstitial fibrosis, periductal inflammation and periphlebitis. **Conclusion** It is very important to consider the possibility of an autoimmune pancreatitis in every patient with pancreatic masses or biliary obstruction, and the specific signs should be carefully searched. In these patients the steroid treatment could prevent an aggressive intervention, with high morbility and mortality. However, the use of steroid may result in delaying pancreatic cancer surgery, which could lead to cancer progression in several cases. Therefore a correct diagnosis is essential for the selection of the patients who undergo to medical therapy.

### The Clinical Challenge of Autoimmune Pancreatitis

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**Context** A small percentage of pancreatic masses resected for suspected malignancy are found instead to be a form of chronic pancreatitis characterized by a lymphoplasmacytic IgG4+infiltrate and a high serum IgG4 concentration, named autoimmune pancreatitis. The five cardinal features of autoimmune pancreatitis are: characteristic histology, imaging, serology, other organ involvement, and response to steroid therapy. **Aim** In this study we try to identify some clinical and pathological features linked to autoimmune pancreatitis in our patients. **Methods** Between 2000 and 2007, 62 consecutive resections for pancreatic masses were performed. Histopathological resected specimens and clinical features of the patients were retrospectively studied. **Results** In two cases (3.2%) a chronic pancreatitis was found, instead of cancer. Radiological and endoscopical imaging did not show specific signs. Clinically, in both cases, there were obstructive jaundice, abdominal pain and weight loss, symptoms not different from the cancer group. Histology showed characteristic features, as lymphoplasmacytic infiltration (with high level of IgG4), interstitial fibrosis, periductal inflammation, and periphlebitis. No other organs were involved. Serologically, the serum IgG4 concentrations were elevated in just one of the two patients, but they were elevated in two patients of the cancer group. **Conclusion** In our patients there were not radiological and clinical features of autoimmune pancreatitis, and no other organ were involved. Generally the characteristic signs of an autoimmune pancreatitis were not so easy to find and should be accurately searched. In front of pancreatic masses the possibility of an autoimmune pancreatitis should be always considered.

### Diagnostic Value and Safety of Ultrasound-Guided Pancreatic Biopsy in Pancreatic Masses

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**Context** To plan the treatment of choice in patients with suspicion of pancreatic cancer, especially in those considered not resectable, the percutaneous US-guided biopsy can be...
considered a good option for obtaining histological diagnosis of the solid pancreatic masses. **Aim** To investigate the sensibility (SE), specificity (SP), positive predicting value (PPV), negative predicting value (NPV), and safety (rate of complications) of this procedure. **Methods** Twenty-two patients with a solid pancreatic mass who underwent US-guided pancreatic core biopsy from 2006 to 2008 were included in the study. There were 10 (45.5%) males and 12 (55.5%) females with a mean age 69.5±12.4 years. The tumor was located in pancreatic head in 20 cases (90.9%) and in the body-tail of the gland in 2 (9.1%). Tumour size was 37.4±14.2 mm. Core biopsy was performed with a 18-Gauge needle (Biomol, Hospital Service®) in order to obtain both pathological and cytological specimens. We used an Iu22 ultrasound apparatus with a 1-5 MHz convex probe equipped with a guide attachment. The biopsy was performed with continuous real-time monitoring. The most appropriate approach was chosen after local sterilization with povidone-iodine, which was also used as contact medium for ultrasound. The insertion of the biopsy gun through the skin was done under local anesthesia (Ethyl Chloride®). Tissue core specimens were immediately fixed in 10% formalin, then the residual tissue was put in two different glass slides; thin smears were also prepared and one slide was fixed with isopropyl alcohol and the other with polyethylene glycol. Each pathological specimen was evaluated by two different and dedicated pathologists (one for core biopsy and one for cytologic materials). In most of the cases one (n=19) or two (n=3) passes were carried out. **Results** In all 22 cases we obtained an adequate tissue and cytological sample. The final pathological diagnoses were pancreatic adenocarcinoma in 77.3% of the cases (17/22), neuroendocrine tumors in 13.7% (3/22) and in the remaining two cases breast metastasis (4.5%) and chronic pancreatitis (4.5%). SE, SP, PPV and NPV of core biopsy evaluation were 95%, 100%, 100%, and 50%, respectively. SE and PPV of pancreatic cytologic evaluation were 55% and 96%, respectively; SP and PVN were 0%. No major complications and seeding were observed after the procedure. Pain, defined as the need of analgesics after the procedure, was observed in 27.3% of the patients (6/22). **Conclusion** Ultrasound-guided percutaneous pancreatic biopsy is an effective and safe approach to obtain a diagnosis of pancreatic cancer. As expected, core biopsy evaluation is better than cytological evaluation.

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**Histological, Immunohistochemical and Ultrastructural Features of Pancreatic Islets in a New Murine Diabetes Model with Reduced Beta Cell Mass After Treatment with a Novel Antioxidant Agent**

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**Context** A new mouse model of type 2 diabetes with reduced beta-cell mass and moderate hyperglycemia, has been previously established. As oxidative stress is considered a major mechanism of progressive beta-cell loss in diabetes, we have tested in this model the protective effects of a novel antioxidant agent (IAC, Medestea), obtaining a persistent reduction of hyperglycemic levels. **Aim** To investigate the morphological features of this mouse diabetes model by using light and electron microscopic techniques and to provide insights into the mechanisms of the long lasting protection exerted by IAC. **Methods** Male C57Bl/6 mice were given streptozotocin (STZ, 180 mg/kg i.p.) and...
nicotinamide (NA, 200 mg/kg i.p.); two weeks later, diabetic mice were administered different daily doses of IAC for 5 weeks. Six weeks after the end of IAC treatment, fragments of pancreas were fixed and processed as appropriate for light or electron microscope (EM) analysis. Suitable sections were prepared for ematoxylin-eosin and immunohistochemical staining as well as for EM studies. Results IAC-treated diabetic mice showed a significant reduction of hyperglycemia which persisted after suspension of the treatment. Morphometric evaluation of immunohistochemical analysis revealed that untreated STZ-NA mice had a consistent 20-30% reduction of islet number (IN), total neuroendocrine surface (TNS) and total beta-cell surface (TBCS) with respect to controls. IAC treatment (at both doses of 15 and 30 mg/kg) significantly reversed these changes (P<0.001 for IN, P<0.002 for TNS, and P<0.004 for TBCS, versus untreated STZ-NA mice; no statistical difference versus controls for all parameters). Furthermore, ultrastructural analysis confirmed reduction in beta-cell number and insulin granules in diabetic mice and showed the presence of collagen bundles and amyloid fibrils within the islets. IAC treatment clearly improved ultrastructural alterations. Conclusion In the STZ-NA murine model of type 2 diabetes, the new antioxidant compound IAC was able not only to counteract beta-cell dysfunction and loss associated with oxidative stress but also to reconstitute beta-cell population. Studies are in progress to clarify the underlying mechanisms of such finding, which might open unexpected perspectives in the cellular therapy of diabetes.
5.6, P=0.0009) and 3.3 (95% CI: 1.8-6.2, P<0.0001), respectively. Five-year OS was 17.7% (median: 19 months). The univariate analysis revealed that neither tumor size nor residual tumor after surgery, nor the lymph nodal status were significantly related to OS, whereas the Cox regression, showed that positive lymph nodes and the timing of ERT significantly affect OS, with a HR respectively of 1.6 (95% CI: 1.1-2.3, P=0.008) and 1.4 (95% CI: 1.1-1.8, P=0.008). Patients who remained recurrence-free for more than 2 years achieved a prolonged survival (3- and 5-year OS were 31.9% and 28.4%, respectively, compared to 11.9% and 0 for patients who locally recurred within the first two years from IORT) (P=0.04).

**Conclusions** This analysis examined the broader series ever collected on IORT in pancreatic cancer treatment. Although these results suggest that ERT may contribute to increase the effects of IORT, the 5-year LC of 23.3% and OS of 17.7% seem to confirm the beneficial “sterilizing” effect of IORT on the tumor bed in the patients who had a lower trend to metastasize.

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**Multidetector CT Assessing Neuroendocrine Pancreatic Neoplasms**

**Nature. Comparison with Histological Findings**


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**Context** Neuroendocrine pancreatic neoplasms are rare tumors, which therapeutic approach mainly depends on their clinical and morphological presentation. CT study of neuroendocrine pancreatic neoplasm can evaluate the lesion nature and thus the eventual surgical treatment. **Aim** To evaluate the role of multidetector CT in assessing the nature of neuroendocrine pancreatic neoplasms. **Methods** We analyzed 53 lesions in 34 patients (3 patients had 15, 5 and 2 lesions, respectively). CT was performed before and after 120 mL iodine contrast medium intravenous administration (5 mL/min) in early arterial (15’), pancreatic (30’), venous (70’) and delayed (180’) phases. Three different post-contrastographic patterns were identified: pattern A, including lesions with “early arterial” or “pancreatic” enhancement (15”/30”) and rapid wash-out; pattern B, including lesions with early wash-in and no wash-out and lesions with enhancement only in the “delayed” phase. CT findings were compared with pathological results after surgery. **Results** At histopathology, 24 lesions resulted to be benign, 20 malignant and 9 borderline. At CT, 29/53 lesions showed pattern A (average dimension 14 mm); at histopathology 23 out of 29 resulted to be benign (diameter <2 cm in all cases), 1 malignant (12 mm) and 5 borderline (all <2 cm). Pattern B included 24/49 lesions (average dimension 42 mm); at histopathology 17 out of 24 resulted to be malignant (≥2 cm in all cases; average dimension 45 mm), 4 borderline (average dimension 18 mm) and 1 benign (15 mm). Pattern A showed a positive predictive value (PPV) of 80% in predicting neuroendocrine pancreatic lesions benignity, while pattern B showed a PPV of 79% in predicting malignancy. **Conclusion** Multidetector CT may suggest the nature of neuroendocrine pancreatic neoplasms on the basis of their enhancement pattern. Our series confirm that lesions with diameter greater than 2 cm should be suspected to be malignant.
Predictive Value of Multidetector CT in Determination of Pancreatic Cancer Resectability

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Context Surgeons should be aware that they can increasingly depend on multidetector CT in order to determine the most rational approach in the surgical management of ductal adenocarcinoma of the pancreas. Aim To evaluate the predictive value of multidetector CT in determining surgical resectability of pancreatic cancer. Materials and methods We evaluated 82 patients with ductal adenocarcinoma of the head/uncinate process of the pancreas submitted to surgery. At CT we analyzed the following criteria: vascular encasement, retroperitoneal infiltration, metastases and peritoneal carcinosis. Basing on these analyses we identified 3 different groups of patients: resectable patients (all negative findings); questionably resectable patients (absence of carcinosis and metastases, suspicion of retroperitoneal infiltration or venous infiltration eligible to vascular resection); unresectable patients (metastases and/or carcinosis and/or arterial encasement and/or venous encasement not eligible to vascular resection and/or retroperitoneal macro-infiltration). Pathologic reports and intraoperative findings were considered as the “gold standard”. Results Pancreatic resection was performed in 54 patients, while 28 patients were submitted only to an intraoperative exploration. CT obtained a sensitivity of 66%, 14%, 78%, and 96% in detecting metastases, carcinosis, vascular, and retroperitoneal infiltration, respectively. Thirteen out of 17 patients judged at CT as questionably resectable, underwent pancreatic resection. Considering patients judged as resectable or unresectable at CT, we obtained 90% of sensitivity, 93% of specificity, with a positive predictive value of 93% and a diagnostic accuracy of 90%. Conclusion Multidetector CT can provide valuable preoperative prediction of surgical resectability not only in patients with negative findings but also in the cases judged as questionably resectable.

Accuracy of Imaging Pre-Surgery TNM Stadiation in Funtional and Nonfuntional Pancreatic Neuroendocrine Tumors

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Context TNM staging of pancreatic neuroendocrine tumors including a grading system. Aim Aim of this study is to determine the accuracy of pre-surgery imaging in the stratification of patients with functional and nonfunctional pancreatic neuroendocrine tumors. Methods One-hundred and 71 patients that underwent pancreatic surgery between 1990 and 2004 and with last imaging follow-up made in November 2008 were included in this retrospective study. All patients had histological diagnosis of pancreatic neuroendocrine tumor. All patients underwent pre-surgery ultrasound (US), computed tomography (CT) and magnetic resonance (MR) imaging with TNM stadiation. Survival, defined as time between surgery and death or end of follow-up, was evaluated. Correspondence between predicted survival and observed survival was evaluated.
**Results** Pre-surgery imaging TNM stadiation was quite in agreement to anatomo-pathological gold standard. TNM imaging stadiation was correct in 136 patients (79.5%), was over-estimated in 12 patients (7%) and under-estimated in 23 patients (13.5%) (kappa of concordance equal to 0.645). Association of imaging stadiation with tumoral grading, evaluated with Ki-67 index, had a concordance index of 0.80 (P=0.037).

**Conclusions** TNM imaging stadiation associated with Ki-67 grading index can be considered useful in pre-surgery stratification of patients with functional and nonfunctional pancreatic neuroendocrine tumors.

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**Acinar Cell Carcinoma of the Pancreas: Experience on Nine Cases**

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**Context** Acinar cell carcinoma (ACC) is a rare neoplasm of the exocrine pancreas, representing 1% of primitive pancreatic tumors. Its clinical and biological features and information regarding prognosis and treatment options are unclear. **Aim** To report our experience on nine consecutive cases of ACC observed at a single institution. **Methods** The San Raffaele Scientific Institute Pancreatic Surgery database was reviewed from 1990 to June 2008, and a retrospective analysis was performed for ACC cases histologically diagnosed and surgically treated in that period. **Results** Nine patients were identified, six males and three females, with a median age of 59 years. All patients presented with abdominal pain, nausea and asthenia, and no evidence of lipase hypersecretion syndrome; one patient only showed jaundice. Preoperative cytologic diagnosis was obtained in two cases by EUS-guided FNAB. In two patients the neoplasm was located in the head of the pancreas, in six in the body-tail, and in one the whole pancreas was involved. Each patient underwent surgical resection, including 6 distal pancreatectomies, 2 pancreaticoduodenectomies and one total pancreatectomy. In two cases an associated resection was necessary (one liver and one gastric resection). Median tumor size was 8.3 cm with three patients found to have stage IIA disease, four patients with stage IIB, and two patients with stage IV. Immunohistochemical studies showed in all cases a positivity for chymotrypsin while proving negative (or with focal positivity) for chromogranin and synaptophysin. Four patients underwent postoperative chemotherapy. Five of the nine patients developed recurrent disease (four in the liver and one gastric). Overall median survival was 21.4 months (95%C.I.: 13 to 29.6 months) and median disease-free survival was 19 months. Survival rates at 24 and 36 months were 50% and 25%, respectively, with three patients alive in June 2008. **Conclusion** Acinar cell carcinomas are rare, aggressive and little-known neoplasms, usually diagnosed in an advanced stage. Mostly, they are distally located. Survival is slightly better than that of ductal pancreatic carcinomas. Local aggressiveness is frequent and it does not exclude surgical resection. The role of adjuvant treatment should be better investigated.
Multifocal Intraductal Papillary Mucinous Neoplasms (IPMN) of the Pancreas from Mild Dysplasia to Invasive Carcinoma: A Case Report

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Context IPMNs are pancreatic neoplasms characterized by a wide spectrum of histological lesions ranging from adenoma to invasive carcinoma. We report the case of an elderly patient who underwent a distal splenopancreatectomy for multifocal IPMNs evolved to invasive carcinoma. Case report The patient was a 84-year-old female in excellent conditions, who came to our observation with aspecific digestive symptoms. Tumor markers were as follows: CEA 9.1 ng/mL (reference range: 0-4.6 ng/mL), CA 19-9 720 U/mL (reference range: 0-37 U/mL). Abdominal ultrasonography and CT showed multiple cysts of the whole pancreas and a cancer of the tail without evidence of nodal and distal metastases. Echodendoscopy confirmed the multifocal neoplasia and the biopsy evidenced an invasive carcinoma of the pancreatic tail. In November 2006 the patient underwent distal splenopancreatectomy. The intraoperative ultrasonography confirmed the preoperative findings of multiple cystic lesions of the whole pancreas and permitted to include in the specimen a 2-cm cyst of the isthmus. The histological examination showed an invasive, moderately differentiated carcinoma of the tail with areas of undifferentiated neoplasia and of squamoid differentiation; the carcinoma infiltrated the fibroadipous peripancreatic tissue, but without evidence of regional nodal metastases; a multifocal IPMN was evident in the remaining tissue, with broad histologic spectrum ranging from dysplasia to carcinoma in situ; the 2-cm cyst of the isthmus near the resection margin was a IPMN with non-invasive carcinoma. The post-operative course was uneventful ant the patient was discharged 14 days later. Nineteen months later the patient is in excellent conditions, disease free and with normal levels of CA 19-9. Conclusion We report a patient with multiple IPMNs during the different histological phases of tumoral progression up to infiltrating carcinoma. The surgical indication was set in consideration of the limited extension of the neoplasia without nodal metastases at pre-operative evaluation. In such cases the long term prognosis can be favorable, even in properly selected elderly patients.

Looking at an “Evidenced Based Fast Track” Pancreatic Surgery: Results of a Randomized Clinical Trial

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Context In a previous study [1] we showed that the amylase value in drains (AVD) after pancreatic resection was a predictive factor of postoperative pancreatic fistula (PF) development; in fact, AVD in post-operative day one (POD1) greater than 5,000 U/L is the only significant predictive factor of PF development; therefore, we established this cut-off as the “reference point” in PF prediction. Others [2] demonstrated that early removal of drains on POD4 is an independent factor for reducing the incidence of abdominal complications, while patients with drains still in place after POD8 had a
significantly higher incidence of abdominal complications (P<0.001) and PF (P<0.001). **Aim** To demonstrate that early removal of drains reduces complications in pancreatic resective surgery. **Methods** On this base we planned a randomized clinical trial in patients undergoing to pancreatic surgery, in our institution. The cases with “low risk” (AVD in POD1 ≤5,000 U/L) were randomized to remove drains on POD3 (group A, early drains removal) versus POD 5/6 (group B) that was our usual removing time. Between March 2007 to April 2008 we prospectively randomized all 114 patients with AVD in POD1 <5000 U/L (59% of all resections) in group A (n=57, 50%) and in group B (n=57, 50%). The outcome of the two groups was than compared. **Results** The two groups were homogeneous for the nutritional status of the patients (based on unintentional weight loss greater than 10% during a 6-month period), type of resection (39 pancreaticoduodenectomies and 18 distal resections in the group A versus 36 and 21 in group B, respectively), sex, age, tissue texture and main duct diameter (<3 mm or >3 mm). There was no mortality in both groups. Fifteen patients had abdominal complications in group B (23%) whereas one in group A (P=0.001; OR=11); in particular, 13 PF (22%) were found in group B versus one in group A (P=0.002; OR=7), 15 (21%) fluid collections versus one (P=0.001; OR=12). The pulmonary complications were higher in group B (53% versus 26%; P=0.007; OR=8). In multivariate analysis the predicting risk factors of PF were type of randomization (delayed removal drains in POD5/6) with P<0.003 (OR=24.3; 95%CI: 3-196) and unintentional weight loss (P=0.02; OR=4; 95%CI: 2-12). **Conclusions** When AVD in POD1 is ≤5,000 U/L after pancreatic resection, the “early drains removal” (POD3) of surgical drains, significantly decreases the rate of abdominal and pulmonary complications, leading to a safe “fast track” policy.

**References**
anastomotic duodenal leak in 4 (1.5%); peripancreatic abscess in 3 (1.1%); neurological bladder requiring cystostomy in 2 (0.7%); acute acalculous cholecystitis in 1 (0.3%); and pancreatic fistula in 17 (6.2%), 13 of them required percutaneous, ultrasound guided drainage (76.4%). Drainage was with the free-hand technique (8-14 F). Mean number of drains per patient was 1.5±0.7. There was no significant difference between size of catheter and type of collection. The three abscesses drained were late complications (>3 months), while 10 pancreatic fistulas secondary to vascular complications/technical failures were early complications (<3 months); 3 pancreatic fistula caused by graft pancreatitis and one following biopsy were late complications (>3 months). Mean duration of drainage was 12.2±5 days (range 5-17 days) for abscesses vs. 59.8±58.9 days (range 10-210 days) for pancreatic fistulas (P<0.005). Only one peripancreatic fluid collection was not drained due to technical problems and treated with surgery. No IUGP-related complications were observed. **Conclusions** Based on our experience, IUGPs are safe, have high success rates and should represent first-line treatment options for PT patients.

**Allograft Rejection in Pancreas Transplantation: Evaluation of Color Doppler Ultrasound’s Diagnostic Role Based on 41 Graft Biopsies**


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**Context** Allograft rejection (AR) represents one of the main post-operative complications in pancreas transplantation (PTx) which still causes the majority of procedure failures. **Aim** To retrospectively evaluate the role of color Doppler ultrasound (CDU) in the diagnosis of AR. **Material and methods** Between May 1996 and May 2008, 274 PTx were performed, 173 of them were simultaneous pancreas-kidney procedures (SPKTx) and 101 PTx alone transplants (PTAx). We analyzed a group of 33 patients who underwent percutaneous biopsy of pancreatic graft for suspected AR. The biopsy indications were persistent hyperamylasemia, hyperlipasemia or otherwise unexplained hyperglycemia. CDU was performed in every patient before biopsy and two parameters were analyzed as potential indicators of AR: resistive index (RI) and anteroposterior body gland diameter (APD). **Results** A total of 45 percutaneous biopsies were performed on 33 recipients: 39 (86.7%) ultrasound-guided and 6 (13.3%) CT-guided. One procedure-related pancreatic fistula occurred (2.2%) and was treated with non-operative management. The histological diagnoses of rejection were 29 (64.4%). Mean RI was 0.71±0.11 in patients with biopsy-proved rejection and 0.67±0.08 in rejection-free recipients; a RI >0.80 was measured in 23% of patients with positive histology and in 25% of the no-rejection group. Mean APD was 18.9±9.7 mm in rejection cases and 17.6±4.6 mm in patients with negative histological findings. No statistical difference was found between the two groups of patients, with and without rejection, both for RI and for APD (P NS). **Conclusions** In our experience CDU evaluation of AR plays a significant role only as a safe and effective guide for percutaneous biopsies.
Main Pancreatic Duct Intraductal Papillary Mucinous Tumors: Accuracy of MR Imaging in Predicting Clinical Behavior, Compared to Histopathology

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Context IPMT MR/MRCP imaging characteristics. Aim To retrospectively determine the accuracy of MR imaging, combined with MRCP, in differentiating benign from malignant intraductal papillary mucinous tumors (IPMTs) of the main pancreatic duct (MPD), compared to histopathology. Methods Our study was IRB-approved and informed consent was waived. Twenty-seven patients with histopathologically-proven IPMT of the MDP, underwent MRI/MRPC examination and surgery, with a time interval of 2.4 months. Qualitative image analysis included: site of MPD dilatation (head, body/tail, diffuse), presence/absence of ductal wall nodules, and contrast enhancement of the MPD walls. Quantitative image analysis included: maximum diameter of MPD and of the ductal wall nodules. Results At histopathology, 16/27 (59%) MPD-IPMTs were carcinomas, 6/27 (22%) adenomas, and 5/27 (19%) border-line IPMTs. Main pancreatic duct wall nodules were observed in 9/27 (33%) patients with MPD IPMT; all of them were carcinomas. None of the patients with intraductal papillary mucinous (IPM) adenoma/borderline tumor of the MPD showed nodules of the MPD walls (P<0.05). Ductal wall enhancement was observed in 16/27 (60%) patients with IPMT of the MPD; in 11/27 (40%) patients there was no enhancement of the MPD walls. Twelve out of 16 (75%) patients with MPD-intraductal papillary mucinous (IPM) carcinoma showed ductal wall enhancement, whereas 4/11 (36%) patients with IPM adenoma/borderline tumors showed ductal wall enhancement (P=0.045). The mean maximal diameter of the MPD was 37 mm (range 10-180 mm); in malignant IPMTs it was 50 mm, and in benign IPMTs it was 23 mm. The mean maximal diameter of MPD wall nodules was 10.2 mm (range 3-21 mm). Conclusion In our series, ductal wall nodules and enhancement of the MPD walls are indicative signs of malignant IPMT of the MPD. The site of dilatation may be just suggestive of malignancy.

Intraductal Papillary Mucinous Tumors (IPMT) of Mixed Type: Magnetic Resonance (MR) and MR Cholangiopancreatography (MRCP) Characterization and Pattern, Compared with Histopathology

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Context IPMT MR/MRCP imaging characteristics. Aim To describe IPMT of the mixed type characteristics to MR/MRCP, compared to histopathology. Methods Twenty patients were included in this retrospective study. Inclusion criteria: patients with lesions both of the main pancreatic duct (MPD) and of side branches (mixed IPMT); patients that underwent pancreatic surgery with histopathological study. Exclusion
criteria: patients without pre-surgery MR/CPMR imaging; patients with lesions of the MPD only (MPD IPMT) or lesions of the side branches only (side branches IPMT); patients that did not underwent surgery. Imaging analysis: main diameter and site of MPD dilation (head; body-tail; diffuse); number and dimensions of side branches dilation; parietal nodules; lesion wall enhancement (focal or diffuse). Results were compared to histopathology. Results Main maximum diameter of the MPD was 7 mm in malignant lesions and 5 mm in benign lesions. MPD dilation was in body-tail in 4/7 patients (57%) and diffuse in 3/7 patients (42%) with malignant lesion; MPD dilation was in the head in 8/13 patients (61%), in body-tail in 3/13 patients (23%) and diffuse in 2/13 patients (15%) with benign lesion. Main number of side branches dilation was 3, with main diameter of 35 mm for malignant lesions and 25 mm for benign lesions. Parietal nodules were detected in 5/7 patients (71%) with malignant lesion while no parietal nodules were detected in benign lesions. Wall enhancement was detected in 7/20 patients (35%), and 5/7 of these patients (71%) had malignant lesion. Conclusion Presence of parietal nodules and/or wall lesion enhancement are indicative signs of malignancy in MR/MRCP imaging of IPMT of the mixed type, as evidenced by histopathology correlation.

Carbohydrate Antigen (CA) 19-9 Change During Chemotherapy for Advanced Pancreatic Carcinoma
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Context The assessment of tumor response to chemotherapy (CT) assumes a crucial role to avoid both prolongation of an ineffective treatment and premature interruption of an effective treatment. The evaluation of objective response to therapy is rather unreliable due to the vigorous peritumoral desmoplastic reaction. Among markers of efficacy a decrease of CA 19-9 was proposed by several trials. Aim To assess the correlation between CA 19-9 fall and survival in a large cohort of patients treated at our institution. Methods Eligible criteria: patients with stage III or metastatic adenoCa of the pancreas enrolled in 5 consecutive trials. Patient characteristics: age ≤75 years; PS >50; at least one measurable indicator lesion; adequate bone marrow, kidney and liver function. The 5 trials were: a) PEGF, phase II; b) either gemcitabine alone or PEGF in a phase III trial; c) modified PEGF in a dose-finding study and in d) observational study; e) either PEXG or PDXG in a randomised phase II trial. CA 19-9 measurements were performed at baseline and every 4 weeks and were assayed by the same laboratory (upper reference limit: 37 U/mL). Results No patient was lost to follow-up; mortality: 93% (May 2008). One-hundred and 11 patients (44%) had a complete or partial response to CT, 76 (30%) had a stable disease (SD); 57 (23%) had progressive disease (PD) and 8 (3%) were not assessed. Basal CA 19-9 value greater than the upper reference limit and at least one follow-up CA 19-9 measurement were assessed in 80%, 84% and 86% of patients between group of responders, patients with SD, and PD, respectively. In the group of responders it was registered an increase of CA 19-9 value or decrease <50% in 4 patients (5%); a decrease between 50 and 89% in 33 patients (37%), and a decrease >89% in 52 (58%). Patients with SD: increase of CA 19-9 value or decrease <50% in 23
patients (36%); a decrease between 50 and 89% in 32 patients (50%), and a decrease >89% in 9 patients (14%). Patients with PD: increase of CA 19-9 value or decrease <50% in 40 patients (82%); a decrease between 50 and 89% in 8 patients (37%), and a decrease >89% in one patient (2%). **Conclusions** CA 19-9 is an ideal endpoint for assessment of patients with “unmeasurable” disease; moreover it could be useful to drive treatment decisions in critical situations (continuation of palliative chemotherapy in patients with stable or progressive disease).

**Early Changes of Long Pentraxin 3 (PTX3) Serum Levels in Acute Pancreatitis and Their Potential Association with Disease Severity**

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**Context** Players of inflammation include short pentraxins, such as the liver-synthesized C reactive protein (CRP) and long ones, such as the endothelium synthesized PTX3. In acute pancreatitis (AP) CRP increase follows pancreatic injury, but it is not known whether PTX3 production occurs during pancreatic inflammation. **Aim** To assess PTX3 serum levels early in the course of AP. **Methods** CRP (reference range: 0-1.0 mg/dL), and PTX3 (reference range: 0-3.1 mg/dL) serum levels were assessed in 51 AP patients, at admission and after 6, 12, 18, 24, and 48 hours. Seven patients (13.5%) had severe AP according to the Atlanta classification. **Results** PTX3 at 0 h was 15.5±2.3 mg/dL (mean±SE), 42 (82.4%) patients having levels ≥3.1 mg/dL, while the CRP was 4.6±1.02 mg/dL, 21 (41.2%) patients having levels ≥1.0 mg/dL (P=0.003). PTX3 did not change significantly at 6 h and 12 h, decreased at 18 h (10.1±1.9 mg/dL; P=0.08), steadily until 48 h (9.4±1.4 mg/dL; P=0.03). CRP peaked at 6 h (8.5±1.5 mg/dL; P=0.04), remaining high through 48 h (10±1.3 mg/dL). Two different pt groups were identified as to PTX3 at 0-6 h: group A (n=24; 47%) had PTX3 raising (11.0±2.0 mg/dL and 20.2±4.8 mg/dL; P=0.09), then slowly decreasing through 48 h (11.6±2.3 mg/dL). In group B (n=27, 53%) PTX3 decreased from 0 to 6 h (17.7±3.6 mg/dL and 10.8±2.6 mg/dL; P=0.13), and until 48 h (5.91±1.2 mg/dL; P=0.004), a level lower than in group A (P=0.03). Group A had a CRP increase from 0 to 48 h (2.8±0.7 mg/dL and 11.7±2.0 mg/dL; P<0.001), but group B did not (4.7±1.8 mg/dL and 7.1±1.1 mg/dL; P=0.25). Severe AP occurred only among group A patients (0/27 vs 7/24; P=0.003), although PTX3 levels in severe and mild AP were similar through all time points. **Conclusions** In AP, PTX3 in serum increases earlier and more frequently than CRP, then decreases within 48 h, a trend opposite to that of CRP. Yet, in a fraction of patients, comprising those with severe disease, PTX3 increases in the earliest hours (≤6), does not decreases significantly, and might contribute to the recruitment of other mediators of inflammation.
Pancreatic Cancer Biomarkers Discovery by SELDI-TOF-MS
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Context SELDI-TOF-MS is one of the currently used techniques to identify biomarkers for cancers. Aim Our aim was to explore the application of serum SELDI proteomic patterns to distinguish pancreatic cancer (PC) from chronic pancreatitis (CP), type II diabetes mellitus (DM) or healthy controls (HC). Methods Sera from 12 HC, 24 DM, 126 PC (84 diabetics) and 61 CP (32 diabetics) were analyzed by SELDI-TOF-MS. Spectra, generated on IMAC-30, were clustered and classified using Chipergen Biomarker Wizard and Biomarker Pattern software. Results Peaks present in at least 5% of all spectra were selected. Two decision tree classification algorithms, including or not CA 19-9 as predictor, were constructed. In the absence of CA 19-9 the splitting protein peaks were at 1,526, 1,211 and 3,519 m/z. When CA 19-9 entered the analysis, the former two peaks were maintained as splitters while the 3,519 was replaced by CA 19-9. The two classification trees performed equally in classifying HC (Se=100%) and DM (Se=100%); CA 19-9 tree classified better both CP (Se=89% vs. 79%) and PC (Se=63% vs. 57%). The specificity of this classification tree was 93%, better of CA 19-9 alone (Se=86%, Sp=65%). We then constructed a classification tree considering only diabetic patients. The optimal tree resulted from the following main splitters: 1,211, CA19-9, 7,903, 3,359, 1,802. 100% DM, 97% CP and 77% PC were correctly classified. Conclusion SELDI-TOF-MS allowed the identification of new peptides which, in addition to CA 19-9, allowed to correctly classify the vast majority of PC patients and to distinguish them from CP or DM.

Robotic Radiosurgery in Pancreatic Cancer: Toxicity and Results
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Context The majority of patients with pancreatic cancer has advanced disease at the time of diagnosis and is not amenable for surgery. Stereotactic radiotherapy (SRS) would be an alternative treatment for patients with locally advanced disease. Aim This paper presents the experience at St. Bortolo’s General Hospital with SRS for patients with unresectable pancreatic cancer. Materials and methods Twenty eight patients with locally advanced histological proven pancreatic carcinoma were consecutively treated with SRS using a frameless stereotactic radiosurgery system (CyberKnife, Accuray Sunnyvale, USA): an alpha cradle was used as a comfortable treatment device. Twenty patients were previously transcutaneously implanted with a gold marker on tumor bed for tracking system to correlate breathing and tumor motion. CT and PET scans have been essential for optimal treatment planning. The standard dose varied from 25 Gy in a single fraction to 30 Gy in three fractions within three consecutives days. Eighty percent was the reference dose. Results Evaluation of response was found to be very difficult to radiation and tumor related tissue reaction. No complete response, 3 partial responses, 19 no changes, and 6 progressions of disease were observed. All
patients with local failure had simultaneously distant progression. Only three patients had no local change without distant metastasis. Median time to local or distant progression was 5.6 months. Similar was the median survival time (6 months). SRS was well tolerated. Patients had not deterioration on PS, but all experienced vomiting and nausea. The most common finding was that of post-treatment fatigue (10/28). Three patients developed intestinal ulceration: two required surgical approaches. All patients reduced their

Conclusions SRS is an alternative method of treating patients not suitable for surgery. Local control is 22/28, but distant failure is of 22/28. The poor outcome of these patients is correlated to the natural history and the behavior of this disease, because local control is not correlated with distant control and poor prognosis is not changed. Current research is aimed to defining the optimal method of combining this kind of treatments with other cancer therapies.

Invasive Intraductal Papillary Mucinous Carcinomas of the Pancreas: A Multivariate Analysis of Prognostic Factors

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Context Intraductal papillary mucinous neoplasms (IPMNs) are an increasingly well-recognized group of pancreatic neoplasms. Several Authors described a less aggressive biological behavior in branch-duct IPMNs (BD-IPMNs) compared to main-duct ones (MD-IPMNs). Certain data regarding prognosis for patients with invasive IPMN still lack. Methods The combined databases from the Massachusetts General Hospital and the Policlinico G.B. Rossi, University of Verona, were queried. We retrospectively reviewed clinical and pathological data of all patients with resected, pathologically confirmed, invasive IPMNs between 1990 and 2007. Univariate and multivariate analysis was performed by the Cox regression model to evaluate significant 10-year mortality predictors. Results Invasive intraductal papillary mucinous carcinomas (IPMICs) were diagnosed in 104 patients (55 males and 49 females), median age was 69 years. Recurrent disease was identified in 41 patients (39.4%) and the median overall survival was 109.5 months. Microscopic vascular invasion (hazard ratio: HR 3.46; 95% CI: 1.76-6.80), microscopic neural invasion (HR 2.75; 95% CI: 1.42-5.33), positive margins (HR 2.36; 95% CI: 1.23-4.55) and presence of other neoplasms (HR 2.16; 95% CI: 1.11-4.19) significantly correlated with a poor prognosis; no differences regarding mortality rates was demonstrated between branch duct IPMNs and main duct IPMNs (HR 0.75; 95% CI: 0.29-1.94). Familiar history of pancreatic neoplasms and metastatic lymph nodes proved to be significant predictors of 10-year mortality, as shown through multivariate Cox analysis. Conclusions Despite their different biological behavior, no differences between BD and MD-IPMNs were observed in terms of prognosis when invasiveness occurs. Patients with an invasive IPMN and a familiar history of pancreatic neoplasms or metastatic lymph nodes have a poorer prognosis.
Magnetic Resonance Cholangio-Pancreatography with Secretin Stimulation in the Evaluation of Chronic Pancreatitis

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Context Chronic pancreatitis evaluation with magnetic resonance (MR) is at present a fundamental diagnostic step, combining both morphological and functional information with the association of secretin stimulation in so called MR cholangiopancreatography (MRCP). Wirsung duct and secondary ducts can be better defined and visualized, favoring the detection of abnormalities.

Aims Correlation of morphological and functional data obtained by secretin-MRCP with clinical and biochemical data in a group of patients affected by chronic pancreatitis and acute recurring pancreatitis.

Methods Two groups of patients have been enrolled in our study: 1) 15 subjects with chronic pancreatitis have been studied (9 males and 6 females), 4 with genetic etiology, 8 alcoholics and 3 idiopathics; 2) 10 patients with acute recurring pancreatitis (4 males and 6 females). Other clinical and laboratory parameters have been correlated to imaging findings: amylase, lipase, hepatic cytolysis and cholestasis, fecal elastase, blood glucose concentration, age at onset, and clinical history. Patients were studied with a 1.5 T scanner with T2 weighted single shot fast spin echo and 3D gradient echo T2 weighted sequences. Size of main pancreatic duct (head, body and tail) and duodenal filling before and after secretin stimulation were measured quantitatively. Image analysis included also anatomical variants, visualization of side branches, endoluminal filling defect and acinar filling.

Results Good correlation was found between ductal variations, number of secondary ducts visible, pancreatography, pre- and post-secretin stimulation, duodenal filling and biochemical indexes of exocrine functionality.

Conclusions MRCP with secretin stimulation is proved to be an effective modality in morphological and functional evaluation of patients affected by pancreatitis.

Long-Term Follow-up in an Asymptomatic Traumatic Damage of the Main Pancreatic Duct Revealed by an Isolated Hyperamylasemia

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Context Penetrating or blunt traumas involving the pancreas are unusual events, because of the retroperitoneal anatomic position of the gland. In these rare cases clinical presentation is based on aspecific signs and symptoms and diagnosis may be difficult. The principal cause of morbidity is injury to the main pancreatic duct (MPD) because parenchymal pancreatic injuries, not involving the ductal system, rarely result in pancreas-specific morbidity or death.

Case report We hereby report the case of a 40-year-old man who had a motorcycle accident 13 years ago. After the trauma, mild persistent dorsal pain was investigated by a spinal column X-ray which resulted negative. He did not undergo any other investigation. After some months, pain spontaneously disappeared. Six years ago, during a routinely check-up, a previously unknown hyperamylasemia (two times the normal value) was first recorded. This finding was
later confirmed, and the patient underwent an abdominal US demonstrating MPD dilatation. Four years ago he came to our attention and a magnetic resonance cholangiopancreatography with secretin stimulation (s-MRCP) demonstrated a long proximal MPD stenosis, with distal dilation and signs of chronic pancreatitis in the tail. In this occasion an ERCP was confirmed the stenosis, but the cannulation of the MPD was not feasible. Since then the patient has been managed conservatively, with pancreatic enzyme therapy and low fat diet. He has been asymptomatic, while the mild hyperamylasemia has been confirmed (fluctuating values between 2 and 3 times the normal value), and yearly s-MRCP has demonstrated steadiness of MPD alterations, with a diameter of 5 mm (Figure), without a delayed duodenal filling after secretin stimulation. **Conclusions** MPD traumatic damage is a rare event, usually symptomatic and readily diagnosed. This is a rare case characterized by a long asymptomatic course, and diagnosed in the evaluation of an isolated hyperamylasemia many years after the trauma. s-MRCP seems an optimal method to follow these patients, and although a conservative management was successful until now, a surgical approach will probably be necessary if the MPD dilatation increases to avoid further pancreatic damage.

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**A New Compound Heterozygous Mutation of PRSS1 And CFTR Genes as Cause of Recurrent Acute Pancreatitis**

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**Context** Here, we report a new mutation in the PRSS1 gene, associated with p.F508del mutation in CFTR, in a child affected by recurrent acute pancreatitis. **Case report** A 6-year-old boy was admitted in the hospital with acute abdominal pain, nausea and mild fever. In the previous 13 months he had six similar episodes all followed by quick recovery and complete disappearance of abdominal pain. This time the boy appeared suffering with epigastric pain radiating to the back and moderate abdominal distension. Serum amylase 1,373 U/L (reference range: 0-95 U/L), lipase 1050 U/L (reference range: 13-60 U/L), CRP 95 mg/L (reference range: 0-10 mg/L), eritrosedimentation rate 74 mm/h (reference range: 0-20 mm/h). The child was treated with intravenous fluids plus 20 mg of proton pump inhibitor i.v.. An abdominal ultrasound showed only pancreatic edema. After 7 days with normal clinic and laboratory tests the child was discharged with a hypolipidic diet, 20 mg PPI and pancreatic enzyme supplementation (10,000 U x 6/day) per os. In the attempt to exclude anatomic abnormality, a secretin stimulated magnetic resonance (MRI) was performed showing general increased thickness of parenchyma of the entire pancreas with normal main pancreatic duct. At the last follow-up visit, about 8 months after the last acute pancreatic attach, the child showed a normal anthropometric profile with normal body weight, and did not reported further
abdominal pain; in this occasion PPI was stopped while pancreatic enzyme supplementation was confirmed for a while. Mutation screening for coding regions of PRSS1, SPINK1 and CFTR genes was performed using a direct sequencing approach. No variation in the SPINK1 gene was detected, while a novel variation, c.541A>G (p.S181G), in the exon 4 of PRSS1 gene was revealed. This mutation was never detected in 100 healthy unrelated individuals suggesting a putative mutation. The patient also showed the classical CF p.F508del mutation in the CFTR gene. Both mutation were present in his clinically normal mother and absent in the patient’s father. To explain the phenotypic discordance between mother and proband we applied a comparative genomic hybridization method to detect macrodeletions and macroinsertions on the entire genome of mother and proband DNA’s that was negative. The presence of protective polymorphism G191R as modifier of pancreatic phenotype in the mother was excluded by complete sequences analysis of the PRSS1 gene. **Conclusion** This report extends the spectrum of PRSS1 mutations showing for the first time an exon 4 mutation. The combined genotype CFTR (F508del)/PRSS1 (S181G) could be considered at risk for hereditary pancreatitis. The phenotypic discordance between the proband and his mother could be due to a possible late onset of pancreatic disease, an incomplete penetrance of the mutations or to the presence of unidentified modifier genes.

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**Acinar Cell Carcinoma of the Pancreas: Analysis from a Single Institutional Series of Resected Patients and Literature Review**

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**Context** Acinar cell carcinomas (ACCs) account for 1% of primary pancreatic neoplasms; standardized treatment is not available and few centers reported their experience and results. **Aim** The study reviews our experience and the literature in order to mismatch our results either to series either to case reports. **Methods** Retrospective review from 1990-2007 was performed including patients underwent curative pancreatic resection of neoplasm having features of ACCs. Follow-up was updated to April 2008. **Results** We observed 9 patients with a median age of 53 years. Head localization occurred in 67%. Patients complained: jaundice 33%, back pain 76%, weight loss 56%, abdominal mass 11%. CA 19-9 was higher than normal in 57% of cases. Median tumoral size was 6 cm, 4 patients were stage II, 4 patients were stage III and one was stage IVB. All but one patient had a R0 resection. Patient founded to be stage IVB intraoperatively received also a R0 liver resection. We had no major complications and no mortality. Follow-up is complete for all patients. Median follow up is 31 months. 56% of patients received chemotherapy (gemcitabine). 78% developed distant recurrence being the liver the only organ involved. Recurrence required modification of chemotherapy, ablation techniques or surgery. We had 7 disease related deaths; median overall survival was 31 months, disease free survival was 25.2 months. One patient is alive after several surgical treatments of liver metastases leading to 9 months disease free survival after last treatment and 67 months from pancreatic resection. One patient is alive with local recurrence after 34 months from pancreatic resection. **Conclusions** We need to better qualify the histology of ACCs including cystic variant and excluding other...
similar tumors such as pancreatoblastomas. ACCs are less aggressive than ductal cancer nevertheless the prognosis is rather severe. Adjuvant chemotherapy, mediated from ductal cell carcinoma or from intestinal neoplasms should be more investigated and needs further evaluation. When liver metastases appear an aggressive ablative approach should deserve good results.

Role of VEGF and Its Receptors in Pancreatic Neuroendocrine Tumours
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Context Angiogenesis, a process related to tumor growth and malignancy, is stimulated by several growth factors. Recent studies demonstrated that vascular endothelial growth factor (VEGF) expression is correlated with microvessel density (MVD) and tumor progression in various tumors. Aim We evaluated the correlation among VEGF, VEGFR1, VEGFR2 expression, MVD (anti-CD105 antibody) and clinicopathological parameters (WHO 2004 classification) in a series of 50 patients resected for pancreatic neuroendocrine tumor. Methods: Immunohistochemistry was performed with anti-VEGF, -VEGFR1, -VEGFR2 and -CD105 (endoglin) antibodies. VEGF, VEGFR1 and VEGFR2 expression was blindly scored as product between intensity of staining (score 1-3) and percentage of positive neoplastic cells (score 1-3) by two independent pathologists. Intratumoral MVD was evaluated using Weidner criteria (hot spot method). Statistical analysis was based on the Spearman rank correlation non parametric test. Results VEGF immunoreactive (IR) cells were detected in 48 of 50 tumors. VEGFR1-IR cells were found in 47 of 50 tumors and VEGFR2-IR cells in 30 of 50 tumors. The MVD (mean value 5.91%) was significantly correlated with VEGF expression, but no relationship between MVD or VEGF expression and clinicopathological parameters was observed. VEGFR1 and VEGFR2 expression were significantly correlated with tumor diameter and VEGFR2 expression also with vascular invasion. Conclusions These results suggested that VEGF and its receptors may be involved in tumorigenesis and in tumor progression and aggressiveness inducing vessel permeability and modulating other endothelial functions in neuroendocrine pancreatic tumors.

Prognostic Significance of CK19 Expression in Neuroendocrine Pancreatic Tumors
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Context The prognosis in neuroendocrine pancreatic tumors (NPTs) is based on clinicopathological parameters but a cohort of NPTs shows aggressive behavior despite indolent morphologic features. Recently it has been suggested that CK19, a marker of pancreatic ductal cells which does not stain normal islet cells, is a sensitive predictor of survival. Aim Our aim was to evaluate the prognostic value of pathological parameters
and CK19 expression in a series of 50 patients resected for neuroendocrine pancreatic tumor. **Methods** Tumours were classified according to WHO 2004 classification. The immunohistochemistry was performed with CK19 antibody and the expression in neoplastic cells was scored as 0: negative, 1: <10%, 2: 11-25%, 3: 26-50%, 4: 51-75%, 5: 76-90%, 6: >90%. The statistical analysis was based on the Spearman rank correlation non parametric test. **Results** Ninety percent of cases classified as “uncertain behavior” and neuroendocrine carcinomas were positive to the CK19 reaction, whereas only 25% of neuroendocrine tumors “benign behavior” showed positivity in the neoplastic cells. Statistical analysis showed significant correlation between CK19 expression and pathologic prognostic parameters: tumor size, vascular and perineural invasion, mitotic index, presence of metastasis and morphologic category (benign vs. uncertain behavior and carcinomas) (P<0.001). The majority (8/9) of uncertain behavior tumors was positive for CK19 and 5 of them are alive with disease. **Conclusion** The presence of a ductal marker as CK19 in NPTs raises the possibility that ductal carcinomas and some PETs may share a common histogenesis. The addition of CK19 to the prognostic parameters of NPTs could potentially refine the distinction between benign and aggressive/malignant neoplasms.

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**Apolipoprotein AI Regulatory Protein 1 (ARP-1) Regulates Tumor Behaviour of Mia-Paca-1 Pancreatic Cancer Cell Line**

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**Context** Apolipoprotein regulatory protein 1 (ARP-1), is an orphan nuclear receptor (i.e., a receptor whose ligand have yet to be identified) belonging to the COUP-TFs transcription factor family. ARP-1 regulates the transcription of the target genes binding to specific regions of their promoters as homor etero-dimer. It has been reported that ARP-1 acts both as a transcriptional repressor and as an activator. While the role of this receptor during development is well characterized, its role in adult tissues and cancer disease is poorly investigated. **Aim** To examine the role of ARP-1 in the regulation of tumor behavior in adenocarcinoma cell line MiaPaca-1. **Methods** MiaPaca-1 cell line expressing shRNA against ARP-1 in a Dox inducible manner was produced. ARP-1 silencing was confirmed at the RNA and protein levels. Cell proliferation was evaluated with WST1 colorimetric test. Cell migration was performed using standard Boyden chambers on matrigel-coated filters. Anchorage independent cell growth was evaluated by soft agar colony formation assay. All the experiments were performed using the above mentioned cell line either treated with Dox to induce ARP-1 silencing or untreated to maintain normal expression levels of the gene; moreover, wildtype MiaPaca-1 unspecifically silenced or non silenced were also used as controls. **Results** shRNA production induced by Dox treatment is able to strongly affect ARP-1 mRNA levels without altering the transcription of the closely related COUP-TFI, as demonstrated by RQ-PCR analysis. The same effect is confirmed at the protein level. Moreover we evidenced that silencing of ARP-1 reduces the proliferation rate of MiaPaca-1 cell line at least by 20% compared to controls (P<0.05), cell motility (P<0.05) and anchorage independent growth (P<0.01). **Conclusions** Data reported suggest that ARP-1 is an important regulator of tumor behavior in pancreatic adenocarcinoma cells.
Selecting Families Eligible to Screening for Pancreatic Cancer: Application of a Mendelian Model to a Large Series of Consecutive Cases


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Context A large multicenter study designed to investigate the risk of pancreatic cancer in families of patients with pancreatic ductal adenocarcinoma was recently conducted, in which a series of 570 pedigrees were collected through a structured questionnaire.

Aim Here, we apply the software PancPRO to this series; this is a published program based on a genetic model of pancreatic cancer susceptibility that uses information on affected relatives and population prevalences to calculate individual risk of pancreatic cancer.

Methods To use PancPRO for our purposes, we calculated the lifetime risk, \( R_C \), of developing pancreatic cancer for a hypothetical 40-year-old child of each proband. The baseline lifetime risk calculated by PancPRO for a subject of age 40 and with no family history of cancer, \( R_P \), was 0.011. We used the ratio \( R_C/R_P \) as an indicator of the “familial risk” of pancreatic cancer for each kindred.

Results The 570 \( R_C \) values were included between 0.01 (the baseline value) and 0.13; 81.2% of the values were <0.05, and 3.7% were >0.10. The distribution was clearly bimodal, with the antimode located at \( R_C=0.075 \). A generally accepted threshold for including a relative at risk in a surveillance program is \( R_C/R_P=10 \). Considering this cut-off value, 19 families (3.3%) out of the 570 were included. The mean age of affection by pancreatic cancer in this group (\( n=46 \)) was lower than in all other families (61.1 vs 65.1, \( P_{\text{t-test}}<0.01 \)). A total of 92 first-degree relatives with age >40 years (4.8 subjects per family on average) of these probands would be selected for screening using this approach.

Conclusions Although the genetic model of PancPRO still needs experimental confirmation (i.e., identification of the hypothesized gene), it is a valid instruments to rank families based on family history of pancreatic cancer; it provides a useful framework for evaluating other proposed cut-off criteria in terms of total number of relatives eligible to screening.

Estimation of a System for Grading of Complications After Pancreatic Surgery

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Context Mortality associated with pancreatic resections (PR) is rare in high-volume centers and therefore not a good indicator for the quality of surgery. Morbidity still remains high, but comparison between centers is difficult due to the lack of a unified system for grading of complications. Aim To apply the Clavien grading system [1] on a consecutive series of PR in order to test its utility and ability to discriminate the severity of complications and outcome.

Methods All complications registered prospectively from Jan 2005 until Dec 2007 were retrospectively graded (grade I-II: conservative management;
III: invasive intervention, a) without or b) under general anesthesia; IV: organ failure/ICU treatment, V: death) and correlated to the median length of stay (LOS) and the extent of surgery. Results Overall 194 PR were performed (136 Whipple, 31 distal resections, 14 total, 11 Beger, and 2 segmental), of which 28 were extended pancreatic resections (EPR) with vein- and/or multi-organ resection. Overall complications were encountered in 53% of patients (n=103). The increase in the grade of complications correlated with the length of stay (LOS): 0: LOS 9 days; I-II: 12 days; IIIa: 16 days; IIIb: 19 days; IV: 41 days; V: 17 days. There was no difference in the number of complications depending on the extent of resection, but the EPR group had a shift towards more severe grades (≥IIIb) compared to PR (P=0.006): 0 (48% vs. 39%), I-II (23% vs. 14%), IIIa (18% vs. 14%), IIIb (6.6% vs. 18%), IV (2.4% vs. 7.1%), V (1.8% vs. 7.1%). Delayed gastric emptying (DGE) (12%, n=23) was grade I-II in 87% of cases. Pancreatic leakage (PL) (12%, n=22) was handled in 68% by minimally-invasive procedures (IIIa). Bleeding occurred in 11 patients (5.6%) with a mortality of 27% (grade V) while no patients with DGE or pancreatic leak died. DGE had lower grade complications compared to PL (P<0.001) and PL had lower grades than bleeding (P=0.02). Conclusion The estimated system may be used for morbidity comparisons between centers as it is easily applicable, correlates with LOS, discriminates the severity of complications according to the extent of surgery and highlights the dangerous complications.

Reference

Evidence for Nutritional Recommendations in Chronic Pancreatitis. A Critical Review
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Context Malnutrition in patients with chronic pancreatitis (CP) is multifactorial and is reported to be present in more than 80% of cases. Dietary modifications, particularly by reducing the fat content and enzyme substitution to control the clinical symptoms are generally recommended. Aim To critically review the available data on nutritional recommendation and support in CP based on the current evidence. Methods A search of the relevant literature was performed in PubMed and in the articles’ reference lists. A total of 80 reports were reviewed. Due to the lack of solid data a formal meta-analysis was not possible. Results Alteration in all the processes involved in the digestion and utilization of nutrients have been reported. Abnormal nutritional assessment parameters and nutrient deficiencies were encountered even in CP patients considered to respond well to dietary modifications and enzyme substitution therapy. Data on the impact of malnutrition on outcome, however, are sparse. Evidence is lacking that modifying the dietary components decreases pancreatic stimulation and thus avoids symptoms. No studies are published comparing the effects of various nutritional regiments on outcome in CP. Reversely, pancreatic enzyme activity is enhanced in the presence of the corresponding nutrients. Postprandial levels of CCK decrease proportionally with progression of the pancreatic insufficiency. Decreasing
pancreatic stimulation has not been shown to relieve symptoms. Data are insufficient for the use of enteral and/or parenteral nutritional support, but there is some evidence that proper dietary counseling is equivalent to oral nutritional supplementation. Enteral nutritional support might be beneficial when all conservative measures fail. With adjustment and close monitoring of the enzyme substitution therapy even correction of subclinical malnutrition can be achieved. **Conclusion** The incidence of malnutrition in CP is very high, but its impact on outcome is unknown. There is no firm evidence behind the commonly recommended dietary modifications, which may further deteriorate the state of malnutrition. Some data imply that improvement of nutritional status correlates with decreasing the symptoms of disease.

**Exocrine Pancreatic Function During the Recovery Phase of Acute Pancreatitis**

**Rega D**

**Pezzilli R**

**Simoni P**

**Morselli-Labate AM**

**Ricci C**

**Casadei R**

**Calculi L**

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**Context** From a practical point of view it is important to know the exocrine pancreatic function after an acute episode of pancreatitis in order to cure possible maldigestion. An exocrine pancreatic dysfunction has been reported in humans in the convalescent period after acute pancreatitis, but the data are scarce and conflicting. **Aim** To prospectively assess the exocrine pancreatic function in patients with acute pancreatitis at the time of their refeeding. **Methods** All consecutive patients admitted to our unit with the first attack of acute pancreatitis from January 2006 to December 2006 were enrolled. A fecal sample was collected the day of refeeding from each patient and stored at -20°C until analysis and exocrine pancreatic function was assessed by using the fecal elastase 1 determination (Pancreatic Elastase 1 Stool Test, ScheBo Biotech AG, Giessen, Germany). The Fisher’s exact, the Mann-Whitney, the Pearson’s chi-squared tests and the hierarchical log-linear model were applied. **Results** Seventy-five patients (37 males, 38 females; mean age 61.8 years, range: 20-94 years) were studied. According to the Atlanta criteria, 60 (80.0%) had a mild course of acute pancreatitis and 15 (20.0%) a severe disease. The etiology was due to biliary stones in 61 patients (81.3%), due to alcohol abuse in 1 (1.3%), associated with hypertriglyceridemia in 3 (4.0%); no causes of pancreatitis were found in the remaining 10 patients (13.3%). The mean (±SD) patient refeeding was 11.2±10.2 days (range: 4-43 days) after the attack of acute pancreatitis (mild pancreatitis 6.4±1.7 days, severe pancreatitis 30.5±6.6 days; P<0.001). Pathological values of fecal elastase-1 (less than 200 μg/g) were found in 9 (12.0%) of the 75 studied patients: 7 (11.7%) patients with mild disease and in 2 (13.3%) patients with severe disease (P=1.000). Significant differences in the pathological values of elastase-1 were observed among the various etiologies of the disease (P=0.030): 6 (9.8%; P=0.035) patients with biliary pancreatitis, in the only patient with alcoholic pancreatitis (P=0.126), in one of the 3 patients (33.3%; P=0.708) with hypertriglyceridemia-induced pancreatitis, and in one of the 10 patients (10.0%; P=0.227) with idiopathic pancreatitis. Pathological fecal elastase-1 was not significantly related to the sex (P=0.736), age (P=0.320), and the day of refeeding (P=0.123). **Conclusion** Exocrine pancreatic function should be routinely assessed in patients with acute pancreatitis at the refeeding, especially in those with non-biliary pancreatitis, in order to supplement their diet with pancreatic extracts.
An Italian Survey of Metastatic Pancreatic Adenocarcinoma (PA) Treatment Over the Last Decade

Reni M1, Cereda S1, Pasetto L2, Passardi A3, Milella M4, Cantore M5, Aprile G6, Tronconi MC7, Berardi R8, Zerbi A9, Balzano G9, Di Carlo V9, Falconi M10

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Context Since gemcitabine (G) became the standard treatment for patients with metastatic PA, combination chemotherapy (CHT) obtained conflicting results on survival (OS) improvement. Aim A series of 767 patients treated between Jan 97 and Dec 2006 in 10 Italian centers was analyzed. Methods Data on patient characteristics, diagnosis, treatment and outcome were provided. Inclusion criteria were: histological or cytological diagnosis of metastatic PA; age >18 years, performance status (PS) > 3, no prior CHT. Results Median age was 62 years; median PS was 1. G was included in upfront treatment in 675 patients (88%). Single agent CHT was used in 425 patients (55%; G 416); doublets in 116 patients (15%; G-based 109); G-free triplets in 76 patients (10%); G-based 4-drug regimens in 150 patients (20%). With respect to treatment trends (1997-2001 versus 2002-2006), G alone was the most used therapy in both periods (49%; 57%); G-fluoropyrimidine doublets were administered in 8% and 2% of cases; G-platinating agent doublets in 1% and 14%; G-free triplets in 17% and 7%; G-based 4-drug regimens in 21% and 19%. Median and 1-year survival for all patients was 6.7 months and 22%, respectively. Patients’ characteristics, outcome and results of univariate analyses are reported in the Table. Multivariate analysis confirmed that PS, basal CA 19-9 and 4-drug regimens use are independent predictors for OS. Conclusions This survey confirms the prognostic value of PS and CA 19-9 in metastatic PA. Data suggest that OS may be improved by G-platinum doublets when compared to G alone and that 4-drug regimens may be superior in terms of response rate and OS to both G alone and G-platinum doublets.

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<th>P value</th>
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<td>9.0</td>
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</tr>
</tbody>
</table>

G+PC: G+platinum compound; URL: upper reference limit

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A Clinical Practice Survey of Stage III Pancreatic Carcinoma (PC) Treatment

Reni M1, Cantore M2, Berardi R3, Tronconi MC4, Aprile G5, Milella M6, Cereda S1, Zerbi A7, Balzano G7, Di Carlo V7, Falconi M8

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Aim To assess treatment trends and efficacy in stage III PC, a series of 623 patients treated between 1997 and 2006 in 10 Italian centers was analyzed. Methods Data on patient characteristics, treatment and outcome were collected. Inclusion criteria were: histological or cytological diagnosis of stage III PC; age >18 years, performance status (PS) >3, no prior chemotherapy or radiotherapy. Results Median age was 63 years; median PS was 1. Upfront chemoradiation was rarely used (6%). Most of patients (94%) received upfront chemotherapy with 19 different regimens including gemcitabine (G) in 508 cases (81.5%). Treatment consisted of: G (n=325; 52%), G-platinum compound doublets (n=75; 12%), G-fluoropyrimidine doublets (n=18; 3%); G-based 4-drug combinations (n=90; 14.5%), fluorouracil (n=18; 3%) and intra-arterial G-free triplets (n=57; 9%). The use of G-platinum compound doublets and of 4-drug regimens increased over time (1997-2001: 2% and 9%; 2002-2006: 19% and 18%, respectively) while the inverse trend was observed for G-fluoropyrimidine doublets (5% and 1%), chemoradiation (9% and 4%) and intra-arterial treatment (14% and 6%). G alone was extensively used in both periods (56%; 49%). Median, 1-year and 2-year survival (OS) for all patients was 10.9 months, 43% and 11%, respectively. Results of univariate analyses are reported in the Table. Multivariate analysis stratified by center and year of diagnosis showed that CA 19-9 (HR 1.27; 95%CI: 1.03-1.58; P=0.03) and 4-drug regimen use (HR 0.66; 95%CI: 0.46-0.94; P=0.02) independently predict OS. Conclusions This very large survey shows that upfront chemotherapy is a widely used therapeutic strategy for stage III PC. No standard treatment exists. However, the addition of a platinum compound to G seems to improve OS over G alone. Further OS prolongation may be yielded with 4-drug regimens.

<table>
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G+PC: G+platinum compound; URL: upper reference limit

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Long-Term Survival in Neuroendocrine Tumors of the Pancreas
Ricci C1, Campana D2, Morselli-Labate AM2, Antonacci N1, Casadei R1, Pezzilli R2, Rega D1, Calculi L3, Santini D4, D’Ambra M1, Monari F1, Tomassetti P2, Minni F1
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Context The natural history of pancreatic neuroendocrine tumors (PNET) remains poorly defined and factors predicting long term survival were rarely described. Aim To evaluate factors influencing long term survival. Methods This study included a total of 76 patients having PNET admitted to our unit from 1980 to 2008. There were seventy-six patients (36 male, 40 female with mean age 54±14.1 years). Twenty-eight had functioning tumors (36.8%), 40 non-functioning (52.6%), and 8 MEN 1 (10.5%). Symptoms were present in 58 cases (76.3%), while the remaining 18 cases (23.7%) were asymptomatic. The tumor was single in 69 cases (90.8%) and multiple in 7 (9.2%). The neoplasia was located in the pancreatic head in 22 cases (28.9%), in the body in 31 (40.9%), in the tail in 20 (26.3%), and it was diffuse throughout the gland in 3 cases (3.9%). Seventy-one PNET patients underwent tumor resection (93.4%) and the margins were histologically R0 in 67 cases (88.2%) and R2 in 4 (5.2%). The tumor size was 4±2.7 cm, Ki-67 <2% was present in 14 cases (18.5%), ≥2% in 21 cases (27.6%), and this evaluation was not available in 41 cases (53.9%). According to WHO stage, 44 cases had well differentiated endocrine tumors (57.9%), 20 well differentiated endocrine carcinomas (26.3%) and 12 poorly differentiated endocrine carcinomas (15.8%). According to TNM stage, 21 patients (27.6%) were stage I, 30 (39.5%) stage II, 15 (19.7%) stage III and the remaining 10 (13.2%) stage 4. Survival curves were calculated using Kaplan-Meier method. Cox regression was applied to identify prognostic factors related to survival. Results The mean follow-up period was 8.5±7.1 years; the mean overall survival and relative survival period were 19.2±1.5 years and 21.6±1.42 years, respectively. Both fifteen-year overall and relative survival rates were 63.5% and 73%, respectively. The relative survival rate was significantly low in patients with tumor size >4 cm (P=0.024), Ki-67 >2% (P=0.021), R0 resection (P=0.001), metastatic node (P=0.005) and liver metastases (P<0.001), WHO (P=0.001) and TNM stages (P=0.027). Conclusion Several factors can influence long term survival. In particular, the small size of tumor, the absence of liver and node metastasis and Ki-67 are related to a better survival rate. Radical surgery continues to have a central role the therapeutic approach to PNET.

Are There Prognostic Factors Related to Recurrence in Neuroendocrine Pancreatic Tumors?
Ricci C1, Campana D2, Morselli-Labate AM2, Antonacci N1, Casadei R1, Pezzilli R2, Rega D1, Calculi L3, Santini D4, D’Ambra M1, Alagna V1, Tomassetti P2, Minni F1
1Surgical Unit, 2Department of Digestive Diseases and Internal Medicine, 3Radiological Unit, 4Pathology Unit, S.Orsola-Malpighi Hospital, University of Bologna. Bologna, Italy

Context Recurrence rate in resected neuroendocrine pancreatic tumors is rarely reported in the literature. Usually tumor recurrence occurred in the liver with a median time of about 12 months. To our knowledge, prognostic factors related to recurrence have been rarely reported. Aim To individuate the possible factors related to the appearance of
recurrences. **Methods** This study included a total of 65 patients having PNET admitted to our unit from 1980 to 2008 who underwent surgical R0 resection. There were 30 males, 35 females with mean age 52.3±13.8 years; 24 patients (36.9%) had functioning tumors, 33 (50.8%) non-functioning and 8 (12.3%) MEN 1. Symptoms were present in 50 cases (76.9%), while 15 patients (23.1%) were asymptomatic. The tumors was single in 58 cases (89.2%) and multiple in 7 (10.8%); the neoplasia was located in the pancreatic head in 19 cases (29.2%), in the body in 25 (38.5%), in the tail in 18 (27.7%) and it was diffuse throughout the gland in 3 cases (4.6%). Tumor size was 3.2±2.3 cm, Ki-67 was <2% in 13 cases (20%), ≥2% in 15 cases (23.1%), not available in the remaining 37 (56.9%). According to WHO stage, 43 patients (66.2%) had well differentiated endocrine tumors, 18 (27.7%) well differentiated endocrine carcinomas and 4 (6.2%) poorly differentiated endocrine carcinomas. According to TNM stage, 21 patients (32.3%) were stage I, 29 (44.6%) stage II, 13 (20.0%) stage III and 3 (3.1%) stage 4. Recurrence rate were calculated using Kaplan-Meier method. Cox regression was applied to identify prognostic factors. **Results** Recurrence rate was 24.5% (16 cases). Mean time to recurrence was of 7.3±4.5 years. Recurrence rate at 5, 10, and 15 years was 11.4%, 21.1% and 39.6%, respectively. The liver was the most common site of recurrence (12 cases, 75%). The factors significantly and positively related to recurrence were the presence of MEN 1 (P=0.047), Ki-67 ≥2% (P=0.008), metastatic node (P=0.05) and liver metastases (P=0.042), WHO (P=0.026) and TNM stage (P=0.019). **Conclusion** Several factors can determine the onset of recurrence. In particular, recurrence rate is high in patients with MEN 1, Ki-67 ≥2%, presence of nodal and liver metastasis, poorly differentiated carcinomas and stage III and IV.

**Radiofrequency Ablation of Unresectable Pancreatic Carcinoma: Preliminary Results**

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**Context** Despite improvements in diagnosis and therapy, the prognosis of patients with pancreatic adenocarcinoma remains poor. Pancreatic cancer is locally advanced without distant metastases and pancreatic resection is not possible because of the vascular involvement in about 40% of cases. Palliative treatments of these cases did not allow a good quality of life as well as a significant improvement in long-term survival. Radiofrequency ablation (RFA) could be a new treatment option. **Aim** A pilot prospective non-randomized study about efficacy and safety of intraoperative RFA in patients with unresectable, locally advanced, non-metastatic pancreatic head carcinoma was carried out. **Methods** The study started on October 2007. The selection criteria of eligible patients are based on past and present medical history, imaging findings (thoraco-abdominal multidetector CT, liver CEUS) and core biopsy. RFA is the first step of the surgical procedure and it is carried out by using the Cool-tip™ RFAblation system (Radionics) on the mobilized pancreatic head followed by biliary by-pass and gastrojejunal-anastomosis. Intra- and post-operative morbidity and mortality, control of chronic pain and QoL were evaluated as well as the overall survival at 24 months. **Results** Seven patients (3 males and 4 female, mean age 66.1±9.9 years, range 48-80 years) entered
into the study and 5 (71.4%) patients were eligible for the treatment according to the selection criteria. The RFA procedure was carried out in 3 of the 5 patients (60.0%); in two cases (40.0%) RFA was not performed because technical difficulties in one case and due to upstage of the neoplasia in the remaining one. In all the three cases in which RFA was carried out, we achieved a complete necrosis of the lesions. No intra-operative complication was observed. Biliary fistula developed 7 days after the procedure as post-operative major complications in one patient (33.3%); all three patients developed ascites after a mean of 8.6 days after RFA (range 7-9 days). One patient is still alive but he had a progression of the disease 5 months after operation and 2 patients dead (one at 3 months and one at 4 months after the treatment). Data about control of pain and quality of life assessment are not available due to the poor clinical conditions of all three patients. Conclusion In our experience, RFA is a safe procedure, but it is possible only in 60% of the patients and the post-operative complications are too high. Finally, the survival rate, the control of pain and the quality of life are poor. In our opinion, this procedure should not be routinely used in patients with locally advanced non metastatic adenocarcinoma.

Fagan’s Nomogram: Is It Useful in Routine Clinical Setting?

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Context The differential diagnosis between pancreatic cancer and chronic pancreatitis can be sometimes very difficult because the clinical symptoms and imaging findings may be similar. Evidence-based medicine (EBM) allows us to apply evidence gained from the scientific method to medical practice. In the last years EBM stressed the attention not only on the evaluation of therapeutic strategies but also on the efficacy of diagnostic phase. Furthermore, the Fagan nomogram, that is a graphical tool for estimating how much the result on a diagnostic test changes the probability that a patient has a disease, may be used. To use this tool, there is the need to provide the best estimate of the probability of the disease prior to testing and this is usually related to the prevalence of the disease, though this may be modified up or down on the basis of certain risk factors that are present in the patient pool or possibly in a particular patient. There is also the need to know the likelihood ratio for the diagnostic test. Case report A 64-year-old woman previously operated for breast cancer and coronary heart disease, was admitted to our Department for transient ischemic attack. During the hospital stay, laboratory tests showed increase of serum levels of total bilirubin (3.81 mg/dL) and conjugated bilirubin (3.23 mg/dL), alkaline phosphatases (2,120 U/L; reference range: 98-280 U/L), gamma-glutamyltranspeptidase (2,116 U/L; reference range: 5-36 U/L) and CA 19-9 (165 U/mL; reference range: 0-37 U/mL). Ultrasonography showed a solid, ipo-echogenic mass of the pancreatic head of 18x25mm in diameter with common bile duct dilatation. The patient had no history of alcohol consumption or pancreatic cancer. She did no smoke and she had history of gallstones. In order to reach a diagnosis distinguishing between pancreatic cancer and chronic pancreatitis we applied the EBM method; thus, the Fagan’s nomogram was used. According to the evidence present in literature, radiological examinations were performed, their specificity and sensitivity...
evaluated, likelihood ratio calculated and Fagan’s nomogram used. The patient underwent US, CT, ERCP, MRCP, EUS, PET with 18-Fluorodeoxyglucose (FDG) and core biopsy. At the end of the diagnostic phase, the result of Fagan’s nomogram was able to exclude pancreatic cancer in the head of the pancreas. Diagnosis of focal chronic pancreatitis with cholangitis was made. The patient underwent surgery and a bilo-digestive anastomosis with cholecystectomy was performed. At present, at one year from the diagnosis, the patient is well and she has no symptoms. Conclusion The use of the EBM method and the application of Fagan’s nomogram can be useful instruments to plan the proper examinations and to allow a correct diagnosis, especially in cases in which differential diagnosis is difficult. Of course, we need of larger clinical studies to confirm these initial promising results.

**Effects of Toll-Like Receptor 9 Ligands on Human Pancreatic Carcinoma Cells**

Rocchi J¹, Chifenti B², Ricci V¹, Funel N², Collecchi P², Del Chiario M³, Pollina LE², Mosca F³, Campani D², Boggi U³, Pistello M¹, Cavazzana A², Bevilacqua G², Ceccherini Nelli L¹, Maggi F¹

¹Virology Section and Retrovirus Centre, Department of Experimental Pathology, ²Division of Surgical Pathology, Molecular and Ultrastructural Pathology and ³Division of General Surgery and Transplants, Department of Oncology, Transplants and Advanced Technologies in Medicine, University of Pisa, Pisa, Italy

**Context** Pancreatic cancer is a devastating disease with most patients dying within 6-8 months after diagnosis. Thus, the development of more effective therapeutic strategies for treating these patients is absolutely needed. A potential novel strategy is targeted immunotherapy. The recent discovery of Toll-like receptors (TLRs), innate immunospecific receptors activated by pathogen-associated molecular patterns, provides new targets to specifically activate this immunity. Among TLRs, TLR9 is expressed by various normal and tumor cells and its activation by DNA containing unmethylated CpG motifs leads to a cascade of molecular events that culminate in the induction of several inflammatory mediators, such as cytokines and nitric oxide (NO), and in the modulation of selected cellular genes expression. **Aim** The study was performed to demonstrate the presence of TLR9 in four human pancreatic carcinoma cell lines (PCCs: PP78, PP109, PP161, and PP117) and to investigate whether its activation by selected oligodeoxynucleotides containing CpG motifs (CpG ODNs) could affect the in vitro characteristics of PP78 and PP109 PCCs.

**Methods** TLR9 expression was assessed by using molecular (RT-PCR and/or real-time PCR, and DNA sequencing), and immunological assays (immunofluorescence and Western Blot analysis). Cell viability and cell cycle parameters were checked by trypan blue exclusion and FACS analysis, respectively. NO production was measured by the Griess reagent. Synthetic CpG ODNs were used as TLR9 ligands for cell stimulation; their specificity was ensured by the use of an ODN that, containing GpC dinucleotides instead of CpGs, can be used as negative control. **Results** TLR9 mRNA and protein were both expressed at basal levels in all PCCs. CpG ODNs treatment of PP78 and PP109 PCCs only slightly increased the TLR9 expression, but it reduced significantly the cell proliferation. Interestingly, the control ODN showed no or minimal effect on cell growth. CpG ODNs also induced a delay in S-phase followed by a G0/G1 arrest and enhanced NO production in PP78 cells. **Conclusions** Our results indicate that TLR9 ligands produce an evident anti-proliferative effect in PCCs and significantly modulate cell cycle progression.
Tumor Size at Presentation is the Key for Managing Serous Cystadenoma of the Pancreas
Department of Surgery, University of Verona. Verona, Italy

Context Since serous cystic tumors (SCTs) are rarely malignant, their optimal management (surgical vs. surveillance) is still unclear. A surgical approach is generally limited to symptomatic patients and in case of doubtful preoperative diagnosis. Aim To analyze clinical presentation, diagnostic work up, surgical vs. nonoperative management and outcomes of patients with SCTs, evaluating a possible correlation between tumor-size at presentation and its growth rate during follow-up. Methods From February 1990 to April 2007, 241 patients with a clinico-radiological or pathological diagnosis of SCT were recorded in our database and data regarding symptoms, treatment and outcomes analyzed. Fifty-six patients with serial magnetic resonance cholangiopancreatography (MRCP) imaging were identified, and tumor growth rates calculated. Results Mean age at presentation was 54 years and 81% of patients were female. Seventy-one percent of patients were asymptomatic. The most common symptoms were abdominal pain (75.6%), acute pancreatitis (8.6%), and weight loss (7.1%). One-hundred and 17 patients (48.5%) underwent clinical observation with a median follow-up of 31 months. Overall, 94 patients underwent resection, with no mortality and an overall morbidity of 46%; final diagnosis at pathological examination was serous cystadenoma in all. SCTs were located in pancreatic body-tail in 56.5% of resected patients and in 39% of those who underwent non-operative management (P<0.05). The median growth rate for tumors <4 cm at presentation (n=43) was 0.096 cm/year, while it was 0.42 cm/year for those larger than 4 cm (n=13) (P<0.05). Conclusions In our experience SCTs are a benign neoplasm affecting preferentially female patients with symptoms in only 1/3 of the cases. SCTs larger than 4 cm are associated with faster growth. Surgical resection should be considered in symptomatic patients and in SCTs >4 cm at presentation, considering the significant risk of tumor-growth. Non-operative management is advisable in small asymptomatic SCTs.

Apolipoprotein in a Series of GEP-NET
Russo D1, Raggi F1, Ultimieri F1, Del Chiario M3, Brogioni S1, Lombardi M1, Funel N, Campani D2, Manetti L1, Raffaelli V1, Boggi U3, Martino E1, Bogazzi F1
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Context Neuroendocrine tumors of the gastroenteropancreatic tract (GEP NETs) represent a rare and heterogeneous group of tumors. The main cause in the development and progression of cancer is often due to escape from apoptosis. Recent knowledge on apoptosis has provided the basis for novel target therapies that exploit apoptosis to treat cancer. Aim The aim of the study was to investigate the prevalence and mechanisms of apoptosis in a series of GEP NETs. Methods The level of apoptosis was evaluated in bioptic samples of GEP NET obtained from 10 patients and 8 controls during surgery. Apoptosis was evaluated by annexin V; expression of pro- and anti-apoptotic proteins was assessed by Western Blot. Results Apoptosis degree was lower (58% reduction) in GEP NET than in control sample (P<0.05). Cytoplasmic level of cytochrome-c was lower
in GEP NET than in controls. To further explore the mechanisms underlying the reduced release of cytochrome-c in GEP-NET, the level of expression of anti- and pro-apoptotic proteins was measured. The expression of pro-apoptotic proteins (Bax, p53, Apaf-1, TRAIL) was reduced; on the opposite, the expression of anti-apoptotic proteins (IAP, AKT, GSK-3beta, ERK 1/2, Bcl-2) was higher in GEP NET than in controls. In addition, caspase-8 and caspase-3 expression was reduced in GEP NET sample.

**Conclusions** In conclusion, most GEP-NETs have reduced apoptosis, which is associated with increased anti-apoptotic proteins and lower pro-apoptotic proteins and caspase. This change in apoptosis might be a mechanism underlying GEP NET tumorigenesis.

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**Low-Dose Radiotherapy Enhances Cellular Growth in a In Vitro Model for Pancreatic Ductal Adenocarcinoma**

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**Context** The role of radiotherapy in pancreas ductal adenocarcinoma (PDAC) treatment remains controversial. Many studies show that radiation stimulates cancer cell dividing, invasion, and metastasis [1, 2]. **Aim** The purpose of this work is to observe cancer cell growth speed after different doses of radiation. **Methods** PP117 and PP78 are two primary cell cultures (PCCs) that have been derived from two PDAC patients which were submitted to surgical resection of pancreas. Before 2 days of the treatment, cells were seeded in 6-well plates. Different doses of radiation (1.14 Gy, 2.28 Gy, and 4.56 Gy at dose rate 3.82 Gy/min) were applied on PP117 and PP78. The experiments were carried out for 9 days and cells were counted at 0, 2nd, 5th, 7th, and 9th days. Cytotoxicity curve was established after counting viable cells by trypan blue exclusion method. **Results** The treatment with radiation produced different cancer cell growths in association with the dose administered at the fifth day; PP78 cells treated with 1.2 Gy and 2.4 Gy showed higher slope of growth-curve than non-treated cells. Also in the fifth day, PP117 showed higher slope of growth-curve in all used doses respect to non treated cells (P=0.010). The two primary cell cultures presented the same growth toward each radiation dose. **Conclusion** These results suggest that low therapeutic doses increase the cellular growth of PDAC in vitro in our model. Further investigations on cytotoxicity and molecular genetics after radiation treatment can explain better the behavior of PDAC in vitro and could optimize radiotherapy in pancreas ductal adenocarcinoma cure.

**References**

Transfection of SIRNA for ERK1-2 in Primary Pancreatic Cancer Cells Cultures by Electroporation Reduce the Cell Growth In Vitro
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Context As pancreatic cancer therapies have failed against the treatment of the pancreatic cancer, innovation of novel therapies is a must. Small interfering RNA (siRNA) appears to be a new strategy to inhibit activated oncogenes products. Electroporation (EP) is an efficient method to increase cell membrane permeability to macromolecules such siRNA. Extracellular signal-related kinase ERK1/2 pathway has a critical role in cancer cell growth, survival and drug resistance. Aim The objective is to detect levels of targeted ERK1/2 by siRNA inserted using electroporation, in primary pancreatic cancer cell culture (PPCCC). Methods Primary pancreatic cancer cell culture no. PP117 were chosen randomly from nine PPCCCs that we have established in our laboratory. PP117 were grown in RPMI 1640 (supplemented with 10% Fetal Calf Serum 1% L-Glutamine and 1% streptomycin) at 37°C, in 5% CO2. The transfection was performed using three different concentrations of antisense ERK1/2 siRNA (20 nM, 40 nM and 80 nM). Also, different electrical pulse protocols were applied while electroporation. After EP the cells were placed in culture slides (Chamber slides multi wells) to be examined by immuno-cytochemistry after 2 days of the transfection using monoclonal antibodies for ERK1/2 (cell signaling). The staining was performed using DAB coloration. Results Transfected cells with ERK1/2 siRNA showed different low level of ERK1/2 expression compared with the control cells. Also we found that the treated cells with 80 nM concentration showed a lower number of cells respect to control (not-transfected). Conclusion ERK1/2 is upregulated to sustain cancer cell survival, which resists apoptosis induced by chemotherapeutic agents. Modulation and targeting ERK1/2 will provoke cancer cell sensitivity to chemotherapeutic agents. Our future prospective is to study ERK1/2 siRNA in other PPCCCs and to investigate chemotherapy efficacy on siRNA treated cells.

MR Imaging versus PET-CT in the Differential Diagnosis of Focal Pancreatic Lesions
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Context The diagnostic approach for pancreatic lesions has evolved in the past few years owing to the improvements in medical imaging technology. In particular, advances in technology for multi-detector CT, MRI and PET-CT have improved the ability to detect focal pancreatic lesions. Aim Our study is aimed to compare MR imaging and PET-CT in the differential diagnosis of benign and malignant lesions of the pancreas. Methods
We retrospectively analyzed 30 patients who had undergone MR imaging and PET-CT for focal pancreatic lesion. Final diagnoses, based on surgery and/or imaging follow-up, were: 12 intraductal papillary mucinous tumors (IPMTs), 4 mucinous cystadenomas, 3 serous cystadenomas, 3 endocrine tumors (2 benign and 1 malignant), 4 focal chronic pancreatitis, and 4 adenocarcinomas (3 ductal and 1 acinar cell carcinoma). All patients underwent MRI at 1.5 T-device (Signa EXCITE, GE Healthcare) and PET-CT (64 slices; Discovery VCT, GE Healthcare). MR protocol included axial T1w/T2w images, 2D/3D MRCP and pre- and post-contrast 3D SPGR T1w sequences. PET-CT protocol included image fusion of unenhanced total body low-dose CT scan and total body PET scan performed 60 min after infusion of 18F-FDG (at the dosage of 10 mCu). Different observers (two in conference for each technique) blindly evaluated detection of focal pancreatic lesions and differentiation between benign and malignant masses. 

**Results** MR imaging correctly characterized all benign lesions and classified as malignant 4/5 lesions (1 FN, acinar cell carcinoma), whereas PET-CT characterized all benign lesions and classified as malignant 4/5 masses (1 FN, malignant endocrine tumor). Both MR and PET-CT showed sensitivity of 96% and specificity of 100%. **Conclusion** MR imaging and PET-CT showed equal high sensitivity and specificity in the differentiation between benign and malignant focal lesions of the pancreas.

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**Insulin Independence in IDDM Patients After Transplantation of Pancreas from Pediatric Donors**

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**Context** Pancreas from pediatric donors could represent a novel source available for transplantation in IDDM patients. **Aim** To verify if pancreata from pediatric donors are able to restore metabolic control in type 1 diabetic patients. **Methods** Between May 2004 and April 2008, 13 IDDM patients received pancreas transplants removed from pediatric donors (age between 12 and 17 years). All of them received the whole organ with enteric diversion of exocrine secretion but 8 with systemic-venous and 5 with portal-venous graft drainage. Pancreas functionality has been evaluated by measurement of HgbA1 values before transplantation and 1 year after the operation; plasma glucose and insulin values are available from oral glucose tolerance test (OGTT) on 2 patients 4 months after the operation. **Results** Donor mean weight was 59 kg (range 42 to 75 kg) and mean BMI was 20.9 kg/m² (range 17.9 to 23.4 kg/m²). After 1 year, patient survival rate is 92%, while pancreas graft survival is 61.5%, 40% for portal and 75% for systemic drainage. Two patients with portal drainage developed graft thrombosis and one interrupted immunosuppressive therapy because of the onset of Moskowitz syndrome. One patient with systemic drainage had an acute rejection episode and one developed graft thrombosis. One year after the operation mean HgbA1 was 4.9% (range 4.6 to 5.4%); during OGTT mean basal glucose was 81.9 mg/dL and mean basal insulin was 9.1 μU/mL, at 120 minutes mean glucose was 88.3 mg/dL and mean insulin was 42.4 μU/mL. **Conclusion** These preliminary results show that pancreas transplantation from pediatric donors can restore long term metabolic control in IDDM patients.
Onset of Exocrine and Endocrine Insufficiency in Patients Suffering from Autoimmune Pancreatitis (AIP)


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Context
Autoimmune pancreatitis (AIP) is a particular form of pancreatitis where an immune-mediated mechanism has been postulated. Few data are available from the literature for the long-term outcome of the disease. Aim To investigate the onset of exocrine and endocrine insufficiency in patients suffering from AIP compared to patients suffering from other forms of chronic pancreatitis (CP). Patients and methods Patients suffering from AIP, from CP associated with daily alcohol intake higher than 80 g/day for at least 5 years (ACP), and from idiopathic CP (ICP) were enrolled. Inclusion criteria were: admission from 1996 to 2006; clinical onset of the disease within one year from the admission; no previous diagnosis of chronic pancreatitis. Definitive diagnosis of CP based on the basis of clinical history, radiological investigations, pancreatic function tests, histology, and surgical evidence. All patients were therefore followed at least every two years. Exocrine pancreatic insufficiency was diagnosed on the basis of fecal fat output >7 g/day or fecal elastase-1 lower than 100 μg/g of stool. Endocrine pancreatic insufficiency (diabetes) was diagnosed on the basis of fasting serum glucose levels higher than 127 mg/L or abnormal OGTT.

Results
Seventy AIP patients (46 M and 29 F; mean age 43.1±15.4 years), 57 ACP (54 M and 3 F; mean age 43.9±9.7 years) and 40 ICP (18 M and 22 F; mean age 43.6±13 years) were studied. The survival curve for the onset of pancreatic exocrine and endocrine insufficiency was similar in AIP compared to ACP and ICP. Exocrine pancreatic insufficiency, but not endocrine, was significantly correlated with pancreatic surgery in AIP but not in non AIP-CP groups (P<0.0001).

Conclusions
The onset of exocrine and endocrine insufficiency in AIP is similar to that observed in ACP and ICP. This indicates that the inflammatory process in AIP is chronic, with a progressive destruction of pancreatic parenchyma, even in the absence of clinical signs and symptoms.

Easy Management of Pancreaticoduodenectomy Early Massive Hemorrhage After Reconstruction with Anterior Pancreogastroanastomosis


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Context
Early massive hemorrhage after pancreaticoduodenectomy is a troublesome complication leading to emergency reoperation in order to guarantee a quick hemostasis. A new technique of pancreogastroanastomosis using an anterior gastrotomy has been recently described. Case report We report a case of management of early massive hemorrhage after pancreaticoduodenectomy being possible thanks to this
technique. A review of the literature is presented. Pancreagogastroanastomosis with anterior gastrotomy allowed easy management of postoperative massive hemorrhage. \textbf{Conclusions.} After pancreaticoduodenectomy, reconstruction with anterior gastrotomy pancreagogastroanastomosis adds to benefit of quick diagnosis and easy management of early bleeding. Abdominal CT scan in a 68-year-old man undergone to pancreaticoduodenectomy and suffering from early massive hemorrhage: a huge amount of blood is demonstrated in the stomach after a pancreagogastroanastomosis (Figure).

\textbf{Mapping of Phosphoinositide 3-Kinase Pathways in Pancreatic Cancer}

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\textbf{Context} Several genetic and epigenetic disturbances have been identified in human pancreatic cancer such as mutations in K-ras oncogene. One key downstream target of the Ras family is phosphoinositide 3-kinase (PI3K), the enzyme responsible for generation of the 3-phosphorylated phosphoinositides and activation of the protein kinase B/Akt. Hyperactivation of Akt has been observed in pancreatic cancer and represents a biological indicator of the aggressiveness of the disease. \textbf{Aim} To gain further insight into the mechanism underlying the development and progression of pancreatic cancer we decided to assess precisely the pattern of expression and intracellular localization of the different PI3K isoforms, their lipid products and their major molecular targets in pancreatic cancer tissues compared to normal counterparts. \textbf{Methods} To study the molecular events associated with PDAC we used an immunohistochemical analysis to dissect the PI3K/Akt pathway \textit{in vivo}. The protein expression of PI3K/Akt pathway in a panel of 25 PDAC specimens was compared with 5 pancreas tissues from donors. \textbf{Results} Our preliminary data demonstrate that human pancreatic cancer tissues express high levels of one specific PI3K isoform, namely the class IB catalytic subunit p110gamma, compared to normal pancreatic tissues from healthy donors. These data represent the first identification of a tumor-specific accumulation of p110gamma in human cancer. Furthermore we found that selective inhibition of p110gamma is able to block proliferation and induce apoptosis in different pancreatic cell lines. \textbf{Conclusions} Based on these results we hypothesize that p110gamma overexpression is a key event in pancreatic cancer progression associated with its high resistance to apoptosis and its chemoresistance.

\textbf{Report of Isolated Pancreatic Tuberculosis Diagnosed with EUS-FNA Cytology}

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\textbf{Context} Pancreatic tuberculosis (PT) is a rare cause of pancreatic disease, especially in immunocompetent subjects also in non endemic areas. Pancreatic involvement could
be associated with miliary tuberculosis; it poses problems in diagnosis, mimicking a pancreatic neoplasm. **Case report** A 33-year-old East European woman was admitted to ER of a country hospital with nausea and vomiting, diarrhea and abdominal pain localized to the epigastrium. Mild lack of appetite in the last month but no weight loss. Transabdominal US revealed: hepatomegaly and cystic mass in the head of the pancreas. Chest and abdominal contrast enhanced CT scan evidenced a inhomogeneous, hypodense and partially necrotic pancreatic head mass, portal vein and mesenteric vessels compression without vascular infiltration. Retropancreatic and celiac-mesenteric axis lymphadenopathy were also found. Than she was submitted to EUS that revealed: inhomogeneous and partially cystic mass of the head and of the uncinate process of the pancreas and peripancreatic and hepatogastric ligament lymphadenopathy. A EUS-FNA was performed on celiac axis adenopathy; cytological analysis revealed cellular debris and necrotic material, acid fast bacilli positivity with typical disposition. Also polymerase chain reaction (PCR) confirmed PT. Multi-drug anti tuberculosis chemotherapy was done. After 10 months of therapy, she was without symptoms: a follow-up abdominal CT scan revealed an important reduction of pancreatic head mass and peripancreatic lymph nodes. **Conclusion** PT can present with a wide spectrum of symptoms and should be considered with high index of suspicion in young and not jaundiced patient with hypodense pancreatic head mass and peripancreatic lymphadenopathy. EUS and EUS FNA cytology are important tools for differential diagnosis with other pancreatic head mass. PCR offers possibility of reliable and quick diagnosis, even faster than microscopy and cell culture. If PT is suspected, every effort should be made to confirm the diagnosis in order to prevent unnecessary laparotomy: multi-drug anti tuberculosis chemotherapy is effective and PT is often a curable disease.

**Solid Pseudopapillary Tumor of the Pancreas: Our Experience**

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**Context** The solid pseudopapillary tumor of the pancreas (SPTP) constitutes a distinct clinical-pathological entity that differentiates from the other cystic pancreatic neoplasms for the young age of onset (almost female sex) and the low degree of malignancy. The SPTP is a rare neoplasm that has made a progressive increase of incidence; the tumor is generally of great dimensions and constantly presents a capsule. The diagnosis in most cases is determined by compressive symptoms or finding of a palpable mass, or occasionally during abdominal imaging (20%). CT and MR are not always sufficient to certainly differentiate between this tumor and other cystic neoplasms of the pancreas; cytological examination in most cases makes diagnosis of SPTP; the malignancy of these neoplasms is attenuated with capsular invasion, lymphonodal diffusion and only rarely liver and peritoneal metastasization. The surgical treatment has to be radical since the malignancy can only be defined by postoperative histological examination and constitutes three options: pancreaticoduodenectomy (DCP), intermediate pancreatectomy, distal pancreatectomy; intraoperative histological examination is mandatory for the diagnostic confirmation and for the evaluation of negativity of the pancreatic stump. Survival after radical resection is excellent. Moreover, in metastatic form to the liver, an aggressive attitude may be still curative and assure longer survivals. **Case report** We report our experience related to three women (age: 28, 19, 8 years; average 18 years) operated between 1995 and 2000 for SPTP. Two patients were asymptomatic and the finding of the tumor was occasional; the third patient presented jaundice and
abdominal pain. The average diameter of the tumors was 6 cm (4, 7, 7 cm). In all cases the value of the tumor markers were normal and only in one case the pre-operative diagnosis was correct. For the two tumors of the head, in one case was performed an enucleo-resection in relationship to esofitic location, in the other, a DCP was made. In the somatopancreatic tumor a distal splenopancreatectomy was performed; only in one case (DCP) the capsule and the surrounding parenchyma were infiltrated by neoplasm. Neither mortality nor operating morbidity was observed. The follow-up performed with CT did not found relapse in any of the three patients after 8, 10 and 13 years.

Atypical Colon Wall Metastases from Pancreatic Tail Cancer
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Context The most frequent metastases from mucinous adenocarcinoma of the pancreas is the peritoneum. Rare sites of metastases are: ovary, vagina and blood. Here we report a case of mucinous adenocarcinoma of the pancreas which presented with symptoms of intestinal occlusion from colonic metastases.

Case report A 83-year-old woman with no history of abdominal surgery presented at our department with abdominal distension and closed bowel to gas and faeces suggesting intestinal occlusion. Abdominal radiography and CT scan confirmed the bowel occlusion showing a stenosis in the left colon. A laparotomy was performed and we have found three tumoral masses in the colon: one in the splenic flexure, one in the descending colon, and one in the sigma. The mass in the splenic flexure involved the pancreatic tail and the splenic ilum. An en-bloc resection of left colon, pancreatic tail and spleen was performed. The postoperative course was uneventful and the patient was discharged on the eleventh post-operative day. The final histological analysis revealed a mucinous adenocarcinoma of the pancreatic tail metastasizing in the left colon in three different distally located sites: splenic flexure, descending colon and sigma. After four months of follow-up the patients is free from disease. Conclusion Pancreatic cancer is one of the most invasive and aggressive tumor. The mucinous form has as primary target of metastasis the peritoneal sierosa, determining also peritoneal carcinomatosis. In our case it is not simple to explain this unusual kind of tumoral diffusion. Several hypotheses could be formulated: retrograde diffusion through lymphatic system, implant after fall of tumoral cell, diffusion by peritoneal sierosa. To our knowledge this is the first case of a mucinous adenocarcinoma of the tail of the pancreas metastasizing on the colon reported in the literature.

Outcome of Pancreatic Resection for Metastatic Colorectal Cancer
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Context The incidence of metastases to the pancreas from colorectal cancer is very low. The benefit of resection of pancreatic metastasis is not clearly defined. Aim In this study we evaluated the outcome of patients undergoing pancreatic resection for metastatic colorectal cancer to the pancreas. Methods Nine patients underwent pancreatic resection for metastatic colorectal cancer from December 1980 to December 2006. The primary cancer were colon (n=7) and rectal carcinoma (n=2). The median interval
between primary treatment and detection of pancreatic metastases was 32.5 months. In three cases pancreatic metastases were synchronous with the primary tumor. **Results** Five patients underwent pancreaticoduodenectomy, and 4 underwent distal pancreatectomy. Associated resection of extrapancreatic lesions was performed in 4 patients, including 3 colectomies and one left hepatectomy. There was no postoperative mortality, but 2 patients experienced complications (one pancreatic and one biliary fistula). Survival averaged 19.8 months (range 5-30 months, median 17.0 months): 7 patients died for metastatic disease from 10 to 33 months after surgery, one patient died for unrelated disease after 5 months, and one patient is alive with hepatic metastases 30 months after operation. **Conclusion** Surgical resection can be performed safely in patients with isolated pancreatic metastases from colorectal cancer, and in selected patients with extrapancreatic disease. Although long-term survival is a rare event, surgery has to be considered in the multimodality approach for good palliation of metastatic carcinoma of the colon and rectum.

A Reappraisal of Distal Pancreatectomy for Carcinoma of the Body and Tail of the Pancreas

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**Context** Adenocarcinoma of the body and tail of the pancreas has historically been considered a disease with dismal prognosis and only few patients (2%) survive five years [1]. Recently, encouraging resources are reported after surgical removal of left-sided pancreatic cancer even after resection for locally advanced disease. **Aim** To determine the outcome of patients undergoing distal pancreatectomy for carcinoma of the body and tail of the pancreas. Analysis of the more recent literature is also included. **Methods** Between 1980 and 2006, 68 patients with invasive carcinoma of the left-sided pancreas underwent distal pancreatectomy. Univariate and multivariate models were used to analyze the impact of clinicopathological factors on long-term survival. **Results** Operative morbidity and mortality were 28% and 4.4%, respectively. Twenty-two patients (32%) underwent extended resection of involved adjacent organs. The median survival time was 11.2 months, and 5-year survival rate was 20%. Six patients survived more than five years: three died for unrelated disease, one died for liver metastases seven years after surgery, two are alive and disease-free after seven and eight years, respectively. During the follow-up seven patients were re-operated for recurrent cancer: five had radical resections, one palliative resections and one by-pass surgery. Stage, extent and radicality of resection significantly affected survival in univariate analysis but none of clinicopathological factors was shown to influence survival in the multivariate model. Analysis of recent literature shows better results in term of operative mortality and crude 5-year survival in the last decade (8%), also after extended resection. **Conclusion** Distal pancreatectomy may offer long-term survival in selected patients with adenocarcinoma of the body and tail of the pancreas. En bloc resection of involved adjacent organs is justified whenever necessary to achieve complete resection of the tumor.

**Reference**

Low Frequency of Microsatellite Instability among European Patients with Pancreatic Cancer
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Context Inherited and acquired defects of the mismatch repair (mmr) genes are responsible for gastrointestinal cancers with microsatellite instability (MSI), which account for 10-15% of the cases. However, the reported prevalence of the MSI phenotype among pancreatic tumors varies widely from 1% to 10%, and the contribution to the inherited burden of pancreatic tumors remains to be determined. Aim To assess the prevalence of tumors with the MSI phenotype among pancreatic neoplasms in Caucasian patients. Materials and methods We studied the prevalence of the MSI phenotype among 135 consecutive pancreatic tumor resections performed at an Italian and at a German referral center. Specimens from Italy comprised 10 ampullary cancers, 6 endocrine tumors and 57 pancreatic ductal adenocarcinomas (PDAC), and those from Germany 62 PDAC. MSI status was determined by taking advantage of mononucleotide repeat markers (BAT25 and BAT26), which are almost monomorphic in Caucasians. Results Only one out 119 (0.8%) PDAC showed MSI, and was identified in a 77-year-old Italian patient (1.7%), as compared to 1 out 10 ampullary cancers (10%, P=0.2), and 1 out of 6 endocrine tumors (17%; P=0.09; MSI in PDAC vs. other histotypes, P=0.04). As to the underlying MMR deficiency, the MSI PDAC was hMLH1-deficient, the ampullary one was hMSH2-deficient, from a hereditary non-polyposis colorectal cancer pathogenic mutation carrier (hMSH2 exon15, codon 846, C->T transition at nucleotide 2536, leading to a stop codon and to a truncated protein), and the defect in the gastrinoma remains to be determined. Conclusions The prevalence of MSI was higher in pancreatic tumors other than PDAC in European patients. In PDAC MSI is a rare phenomenon, which likely does not contribute to the burden of pancreatic cancer, while it might be encountered in less frequent, susceptible to radical surgery, pancreatic neoplasms which might arise in the context of HNPCC.

Mutational Assay of the Neprylisin Gene Promoter in Human Pancreatic Disorder: Preliminary Results
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Context Neprylisin, also known as neutral endopeptidase (NEP), is a cell surface metallopeptidase involved in the inactivation of different neuropeptides, such as substance P. Previous studies have reported an activation of the SP/NK1 pathway in patient with chronic pancreatitis and pancreatic cancer influencing the pain sensation and the tumor growth. These studies did not show changes in NEP expression in pancreatic disorders. The absence of high NEP level might sustain the high level of neuropeptides
in patient with pancreatic cancer and chronic pancreatitis. In addition, loss of NEP expression through the hypermethylation or polymorphisms of the MME promoter has been shown to result in Akt kinase activation and contributes to the clinical progression of prostate cancer. **Aim** To analyze the NEP promoter gene for polymorphism or hypermethylation in patient with chronic pancreatitis and pancreatic cancer. **Methods** DNA was obtained from 20 patients who underwent surgery for chronic pancreatitis, 20 for pancreatic cancer and 10 organ donors. In addition, serum DNA obtained from pancreatic cancer patients and chronic pancreatitis was compared with 95 healthy donors. Gene screening of the NEP codifying region was done by using DHPLC (denaturing high performance liquid chromatography). Methylation assay was done by using methylation-specific polymerase chain reaction (MSP). **Results** NEP codifying region analysis demonstrates 7 polymorphisms. Two of them (439+28 G>T; 1497+20 A>G) on the exon 4 in one patient with pancreatic cancer and on the exon 14 in one patient with chronic pancreatitis were not described before. These polymorphisms were not present in the donors group. In addition, MSP analysis suggests a NEP hypomethylation for both promoter CpG islets in most of the pancreatic cancer and chronic pancreatitis tissue samples when compared with normal group. **Conclusions** Our preliminary results demonstrated for the first time two new polymorphisms in NEP promoter gene in patients with chronic pancreatitis and pancreatic cancer. The hypomethylation of the NEP promoter gene confirms the important role of the SP/NK1 pathway in these and suggest the existence of an additional path sustaining the neuropeptides alterations in pancreatic disorders.

**Magnetic Resonance Imaging in the Assessment of Cystic Pancreatic Lesions and Comparison with Echoendoscopy Rates**

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**Context** Cystic pancreatic lesions include a variety of congenital, inflammatory and neoplastic diseases. **Aim** To assess the accuracy of magnetic resonance (MR) in the characterization of pancreatic cystic lesions, in comparison with endoscopic ultrasound (EUS) and with EUS-guided fine needle aspiration (EUS-FNA). **Methods** We studied 48 patients with MRI and EUS. MRI was performed with a 1.5 T scanner, using an 8 channel phased array coil, employing basal axial and coronal 2D fast spoiled GRE (T1 weighted) and half Fourier fast spin echo (T2 weighted) sequences; cholangiopancreatography was obtained in oblique coronal plane with a strongly T2 weighted half Fourier fast spin echo. Finally dynamic contrast enhanced (Gd-BOPTA, 0.2 mmol/kg) study was obtained, using a 3D fast spoiled GRE sequence. The following features were analyzed: number, location, size, contrast enhancement, dilatation of the ductal system and communication with main pancreatic duct or with secondary ducts. Final diagnosis was based on pathology. MRI data were compared with EUS data in all patients, while pathologic data were available in 39 patients. **Results** Diagnostic agreement between MRI and EUS was 77% (37 patients out of 48); MRI diagnosis was confirmed by pathology in 70.3% of cases (26 patients out of 37); 8 patients did not undergo EUS-FNA, in 2 cases pathology was uncertain and only in one case MRI and EUS diagnosis were not confirmed by pathological data. MRI and EUS were discordant in 23% of cases (11 patients out of
Among them, 6 patients were correctly diagnosed by EUS (54.5%), and 2 patients by MRI (18%). In one patient EUS-FNA was not performed, in one patient it was non-diagnostic and in one case pathology did not confirm MRI-EUS diagnosis. **Conclusion**

**Severe Acute Biliary Pancreatitis: A Proposal for a Minimvasive Approach**

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**Context** Acute biliary pancreatitis (ABP) is about 75% in our country. Severe acute biliary pancreatitis (SAP) is about 20% of all the pancreatitis. Relapse of the untreated pancreatitis is >20%. **Aim** The aim of the study was to define a mini-invasive therapeutic program in a very hard clinical condition: the key points of the therapy are the removal of the Vater’s papilla obstacle for the biliary flow, the treatment of the peripancreatic fluid gatherings and at least, of the gallstones. **Methods** In the period 1999-2007, 198 patients were admitted: 172 mild/moderate ABP, 26 severe. Among the SAP, CT-scan revealed 18 necrotizing cases, and 8 cases with pancreatic edema. Within 72 hours an ERCP/ES was programmed in all patients to remove the biliary obstacle and successfully executed in 16 cases; in 7 cases the procedure was delayed after 10 days because of the temporary papillary impracticably, and non practicable in 3 cases. Among the peripancreatic gatherings there was the CT-scan guided percutaneous drainage for one infected gathering and two intrahepatic ones; another infected gathering was drained by means laparotomic access. Cholecystectomy for lithiasis was executed within 30 days: laparoscopic in 24 patients, laparotomic in two because of previous abdominal interventions. **Results** In relation with the ERCP/ES, there were 4 post-ERCP pancreatitis (15.4%), failure of the procedure in 3 cases (11.5%) and no cases of cholangitis, hemorrhages or duodenal perforations; the percutaneous drainage showed no morbidity with resolution within 10 days; the cholecystectomy did not have major morbidity. One patient (3.8%) died in 20th day because of DIC. **Conclusion** The mini-invasive approach of the SAP was an efficacious and safe therapeutic program with a long period of resolution (35 days in mean) but satisfying for the results.

**Outcome of Pancreas Transplant with a Minimum Follow-up of 5 Years**


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**Context** Long term graft survival is the main challenge of modern transplantation and seems particularly important for diabetic recipients undergoing transplant at a young age. **Aim** To review our institutional experience with pancreas transplantation with
a minimum follow-up of 5 years. Methods We analyzed the outcomes of 80 consecutive patients who received a simultaneous pancreas-kidney transplantation (SPK; n=66) or pancreas transplant alone (PTA; n=14). Immunosuppression included induction therapy with basiliximab (n=70) or thymoglobulin (n=10) and maintenance with mycophenolate mofetil, steroids and tacrolimus (n=40) or cyclosporine (n=40). The impact of different putative risk factors on long-term patients and grafts survival was investigated by multivariate Cox regression analysis. Results SPK recipients: 5-year actual and 10-year actuarial survival rates were 86% and 78%, respectively. At the same time points, graft function rates were 79% and 75% for the pancreas and 83% and 77% for the kidney, respectively. When death with functioning grafts was censored, 5-year actual and 10-year actuarial pancreas and kidney survival rates were 94% and 96%, respectively. For PTA recipients: 5-year patient and graft actual survival was 100% and 69%, respectively. Main causes of death were cardiovascular events (54%), cancer (15.4%), sepsis (15.4%), bone marrow aplasia (7.1%), and suicide (7.1%). Only pre-existing hepatitis B or C infection (P=0.02; hazard ratio 2.9) significantly affected patients long term survival. Patients with long-term graft function showed excellent metabolic and kidney function parameters; post-transplant quality of life was comparable with average scores of general population and significantly improved compared to the type 1 diabetics. Conclusions The early success of SPK is usually long-term maintained with excellent patient and graft survival rates. Since most demises are caused by cardiovascular events, appropriate candidate selection, strict follow-up and implementation of lifestyle may further improve SPK outcomes. Long-term survival of PTA recipients is also excellent and graft survival is quickly improving.

Zero Thrombosis after Pancreas Transplantation with Cold Ischemia Time Below 10 Hours

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Context Although significant improvements in surgical techniques, vascular thrombosis (VT) accounts for more than 70% of all technical failures after pancreas transplantation (PTx). Aim To assess the outcomes of a consecutive series of PTx and evaluate the predictive values of some putative risk factors for VT. Methods Between May 1996 and November 2007, 461 PTx (94.6% primary) were performed in two European centers: 311 SPK, 27 SPK with a living kidney (SPLK), 87 PTA and 36 PAK. Recipients’ mean age was 40 years (range 20-61 years); 442 PTx were enteric diverted and 250 portal drained. Prophylaxis (heparin, low-dose aspirin and/or warfarin) was systematically given. Daily color-Doppler ultrasound was routinely performed. Impact of 56 variables (putative risk factors of VT) related to donor, recipient, transplantation and postoperative course was investigated by multivariate Cox proportional hazard model. Results One- and 5-year survival rates were 95% and 91% for patients and 86% and 75% for PTx, respectively. PTx failure due to complete VT occurred in 6% of cases after a mean time of 5.8 days from the operation. At univariate analysis cold ischemia time (CIT) was the most significant variable affecting VT (P=0.0001; HR 2.6), followed by steroid
avoidance (P=0.02; HR 2.5) and more recent PTx (P=0.04; HR 2.4). Donor body mass index (P=0.09), thymoglobulin induction (P=0.09), non-local harvesting (P=0.12) and waiting time (P=0.16) failed to reach significance but were included in multivariate test. No VT occurred in 93 PTx (20%) with CIT <10 h. Cox model confirmed CIT as powerful risk factor for VT (P=0.0001; HR 2.7), as well as steroid avoidance (P=0.02; HR 2.6) and more recent PTx (P=0.008; HR 3.2). CIT showed a linear progression increase in HR (from 2.5 to 6.2) every single hour step up from 11 h to 19 h. **Conclusion** VT could be avoided if PTx was performed with CIT <10 h. Logistic strategies to reduce CIT, systematic use of anti-inflammatory drugs as well as strict support of hemodynamic stability in donor and in early post-PTx period could reduce VT rate.

In-Situ Expression of Tumour Stem-Cell Markers in Human Pancreatic Carcinoma

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**Context** Pancreatic carcinoma is biologically-aggressive with a propensity to spread locally and metastasize distally. Emerging evidence shows that tumor growth and propagation are sustained by a rare subset of cancer stem-cells having great proliferative potential and chemoresistance. **Aim** This immunohistochemical study compared expression of tumor stem-cell markers CD133, ABCG2, Nestin, Notch receptors and their related ligands Jagged, in clinical samples (24 human pancreatic adenocarcinomas) with adjacent tissue and normal pancreas counterparts. **Methods** Immunostaining was scored via immunoreactive score (IRS) which considers both staining intensity and percentage of positive cells. The average of ten visual fields from different randomly-chosen areas of each specimen was calculated. **Results** Immunohistochemical staining revealed CD133, Nestin and ABCG2 expression on a very small populations of ductal cells within the pancreatic carcinomas (IRS mean±SE: 0.22±0.06, 0.35±0.07, 0.021±0.021, respectively) and in adjacent tissues (0.25±0.25, 1.0±0.41, 0.25±0.25, respectively). These markers were absent from normal counterparts. Immunoreactivities for members of the Notch signalling pathway Notch-1, 2, 3 and 4 were detectable in ductal pancreatic cancer cells (3±0.44, 0.92±0.26, 0.77±0.22, 0.08±0.04, respectively). By contrast, in adjacent tissues, positive immunosignals were seen for Notch-1 and Nocht-3 (2.75±0.48, 0.5±0.29, respectively), but not for Notch-2 or Notch-4. Normal pancreas counterparts expressed only Notch-3 (3±0). Interestingly, nerves and vascular-smooth-muscle cells of vessels within the tumor mass were selectively immunoreactive for Notch-1 and for Notch-2 and 3, respectively. Jagged-1 and Jagged-2 immunoreactivities were marked by staining in pancreatic carcinoma cells (0.61±0.19, 1.9±0.33, respectively) and in adjacent tissues (1.75±0.63, 2.5±1.26, respectively). Normal pancreas tissue was negative. **Conclusion** Pancreatic carcinoma appears to contain a small subpopulation of cells that possess sufficiently unusual properties to allow them to survive chemotherapy and retain their tumor-forming potential. Identification of this subpopulation may lead to new ways to determine prognosis and optimal therapy.