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LECTURES

Asymptomatic Cystic Tumors: What To Do?

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The number of patients with cystic neoplasm of the pancreas detected by various kinds of imaging modalities has been increasing. Especially, abdominal ultrasonography to be performed as a routine modality in the course of a periodic health check-up has resulted in frequent disclosure of asymptomatic pancreatic diseases. Among the cysts recently discovered during the check-ups we have detected small ones with the size of 10 to 20 mm in diameter which include various kinds of histological types diagnosed as from non-neoplastic to the extent of invasive cancer.
Four most common types of cystic lesions of the pancreas include serous cyst adenomas (SCAs), mucinous cystic neoplasm (MCN: adenomas and adenocarcinomas), pancreatic pseudocysts (PPCs), and intraductal papillary-mucinous tumors (IPMTs). SCAs are not generally considered at risk for malignant progression, and therefore they are resected only if any accompanied local complications exist. MCNs should be treated quickly because they have a high potential malignancy even if they are adenomas. PPCs should be drained if clinically indicated. IPMTs show a wide spectrum of histological type such as intraductal adenoma/adenocarcinoma, carcinoma with stromal invasion, and hyperplasia. IPMTs should be treated on the basis of their degree of malignancy, in such a way as follow-up, function-preserving minimal pancreatectomy, or radical operation with lymphadenectomy. Recently developed imaging modalities such as helical CT, MRI (+MRCP), endoluminal ultrasonography, and pancreatoscopy are capable of revealing the detailed structure of cystic lesions of the pancreas. And it is possible to make differential diagnosis of each histological type. Up to now, there is no effective diagnostic tool to distinguish benign lesions from malignant ones. However, it is possible to distinguish a neoplastic from non-neoplastic lesion and invasive lesion from non-invasive lesion. We experienced 105 IMPT, 10 MCN, and two SCA cases, respectively resected. We also treated some cases of pseudocyst nonoperatively. In this presentation, we will discuss the biological behavior, differential diagnosis, and adequate treatment of cystic tumors of the pancreas.

Vascular Infiltration in Pancreatic Tumor: A Thorny Issue

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Background and Aim The prognosis of patients with pancreatic cancer is extremely poor due to the difficulty of early diagnosis and complexity of the anatomy. Vascular infiltration is one of the critical issues of the resectability of the tumor and a significant prognostic factor. The data of Japanese Pancreatic Cancer Registry were analyzed to clarify the impact of vascular infiltration toghether with vascular resection on the post-operative survival.
Methods Annual requests for data on pancreatic cancer were issued by Japan Pancreas Society (JPS) from 1981 through

2000 to 350 leading hospitals in Japan. Data on 18,495 patients with pancreatic cancer were submitted using standardized classification by JPS, in which major vascular infiltration is assigned to Stage IVa (locally advanced) or IVb (distant spread). The cumulative survival was analyzed by actuarial method.

Results Through the 20 years of experience, the resection rate for pancreatic cancer increased from 30.3% to 45.1%, since aggressive surgery including major vessel resection was performed in many institutions. However, the median survival of Stage IVa disease is increased from 9 to 12 months. Of 18,495 patients, 5,026 patients with histologically confirmed ductal adenocarcinoma underwent pancreatectomy. The 5-year survival of the patients with Stage IVa disease resected was 11.5%, while that of non-resected Stage IVa disease was 3.4%. Microvascular infiltration was observed even in Stage I disease. Portal vein resection and arterial resection were performed in 653 patients (12.9%) and 113 patients (2.2%) respectively. The survival strongly depended on the extent of the disease including vascular infiltration rather than the resection of large vessels. In the patients with locally advanced Stage IVa disease, the resection of the vessels did not improve the survival even if the extent of vessel infiltration was matched.

Conclusions Vessel resection does not have an additional impact on the survival of the patients although pancreatectomy itself significantly improve the survival of the patients. Novel therapeutic modalities for residual carcinoma after pancreatectomy should be investigated.

Future in US Virtual Endoscopy and EUS-FNAB in Pancreatic Diseases

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Background Virtual endoscopy (VE) has been made mainly with computed tomography (CT) and magnetic resonance imaging (MRI). In recent years, we have been able to get VE images using extracorporeal ultrasonography (US), and to get high quality VE images, clearer US images are necessary. Tissue harmonic imaging (THI), which derives from contrast harmonic imaging to emphasize the signals of contrast-enhanced agent, brings us clearer US images. On the other hand, endoscopic ultrasonography guided fine needle aspiration biopsy (EUS-FNAB) has developed greatly more in Europe and U.S. than in Japan. This method is very useful, but there may be a tendency that image diagnosis is undervalued. In Japan, dissemination with EUS-FNAB is reported, and in the cases that a precise diagnosis is made only with images, EUS-FNAB may not be performed.

Aim To clarify the usefulness of newly developing US methods and their influence on EUS-FNAB procedure contrast-enhanced US (CE-US) and virtual endoscopy - as well as contrast enhanced EUS images.

Methods The subjects were 124 patients with pancreatic disorders who underwent CE-US and/or VE, EUS at our department. CE-US: The agent (Levobist, Tanabe, Japan) was adjusted to 300 mg/mL in concentration, and was injected intravenously via 21-gauge needle inserted into the right median antecubital vein, at a rate of 1 mL/sec (8 mL in total volume). The observation procedure is as follows: 1) The target lesions were observed by pulse inversion harmonic mode with low mechanical index (M.I.) value (0.4) for 60 seconds after injection - early phase. VE: After transported to the workstation, raw data were reconstructed to VE images. EUS: In the same way as CE-US of agent

administration, and the enhancement effect of color (power) Doppler images was evaluated how to influence the EUS-FNAB procedure.
Results CE-US: The characteristic vascularities were demonstrated in each disease. VE: The images of VE were similar to resected specimens in 74.5%. EUS: Improved images influenced the EUS-FNAB procedure in 30%.
Conclusions CE-US, VE and EUS may be useful diagnostic modalities in pancreatic diseases.

CFTR Gene Mutation and Chloride Channel Dysfunction in Chronic Pancreatitis: from Gene to Clinics?

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Background and Aim Abnormally high sweat chloride concentration in patients with chronic pancreatitis was reported more than two decades ago. Association of mutations in the *CFTR* gene and chronic pancreatitis has recently been reported from England and the United States. These results suggest that chronic pancreatitis may develop in a group of individuals with impaired CFTR function. The aim of this study was to test if such mutations underlie chronic pancreatitis in Japan, where cystic fibrosis is very rare compared with European countries.
Methods Finger sweat chloride tests were conducted in 25 patients with chronic pancreatitis and 25 healthy volunteers. *CFTR* mutation analyses were conducted in 52 patients with chronic pancreatitis and 108 healthy volunteers.
Results Of 25 patients with chronic pancreatitis, 56% had sweat chloride levels over 60 mmol/L, a level consistent with the diagnosis of cystic fibrosis (CF), while only 16% of 25 healthy subjects exceeded this level. Twenty major *CFTR* mutations (E60X, R117H, R334W, R347P, A455E, ΔI507, ΔF508, G542X, G551D, R553X, 621+1G>T, 1078delT, R1162X, S1251N, W1282X, N1303K, 1717-1G>A, 2183AA>G, 3659delC, 3849+10kbC>T), which cover about 80% of mutations in Caucasian populations, were detected in neither patients nor control subjects. The frequencies of genotypes of TG dinucleotide repeats (TG)n and polythymidine (poly-T) tract of intron 8 between two groups were not significantly different.
Conclusions These results suggest that the impaired *CFTR* function may underlie about a half of our patients with chronic pancreatitis and that the *CFTR* mutations in Japanese patients, if present, are of rare forms.

Expression of Peptide Receptors in Human Pancreatic Cancer Differs from Those in Animal Models

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Background Although the information from animal models is helpful to understand the biology of pancreatic cancer, the discrepancy between species unavoidably results in gaps in the knowledge on human pancreatic cancer.
Aim Visualization and comparison of the

alterations in expression of peptide receptors from normal pancreas to pancreatic cancer in human, hamster and rat.
Methods Storage phosphor autoradiography.
Results In the pancreata of azaserine-treated animals a significantly increased binding capacity of high-affinity receptors for cholecystokinin (CCK) was found. However, the specific CCK-A receptors expressed in normal hamster pancreata were markedly reduced in pancreatic preneoplastic lesions and absent in adenocarcinomas. Furthermore, CCK-B receptors, present in all normal pancreata, were not detected in any of the human pancreatic cancers. An up-regulation of vasoactive intestinal peptide and somatostatin receptors in human pancreatic cancer was opposite to those found in rodent. The differences of secretin receptor between normal pancreas and pancreatic cancer in human are similar to those observed in hamsters and rats. The disappearance of bombesin receptors was observed in human pancreatic cancer and in pancreatic (pre)neoplastic lesions of rodent.
Conclusions The distinct characteristics and spectra of receptors for peptides in pancreata of human and rodent in this study suggest important differences between humans and laboratory animals.

CASE REPORTS

Hemosuccus Pancreaticus Due to Bleeding from a Splenic Artery Aneurysm

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A 64-year-old man experienced several episodes of melena and hemetemesis associated with nausea and epigastric pain radiating to the back, over a 2-year period. He underwent repeated upper and lower GI endoscopic procedures for the same and was detected to have discrete angiodysplastic lesions of the duodenum, ileum and colon. He underwent argon plasma coagulation several times for the above lesions. Due to persistence of GI bleeding, ileocaecal resection (distal 10 cm of ileum) was done for ascending colon angiodysplastic lesions. Despite surgery, bleeding episodes persisted. During the last three months, he had weekly episodes of melena necessitating several blood transfusions. He also underwent 22 further endoscopic procedures (gastroscopy, colonoscopy and enteroscopy). Nuclear scan and angiography were negative. Angiography with heparin perfusion was thus performed and revealed a 4 cm calcified splenic artery aneurysm, without evidence of active bleeding. During the last gastroscopy procedure, oozing of blood from the papilla of Vater was seen. Patient was referred to us for further evaluation. A plain abdominal radiograph showed left hypochondrium calcification. ERCP revealed *hemosuccus pancreaticus* from the major papilla. Pancreatography showed mild uniform dilation of the main pancreatic duct with external smooth compression in the distal-body region and significant duct dilation and irregularity distal to the compression. Biliary and pancreatic sphincterotomy were performed and a 6 Fr. nasopancreatic drain was placed. *Hemosuccus pancreaticus* was presumed to be due to blood leak from the splenic artery aneurysm into the pancreatic duct. Angiographic embolization of the splenic artery with coils was performed. A check nasopancreatogram after 48 hours showed a normal-sized pancreatic duct without compression or irregularity. The nasopancreatic drain was removed and patient was discharged after 4 days. He has had no further episodes of gastrointestinal bleeding since two months.

Pancreatic Neuroendocrine Tumours Associated with von Hippel Lindau Disease: A Case Presentation

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Background Von Hippel, a German ophthalmologist, first recognized the familial nature of retinal hemangioblastomas. However, Arvid Lindau, a Swedish ophthalmologist from Lund is credited with the critical observations that cerebellar and retinal hemangioblastomas are part of a larger "angiomatous lesion of the central nervous system" and that the condition was heritable. Subsequent scattered clinical reports of small families confirmed the association of CNS hemangioblastomas and renal and pancreatic cysts, pheochromocytomas, renal cell carcinomas, and epididymal cystadenomas. Melmon and Rosen summarized these results in a landmark paper in 1964. They described a large VHL family and codified the term "von Hippel-Lindau".
The incidence and natural history of pancreatic neuroendocrine tumours occurring in VHL are not known.
Case report in May 2000 a 25-years-old woman with a diagnosis of von Hippel Lindau disease was referred to the surgical clinic because of a tumor at the body of the pancreas. In 1996 the patients was surgically treated for hemangioblastomas of the CNS. On physical examination, was afebrile, with stable vital signs. A CT scan of the abdomen showed a heterogeneous mass of 2 cm that enhanced after the administration of contrast and occupied the pancreas body, suggesting a localization of VHL disease. We treated this patient surgically with the resection of the body of the pancreas. The histological examination showed a neuroendocrine tumor of the pancreas in patients with VHL disease.
Conclusions Neuroendocrine tumours can occur in patients with hereditary syndromes predisposing to multiple endocrine neoplasia (MEN) and Von Hippel-Lindau disease (VHL). The diagnosis of VHL disease should be suggested in case of familial pheochromocytoma and/or bilateral localizations, but also in case of neuroendocrine tumours of the pancreas associated with another cardinal lesion of the disease. Early screening and treatment of this potentially fatal disease is essential.

Adult Pancreablastoma: Case Report

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Pancreatoblastoma is a rare exocrine tumor of the pancreas occurring in the first decade of life. Adult pancreatoblastoma was reported in eleven cases. A case of adult pancreatoblastoma is herein described. A.M., a 30 year-old male, who presented a retrosternal pain from three years was recovered in our institution. An abdominal ultrasound was performed and showed a large solid mass of the head of the pancreas; a spiral abdominal CT confirmed the presence of the pancreatic mass of the head of the pancreas that appeared to involve the splenic vein, the superior mesenteric vein and inferior vena cava; celiac and superior mesenteric angiography with cavography showed a

neoplastic thrombosis of the superior mesenteric vein and of the inferior vena cava. Echo-guided percutaneous fine needle cytology did not allow a proper diagnosis although it permit to exclude a ductal pancreatic cancer. At laparotomy pancreatic mass of the head did not involve neither superior mesenteric vein or inferior vena cava. A frozen biopsy showed a pancreatic neoplasm with acinar differentiation. Surgical treatment was performed and it consisted in pancreatoduodenectomy according Traverso-Longmire. Histologically the mass was a pancreatoblastoma. Post operative course was uneventful and the patient is alive and without disease at 10 months from operation.
The reported case showed some diagnostic and therapeutic problems. The imaging techniques considered the neoplasm unresectable because of vascular involvement; fine needle cytology did not allow a proper diagnosis although a ductal pancreatic cancer was excluded clearly. However poor clinical symptoms due to a large mass of the head of the pancreas suggested an invasive growth instead of an infiltrative growth of the tumor confirmed at the laparotomy. This latter feature of the pancreatic neoplasm suggested a surgical treatment without adjuvant therapy.

ORAL COMMUNICATIONS

Secretin-MRCP Guided Diagnostic/Therapeutic Algorithm in Recurrent Idiopathic Pancreatitis: Results on Medium Term Follow-up

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Background MRCP has a similar diagnostic accuracy as ERCP in the diagnosis of pancreatic diseases. The administration of secretin enhances the MRCP pancreatic ductal system definition. No data are present in literature about the role of conventional or secretin-MRCP in recurrent acute pancreatitis.
Aim To test the guide role of conventional or secretin-MRCP in the diagnostic and/or therapeutic algorithm of recurrent idiopathic pancreatitis.
Patients and methods Eighteen patients (9 males, 9 females; mean age: 40.8 years) with recurrent acute pancreatitis of unexplained etiology defined as the presence of almost two episodes of pancreatic type pain associated with serum amylase at least double the upper normal limit. The mean number of recurrences was 2.2 (range: 2-5). The mean duration of the disease was 14 months (range: 6-36 months). Secretin completed MRCP only in absence of ductal strictures and/or dilations: a positive secretin test (i.e. delayed ductal emptying = diameter of the main pancreatric duct [MPD] 15 minutes after secretin i.v. injection > 1 mm than basal value) indicated biliary endoscopic sphincterotomy (ES); a negative test indicated an observational follow-up with UDCA oral therapy.
Results Four patients had RMCP evidence of MPD stenosis and were submitted to ERCP with brushing and following surgery in one case and endoscopic dilation and stenting in the other three. Other four patients had RMCP evidence of pancreas divisum without ductal dilation: the two patients with secretin positive test underwent operative ERCP: pancreatic sphincterotomy in one patient, temporary pancreatic stent in the other. The patient submitted to pancreatic sphincterotomy developed after one year an obstructive pancreatitis of the dorsal dominant duct with two small cysts in the body of the

pancreas. Nine patients had a normal RMCP. The single patient with positive secretin test underwent biliary sphincterotomy. Only 1 of the 9 patients with negative secretin test during follow-up (8 months after MRCP) developed another relapse of pancreatitis resolved by biliary sphincterotomy.

Conclusions Secretin RMCP can guide the diagnostic and/or therapeutic algorithm in patients with recurrent idiopathic pancreatitis. Secretin RMCP could select patients for therapeutic ERCP with potential advantages in terms of cost-effectiveness ratio.

Study of Pancreatic Outflow by US-Secretin Test (US-S) and MR Colangiopancreatography (MRCP-S) with Secretin Stimulation: Results of a Comparison in 20 Patients with Acute Recurrent and Chronic Obstructive Pancreatitis

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Background The US-S permits the functional study of pancreatic outflow by measuring the diameter of the main pancreatic duct (MPD) before and after secretin stimulation e.v. This test can also be performed during MRCP-S.

Aim The aim of the study was to compare the pancreatic outflow data obtained with the two procedures in patients with acute recurrent pancreatitis (ARP) and chronic obstructive pancreatitis (COP).

Materials and Methods Twenty patients (13 M, 7 F; mean age 47.3 yrs; range 23-76), 14 ARP (8 M, 6 F; mean age 49.6 yrs, range 23-76) and 6 COP (5 M, 1 F; mean age 41.8 yrs; range 33-60) underwent US-S and MRCP-S, using the same dose of secretin (Secrelux 1 fl). The interval between the 2 examinations was not more than 15 days. The MPD was evaluated with both procedures at time 0 and at 1, 3, 5, 7, 10, 12, and 15 min after stimulation. US-S findings were regarded as normal if the basal MPD was ≤ 2 mm with reversion to normal values within 20 min. At MRCP-S the pancreatic outflow trend was regarded as normal when the basal MPD was ≤ 3 mm with reversion to normal values within 15 min.

Results The pancreatic outflow data proved pathological in 7/20 patients (35%) at US-S and in 4/20 (20%) at MRCP-S. Pancreatic outflow in ARP patients was normal in 12/14 (86%) at US-S and in 11/14 (79%) at MRCP-S, while in COP group pancreatic outflow was normal in 1/6 (17%) at US-S and in 3/6 (50%) at MRCP-S. Concordance between the two procedures amounted to 70%. The concordance was 78.6% in the patients with ARP and 50% in those with COP. The MPD was 1.3 mm (0.5-6.5 mm) at US-S and 1.9 mm (1-8 mm) at MRCP-S. The mean diameter of W at 15 min was 1.8 mm (0.8-8 mm) at US-S and 2.1 mm (1-8 mm) at MRCP-S. In patients with COP the basal MPD was 2.2 and 2.7 mm at US-S and MRCP-S, respectively, while the 15 min diameter was 3 mm with both procedures. In patients with ARP the basal MPD was 0.8 and 1.7 mm at US-S and MRCP-S, respectively, while the respective 15 min diameter where 0.9 and 1.3 mm.

Conclusion In the study of pancreatic outflow, US-S results are in good agreement with those obtained by MRCP-S, particularly in patients with ARP. After prior evaluation with MRCP-S, this procedure can therefore be profitably used in follow-up.

Neurolytic Coeliac Plexus Block: Does Radiologic Imaging Correlate with Good Pain Relief ?

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Background Radiologic imaging is considered one of the most important parameter to evaluate the complete destruction of the coeliac axis during neurolytic coeliac plexus block (NCPB) [1, 2]. Till now, no prospective study evaluated the correlation between the radiologic images and the abolition of coeliac pain after NCPB.
Aim To establish if a good correlation between positive CT images and abolition of coeliac pain 48 hours after NCPB exists and if the cancer spread in pre-aortic area (PA) can influence the efficacy of transaortic coeliac neurolysis (TCN), we have performed a prospective trial.
Method One hundred patients afflicted by pancreatic cancer pain of coeliac type were randomly treated with two different technique of NCPB: group 1 bilateral chemical splanchnicectomy (BCS) 50 patients, and group 2 TCN 50 patients. NCPB was performed under fluoroscopic guidance. Then all the patients underwent CT that was judged positive or negative by a radiologist according to the criteria we already described [2]. Pain relief after 48 hours was assessed in patients with a positive CT by a physician not involved in the study. Statistical analysis was obtained by Fisher's exact test.
Results We achieved 49/50 positive CT with 48/49 (98%) pain relief in group 1 and 30/50 positive CT with 24/30 (80%) pain relief in group 2. In group 2 in 12 patients PA was infiltrated by cancer while in 18 patients it was not. Good pain relief was gained in 7/12 (58%) patients with cancer spread in PA and in 17/18 (94%) patients with PA free. This result was found statistically significative (P=0.025).
Conclusions The probability that a positive CT means the abolition of coeliac pain in the 48 hours next to the block is very high when a BCS is performed. In the overall population of patients undergone TCN the correlation between positive CT images and pain relief is still high (80%). However in these patients the presence of cancer spread in the preaortic area significantly reduces the possibility to obtain both a correct diffusion of the injected solution in the target area and a complete pain relief.

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Pancreatic Carcinoma Pain: The Opinion about Efficiency in Clinical Practice

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Background Most of the patients with advanced pancreatic cancer and up to 60% of the patients, with any stage of the disease, experience significant pain. The cause of cancer pain is treated with radiation, surgery or chemotherapy whenever possible.
Aim The effective management of cancer patients with pain is best accomplished with

co-ordination of several medical services, but the information about the costs of pancreatic cancer pain is limited up to now.
Methods Decision analysis was used to simulate alternative staging strategies. Cost inputs were based on National Health Service (NHS) reimbursements; clinical inputs were obtained from the available literature. Model endpoints of interest were cost per curative treatment of pain.
Results Pancreatic cancer occurs in approximately 29,000 patients per year and it is the fourth leading cause of cancer related-mortality. The World Health Organization (WHO) estimates that 25% of all cancer patients died with unrelieved pain. The economic impact of pancreas cancer is also of great concern. The direct medical care cost of pancreatic cancer pain is related to hospitalization costs. Room and board accounted for 45% of hospitalization costs; long-term costs accounted for 14% and outpatients costs accounted for 9% of direct medical costs. The nearly totality of literature production justify the efficiency in the clinical practice resorting to the use of Evidence Based Medicine (EBM) instead of Health Economics (HE).
Conclusions Defining this patient's population help to reduce direct care costs in pancreatic cancer pain. However, prospective data are lacking in this regard and will need to be addressed in the future. The economical evaluation aims to characterize the efficiency that is most advantageous account cost/result: the awareness of any therapy cost have an ethical significant before than practical; the resources, that can be saved, can be in turn better used for other patients. Which the introduction of the HE in the organization of NHS, there has obviously been a certain reaction on behalf of the medical class characterized by a strong dispute. The answer has thus been development of an alternative current of opinion, the so-called EBM. The history among the various HE school and supporters of EBM is in practice the history of different ethical perspective existing among economists and doctors. The risk of an uncorrected evaluation about efficiency of management of the cancer patients is the different evaluation of ethical perspective: collective (HE) or individual (EBM) and of utilized vehicle: the formulary (ES) and the guidelines (EBM).

Deficiency of Immune Status in Pancreatic Cancer: A Possible Explanation of the Clinical Severity of the Disease

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Introduction The prognosis of cancer depends on either tumor aggressiveness and on the host immune response. It is demonstrated that the count of circulating lymphocytes and in particular of T cells is an independent prognostic variable for overall survival in gastric, colorectal and lung cancer.
Aim Aim of this retrospective study is to evaluate the cell-mediated immune status in operable pancreatic cancer patients and to compare it with other gastrointestinal tract tumor (gastric and colorectal adenocarcinoma).
Methods Patients with pancreatic cancer operated during this past year (n=16; N0M0=10; N+M0=6) were evaluated. Total lymphocytes count, lymphocyte subsets CD3, CD4, CD8 cytotoxic, NK e CD8 suppressor were assessed preoperatively by fac-scan. The observed values were compared with the same parameters, registered in patients with gastric cancer (n=31) and with colorectal cancere (n=51). The median values were analyzed by Student-t test and chi square.
Results Median values of total lympocytes, CD3 e CD4 cells were significantly decreased

in patients with pancreatic cancer, with respect to those observed in gastric and colorectal cancer patients.
Among patients with pancreatic cancer, only 3/16 had lymphocyte total count within total lymphocytes normal values (>1,500/mm^3); only 6/16 had normal counts 3 (>1,020 n/mm^3).
Conclusions Patients with pancreatic cancer display a deeper degree of immunodeficiency since the early stage of disease, with respect to those with other gastro-intestinal tract tumors. The compromised immune status at baseline might have a relevant role on the poor prognosis associated with pancreatic cancer even after surgical radical resection. Further studies will be helpful to evaluate the immune response to trauma in such patients and to evaluate the possibility to impact on the disease prognosis, through administration of lymphocyte growth factor.

n/mm^3 (mean±SD)	Pancreas	Gastric	Colorectal
Total lymphocytes	1,196±385	1,650±567	2,035±192
CD3	752±337	1,088±563	1,324±420
CD4	540±260	611±299	810±280

Pancreatic Cancer Produces Chemokines: Relevant Role of MCP-1 on Tumour Behaviour and Prognosis

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Background Chemokines may control the macrophage infiltrate found in many solid tumour. Tumour associated macrophages (TAM) may be cytotoxic to tumour cells. Indeed TAM may promote tumorigenesis by the production of cytokines.
Aim The aim of this study was to discover whether MCP-1, a CC chemokine able to attract macrophage, is expressed in human pancreatic cancer and to determine whether there is a correlation between MCP-1 levels and clinical prognosis.
Methods and Results MCP-1 secretion and MCP-1 mRNA was evaluated in 12 different lines and 4 primary culture of pancreatic cancer by ELISA and RPA assay. All primary culture and 5/12 of the lines were able to secrete MCP-1. By immunohistochemistry and in situ hybridisation neoplastic duct from surgical specimens appeared positive for MCP-1. By immunohistochemistry (n=15) macrophages appeared the prevalent leukocytes infiltrating pancreatic cancer (CD68+ 49±5%; CD15+ 26±6; CD3+ 22±3; CD1a 3±2%). Serum MCP-1 was higher in patients with pancreatic cancer than in control group (pancreatic adenoK: 434±77 pg/mL, n=51; control group 233±18, n=187; chronic pancreatitis: 270±55, n=7; P=0.0001). The serum MCP-1 decreased after surgical removal of pancreatic cancer (pre surgical 600±214 pg/mL vs. 376±61 pg/mL post surgical, n=17, P=0.07) and portal MCP-1 appeared higher than systemic MCP-1 (404±30 pg/mL vs. 318±29 pg/mL, n=12; P=0.01). Serum MCP-1 appeared in inversion relation to tumour size (P=0.01) and lower in metastatic patients (metastases: 222±20 pg/mL, n=14, not metastases 519±115 pg/mL, n=36; P=0.0009). In resected tumours (n=25) serum MCP-1 appeared higher in pT3 (667±192 pg/mL; n=19) than pT4 (310±54 pg/mL; n=6) and appeared in inversion relation to grading (G1: 784 pg/mL, n=3; G2: 503 pg/mL, n=9; G3: 326 pg/mL, n= 13) and proliferative activity by MIB. To understand if MCP-1 secretion by pancreatic cancer may play a role in clinical outcome we divided patients in terziles: low MCP-1 group (L: 180±8 pg/mL; n=17), medium MCP-1 group

(M: 294±9, n=17), high MCP-1 group (H: 819±200 pg/mL, n=17). Resectability increased with serum MCP-1 (L: 38%, M: 47%, H: 65%). Presence of vascular invasion and metastases decreased with serum MCP-1(vascular invasion L=66%, M=41%, H=40%; metastases: L=63%, M=18%, H=6%; P=0.0007). One year survival in all patients was 11% for L, 40% for M and 68% for H (P=0.02). One year survival in resected patients was 34% for L, 87.5% for M and 100% for H (P=0.02).

Conclusion 1) MCP-1 is produced and released by pancreatic ductal carcinoma; 2) the loss of capacity to secrete MCP-1 by pancreatic cancer induces a more aggressive biological behaviour; 3) serum MCP-1 appeared as a relevant prognostic marker for pancreatic cancer.

Radiation Therapy (RT), Concurrent Gemcitabine (GEM) and Infusional 5-Fluorouracil (5FU) in Patients with Localized Unresectable Pancreatic Adenocarcinoma

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Background GEM and 5FU are active systemic agents in human pancreatic cancer and both are potent radiation sensitizers. Preclinical and clinical studies have confirmed the radiation sensitizing activity of low-dose GEM. Other data indicate that a twice-weekly GEM schedule may result in increased sensitization compared to a once-weekly schedule.

Aim Based upon these observations, we initiated a study to determine the feasibility and effectiveness of RT combined with GEM and continuous infusion (c.i.) 5FU in locally advanced pancreatic adenocarcinoma.

Methods Twenty-six patients with unresectable pancreatic adenocarcinoma, were enrolled in this study between November 1998 and July 2000. Median age was 57 (range: 33-68), median Karnofsky score 90 (range: 80-90). Radiation was delivered using a 4-field technique to 45 Gy followed by a boost of 9-14.4 Gy. GEM was given weekly on Tuesday and Friday at a daily dose of 30 mg/m² and 5FU was administered in c.i. at the daily dose of 200 mg/m² through the entire course of RT. WBC and platelets count was performed twice per week.

Results 26 patients completed the RT program. Two patients failed to complete therapy for reasons other than toxicity and were not valuable. Median follow-up time was 10 months (4-23), median survival time 11 months and median time to progression 8 months. Radiological response was: CR in 1 patient, PR in 5, and no change in 18. Hematological toxicity of grade III was observed in 2 patients, II in 9 and I in 6 and gastrointestinal of grade III in 2 patients, II in 8 and I in 6. Only 5 patients completed the GEM scheduled treatment. In 4 patients 5FU infusion was stopped because of toxicity.

Conclusions Twice-weekly GEM, 5FU and concurrent RT yield satisfactory results in terms of local control and survival. However, 5FU and GEM administered concurrently with RT have a synergistic effect which increases toxicity compared to more conventional treatments. Based on these data we initiated a study with combined RT and GEM at the weekly dose of 40 mg/m². As expected, hematological toxicity seems milder with GEM at lower doses; however, no conclusions can be drawn from the data currently available.

Treatment of Unresectable Pancreatic Carcinoma by Intraluminal Brachytherapy in the Wirsung Duct: A Feasibility Study

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Background and Aim Feasibility and clinical outcome of intraluminal brachytherapy (ILBT) in Wirsung duct in unresectable pancreatic carcinoma patients was evaluated.
Methods Eight patients (7 males, median age: 74 years, range: 52–80 years) with unresectable pancreatic carcinoma of the head or proximal body without distant metastases received ILBT. All patients underwent ERCP for biliary and/or pancreatic stenting along with placement of nasopancreatic ± nasobiliary drain to facilitate placement of the radioactive source. The dose of ILBT administered was 30-50 Gy calculated at 1 cm from the Iridium-192 (^{192}Ir) wire axis. Three patients with an Eastern Cooperative Oncology Group performance score of ≤2, and permissible hematological parameters received combined modality treatment (external beam radiotherapy with 5-fluorouracil followed by ILBT). The remaining 5 patients received ILBT alone. In case of large tumor extended significantly towards the bile duct, a nasobiliary drain was also placed to facilitate placement of an additional radioactive source (1 patient).
Results There were no complications associated with the endoscopic procedure. None treated with combined modality therapy experienced acute toxicity > Grade 2. Radiation induced acute or late toxicity was not recorded in patients treated with ILBT. One patient treated with combined modality treatment developed gastric ulceration and severe bleeding. Dislodgment of the intraluminal source occurred in 3 patients. Repositioning of the source was done in 2 patients, since the 3rd patient had already received a dose of 36 Gy. After ILBT, tumor mass reduction >50% was seen by CT and US in 3 patients. Palliation of jaundice and pain was achieved in all. One and two-year actuarial survival was 37.5% and 12.5% respectively (median survival: 8 months, range: 5-37 months). Five patients had local progression of disease (2 required gastroenterostomy) and 3 had distant metastases.
Conclusion ILBT in the Wirsung duct in patients with unresectable pancreatic carcinoma is safe and feasible. Further randomized controlled studies comparing it to other available modalities are needed.

Adjuvant Chemotherapy in Pancreatic Adenocarcinoma: A 12-Year Experience

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Background Adjuvant therapy in pancreatic ductal adenocarcinoma (PDA) is a controversial issue. Our policy has been to use post-surgical chemotherapy (CHT) followed by radiotherapy (RT) in all suitable patients (pts) ≤70 years.
Aim The aim of this study was to compare the outcome of 3 different CHT regimens used in different periods of time.
Methods Since January '89, 201 pts were resected with curative intent at our institution for PDA. Of those, 6 (3%) died

perioperatively and 56 were followed up elsewhere. In the same period, 25 pts coming from other institutions were referred to our department for post-surgical management. Altogether, 164 pts were evaluated and 97 (59%) received CHT. Until December '93, 28 pts received EF regimen (epirubicin 50 mg/m^2 day 1; 5-fluorouracil 1 g/m^2 days 1-5). Since then and till October '97, 29 pts received PEF (EF plus cisplatin 50 mg/m^2 day 1). Afterwards, 27 pts received PEF-G regimen [J Clin Oncol 2001; 19:2679-86]. Main study group characteristics are reported in the table. Other 13 (13%) pts, uniformly distributed in the 3 periods, received other CHT regimens based on the attending physician's choice.

Results 64 (77%) pts died and 2 were lost at follow-up at 16 and 27 months from surgery. In univariate analyses, male gender (P=0.005), stage 3-4 (P=0.04), N_1 (P=0.01) and tumour grade 3 (P=0.02) were predictive of shorter survival. Pts receiving PEF-G had longer time to progression (TTP; 1-yr DFS 72±9%; median 12.5+ mo.) when compared with both EF (median 11.5 mo.; 1-yr DFS 43±9%; P=0.04) and PEF pts (median 9 mo.; 1-yr DFS 41±9%; P=0.03). PEF-G achieved a longer overall survival (OS; median 16.5+ mo.; 18-mo. OS 60±10%) with respect to both EF (median 16 mo.; 18-mo. OS 46±9%; P=0.055) and PEF regimens (median 18 mo.; 18-mo OS 51±9%; P=0.059). Multivariate analysis showed that PEF-G use, smaller tumour size, stage 1-2, R0 and N0 status were independently related to both longer TTP (P=0.01) and OS (P=0.02). **Conclusions** Despite the less favourable prognostic factors, PEF-G seems to be more active than other CHT regimens in the management of PDA pts. These results deserve to be confirmed with a longer follow-up and to be compared with less toxic CHT regimens, as gemcitabine alone.

Regimen	age	male	PS 2	T size	R1	R2	stage 3-4	N+	G3	EBRT	IORT
EF	55	71%	5%	3.4±1.5	21%	21%	75%	50%	22%	61%	50%
PEF	57	60%	18%	3.3±1.6	31%	10%	79%	75%	25%	59%	79%
PEF-G	55	48%	5%	3.3±1.3	26%	15%	96%	96%	37%	80%	26%

Early Age of Onset in Pancreatic Cancer Families on the EUROPAC Collaborative Register

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Aim Familial pancreatic cancer (PaC) has a high mortality associated with late presentation. The EUROPAC collaborative register was formed in 1998 to identify patients at increased risk of PaC and to develop screening protocols for early detection. With pan-European support, we are gathering families with clustering of PaC for a whole genome linkage search for PaC susceptibility genes.

Results EUROPAC has registered 63 pure families with two or more relatives with PaC, and 23 families where PaC has occurred in association with other cancers (putatively HNPCC, BRCA2, FAMMM, Peutz-Jeghers, etc). Seventy-one percent (45/63) of the pure PaC families have 2 affected members, 24 percent (15/63) have 3 and 5 percent (3/63) have 4+ members. There have been 87 PaC cases (49 female/38 male) in the pure families

for which the median age was 59 (IQR: 51, 67.8). A statistically difference (Mann-Whitney U-test P=0.017) was found between the age of onset in women (median 63, IQR: 54, 68.2) and men (median 54.5, IQR: 47, 65). No statistical difference was found between the median age of diagnosis in the 2-, 3-, and 4+ member families.

Conclusions In contrast to previous studies, familial pancreatic cancer appears to have an earlier age of onset, especially in men.

Diagnostic Accuracy of Chromogranin A (CgA) and Pancreatic Polypeptide (PP) for Non Functioning Pancreatic Endocrine Tumors (NF pETs)

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Background Endocrine tumors (ETs) can be clinically distinguished in two groups: Functioning (F), associated to hormone-related symptoms, and Non Functioning (NF), with only "mass-effect" related symptoms. Unlike F-ETs, no specific tumor marker can be used for NF-ETs. Although non-specific, Chromogranin A (CgA) is widely considered a useful marker for digestive ET. In the past years, also Pancreatic Polypeptide (PP) has been proposed for pancreatic ET. However, no data are available on sensitivity and specificity of both markers in NF pancreatic ET (NF pETs).

Aim To determine the accuracy of CgA and PP, alone or combined, in the diagnosis of NF pETs.

Subjects and Methods 73 pts were included in the study: 24 pts with NF pET, 26 disease free (DF) pts and 23 pts with non Endocrine Tumors (non-ET). All pts had diagnosis confirmed by histology. DF and non-ET were used as control groups. CgA was assessed by ELISA (DAKO A/S, DK) and PP by RIA (Euro-Diagnostica, SW). Cut-off values are 25 U/L and 48 pmol/L for CgA and PP respectively. Plasma levels are expressed as median (range). Considering pts with NF pET, 13 were with liver metastases (extended disease) whereas 11 were without liver involvement (limited disease). Blood samples were collected prior to surgery and before any specific medical therapy was started.

Results CgA values were: 139 U/L (5-531) in NF pETs, 7 U/L (0-40) in DF and 14 U/L (5-300) in non-ETs (NF pETs vs. DF P<0.0001, NF pETs vs. non-ET P<0.01). PP values were: 178 pmol/L (8-200) in NF pETs, 22 pmol/L (0-143) in DF and 18 pmol/L (0-156) in non-ETs (NF pETs vs. DF P<0.01, NF pETs vs. non-ETs P<0.01). Sensitivity was 67% and 53% for CgA and PP respectively. CgA specificity was 88% vs. DF and 61% vs. non-ETs and PP specificity was 83% vs. DF and 67% vs non-ETs. Combining CgA and PP, sensitivity was 87% and specificity vs. DF 70% (50% vs. non-ETs). In pts with extended disease CgA and PP values were 265 U/L (10-500) and 197 pmol/L (8-200) respectively and in pts with limited disease 128 U/L (48-207) and 26 pmol/L (12-200) respectively.

Conclusions CgA has confirmed to be a useful tumor marker for NF pETs with a sensitivity of 67% and a specificity of 88% (vs. DF pts). Although PP alone had lower sensitivity (53%), the combination of CgA and PP improved sensitivity up to 87% (plus 20% than CgA alone). No correlation was found between both tumor markers levels and disease extension.

Cross-Imaging Characterization of Intraductal Papillary Mucinous Tumors of Collateral Branches

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Background Debate is present in Literature regarding which is the best way to manage the IPMTs of the collateral branches; direct surgery vs. following up strategy ?
Aim To establish the existence of cross-sectional Imaging criteria able to define the IPMTs nature and to influence the clinical management.
Methods All available CT and MR/MRCP studies of 29 patients who underwent surgical resection were considered. The pathological exams revealed 11 benign IPMTs and 18 malignant. Two observers retrospectively reviewed all the images, searching for signs indicative of either benignity or malignancy. We applied t-Student and Mann-Whitney rank sum test.
Results None Imaging single sign showed a significantly different distribution in benign vs. malignant lesions. However thick wall, round morphology and parietal nodules never appeared in the benign lesions. We considered thick wall, parietal nodules and MPD dilation like an expression of developing neoplasia. We defined these criteria as "major criteria". We defined as "minor criteria" those less consistently associated with malignant lesions (gland atrophy, multiple lesions, round morphology and unilocular architecture). Major criteria demonstrated to be significantly associated with malignant lesions (P=0.047). The coexistence of minor and major criteria were significantly more present in malignant lesions (P=0.032).
Conclusions The absence of minor and major criteria indicate with high probability that the IPMT is benign; therefore it can be following up. On the contrary in the presence of the major criteria (even if single) or major plus minor criteria the IPMT must to be surgically removed.

Role of 18-FDG-Positron Emission Tomography in Preoperative Evaluation of Patients with Cystic Lesions of the Pancreas

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Background The differential diagnosis between benign and malignant cystic lesions of the pancreas based on conventional imaging (CT or US-scan, MRI) is still unreliable in a number of patients.
Aim Aim of this study was to investigate the usefulness of 18-FDG-Positron Emission Tomography (PET) in the differential diagnosis between benign and malignant cystic lesions of the pancreas.
Patients and Methods In a 5-year period, 70 patients with suspected cystic tumor of the pancreas underwent 18-FDG-PET in addition to serum Ca19-9 assay, CT-scan and, in some cases, to MRI or ERCP. The 18-FDG PET was analyzed both visually and using the Standard Uptake Value (SUV). Positivity was defined as focal tracer uptake with a SUV >2.5. The accuracy of 18-FDG PET and CT

were determined for evaluation of preoperative diagnosis of malignant cyst.
Results Twenty-two patients had a malignant tumor (Mucinous cystic tumor: 9; Adenocarcinoma with cystic degeneration: 6; Endocrine: 2; Solid-cystic tumor: 2; Intraductal papillary mucinous tumor (IPMT): 2). FDG-PET correctly diagnosed a malignant lesion in 21 patients (94%) with a SUV range from 2.6 to 12.0. Fourteen patients (64%) were correctly identified as having malignancy by CT scan and/or CA 19-9 assay. Forty-eight patients had benign lesions (Serous cystadenoma: 13; Pseudocyst: 10; Mucinous cystic tumor: 9; IPMT: 9; Endocrine: 1, Other uncommon benign cysts: 6). Only one mucinous cystic tumor showed increased 18-FDG uptake (SUV 2.6). Six patients with benign cyst showed CT findings of malignancy. Sensitivity, specificity, positive and negative predictive values and accuracy of 18-FDG PET and CT scan in detecting malignant cystic tumors were 95%, 98%, 95%, 98%,97% and 64%, 87%, 70%, 84%,80% respectively.
Conclusion 18-FDG-PET is more accurate than CT in detecting malignant pancreatic cystic lesions and should be used, in combination with CT and tumor markers assay, in the evaluation of pancreatic cystic lesions. Positivity of 18-FDG-PET strongly suggest malignancy and, therefore, a must of resection.

Pancreatectomy Associated to Vascular Resection

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Background Vascular infiltration is generally considered a contraindication to pancreatectomy.
Aim The aim of this study is to evaluate the outcome of vascular resection associated to pancreatectomies.
Methods Eighty-one pancreatectomies (16%) out of 505 performed November 1987 and April 2001 were associated to vascular resection. There were 44 males (54.3%) and 37 females (45.7%); mean age was 63.4±9.7 years (range 38-84 years).
Results Operative morbidity and mortality rates were 33.7% and 4%, respectively. Pancreatic cancer was diagnosed in 67 patients (82.7%), with vascular infiltration confirmed by histology in 57% of them. Overall survival rates at 1, 3 and 5 years were 53%, 17.5% and 5.8 %, respectively. Patients with vascular thrombosis, encasement or infiltration of multiple vessels showed the worst outcome and no patient has long-term survival. One, three and five years survival rates were similar for patients with limited vascular infiltration (<180°) and for those in whom vascular infiltration was not confirmed histologically (62.2%; 15.6%; 0% vs. 58.3%; 13.2%; 13.2 %; P NS). Thirteen patients diagnosed with low grade malignancies (cystic tumours, silent neuroendocrine tumours or periampullar tumours) had an improved long-term outcome with 1, 3 and 5 year survival (rates of 81.2%, 68.2% and 68.2%, respectively).
Conclusions Vascular resections do not increase significantly morbidity and mortality rates associated to pancreatectomies. For pancreatic cancer vascular resection should be considered in case of limited/suspected vascular infiltration. More locally advanced ductal carcinoma should undergo neoadjuvant chemo-radiotherapy. For low grade malignancies vascular resections should be performed more widely since local disease control may be associated to long term survival or cure.

The Genetic Alterations of the Pancreatic Carcinoma and Clinical Applications

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Background Recent research on pancreatic cancer detected a progression pathway from a intraepithelial neoplasia (PanIN) to a malignant carcinoma. This new acquisition might have applications in clinical common activity.
Aim In this research we studied the most frequent altered genes in pancreatic cancer (k-ras, p16, p53, DPC4). The aim of our study is to evaluate the usefulness of these alterations in clinical applications, i.e. early and differential diagnosis.
Methods We studied genetic alterations in paraffin embedded specimens of 10 patients affected by pancreatic cancer, in frozen tumoral sections of 5 patients and in the duodenal juice of 30 patients with pancreatic carcinoma (biopsy and histopathology confirmation), for k-ras mutation, p-16, p53, and DPC4 alterations. The duodenal juice was obtained by biliary percutaneous drainage. The analysis was performed by quantitative PCR (Termal Cycler Perkin-Elmer 480 e 2400), study of microsatellites instability and sequencing analysis of the genes (ABI PRISM 377 and Abi Prism 310 sequencing analysis).
Results We foud RER+ and LOH- detectable also in the duodenal juice for k-ras and DPC4. The percentage for the microsatellite D18s46 and for D18s47 is informative with reference to the literature.
Conclusions Molecular genetic study performed on duodenal juice is a feasible approach for differential diagnosis and early diagnosis of pancreatic cancer.

Role of Inflammatory Cells in the Production of Angiogenetic Factors in Human Pancreatic Cancer

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Introduction Complex stromal and epithelial interactions play an important role in the relationship between malignant neoplasms and the host tissue response and have a great influence on some aspects of tumor growth, such as local invasion and metastasis. The study of such interactions is mainly useful to get a deeper knowledge of the biology of pancreatic cancer, an aggressive disease with a dismal prognosis.
Aim Characterization of the inflammatory cell infiltrate in pancreatic cancer tissue samples. Evaluation of the role of the inflammatory cells in the production of growth factors with mitogenic and pro-angiogenic properties, like basic fibroblast growth factor (bFGF) e vascular endothelial growth factor (VEGF).
Methods Thirty paraffin-embedded tissue samples obtained from patients affected by pancreatic ductal adenocarcinoma were subjected to immunostaining for bFGF and VEGF. The intratumoral microvessel density (IMD) was evaluated by counting the number of CD34-immunoreactive vessels in the three areas of highest vascularization of each

cancer specimen. To identify the bFGF and VEGF-positive inflammatory cells, a double immunostaining with antibodies directed to CD68 (macrophages), CD20 (B lymphocytes) and tryptase (mast cells) was performed. Five samples of normal pancreas were used as controls. The findings were correlated with the clinicopathological data of the patients.

Results In the normal pancreas the expression of bFGF was focal in fibroblasts and acinar cells. VEGF was expressed in acinar and endocrine cells and in a small number of mononuclear inflammatory cells (mean 8.2/cm^2, range 3.5-11.8). In the tumor samples, bFGF was expressed in cancer cells in 22 cases (73%) and in CD68 and/or tryptase-positive inflammatory cells (mean 7.5/cm^2, range 0-44) in 20 cases (67%). bFGF overexpression in cancer cells was significantly correlated with high IMD (P=0.004). The number of bFGF-positive inflammatory cells was higher in bigger tumors (P=0.03) and in those with high IMD (P=0.03). VEGF was expressed in the neoplastic cells in 29 cases (96%) and in CD68 and/or tryptase-positive inflammatory cells (mean 73.5/cm^2, range 2-305) in all the examined cases. The expression of VEGF in the cancer cells showed a tendency to a direct correlation with the T status of the tumors (P=0.057). The number of VEGF-immunoreactive inflammatory cells was higher in the cancer specimens than in the normal tissues (P<0.001), but it was not associated with IMD or with any other parameter indicating local or distant spread. Only high IMD was significantly correlated with advanced stage of the disease (P=0.04).

Conclusions The inflammatory cells, mostly macrophages and mast cells, accumulate in the tumor tissue and give a substantial contribution to the production of growth factors, which are responsible for the invasive capacity of ductal pancreatic adenocarcinoma.

Pancreatic Cancer Associated Diabetogenic Peptide Induces Nitric Oxide Synthesis in Rat Hepatocytes

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Background The pancreatic cancer cell line MIA PaCa 2 produces a low molecular weight peptide able to block glycolysis of isolated and perfused rat hepatocytes.

Aim In this study we verified whether MIA PaCa 2 conditioned medium (CM) and its low molecular weight (<10,000 Da) fraction (LMWCM) alter hepatocytes glucose metabolism by 1. inducing nitric oxide (NO) production and 2. inhibiting glyceraldehyde-3-phospate dehydrogenase (GAPDH) mRNA synthesis.

Methods A separate set of five different experiments were performed. Isolated and perfused rat hepatocytes were incubated for two hours with: 1. non conditioned medium (NCM); 2. CM and 3. LMWCM. In the hepatocytes supernatants we measured glucose, lactate, nitrate and nitrite levels (colorimetric assay), which are final products of NO *in vivo*. Total RNA was extracted from lysed hepatocytes; after reverse transcription into cDNA, a quantitative PCR was performed to measure the number of GAPDH mRNA copies by means of a commercial kit (BioSource, USA).

Results Glucose levels declined similarly in the different experimental conditions. Lactate significantly decreased over time in CM (F=4.7, P<0.05) and in LMWCM (F=4.1, P<0.05), but not in NCM (F=1.6, P NS). Nitrate production was significantly higher in LMWCM with respect to NCM after 30 (t=2.3, P<0.05), 60 (t=3.7, P<0.01), 90 (t=2.9, P<0.05) and 120 (t=5.0, P<0.01) minutes of incubation. A similar pattern was observed in

CM, although the variations were not statistically significant. The number of GAPDH mRNA copies was reduced in LMWCM (40,000) with respect to NCM (63,000) after 120 minutes of incubation.
Conclusions The low molecular weight pancreatic cancer associated diabetogenic peptide induces the production of NO in isolated and perfused rat hepatocytes. NO might alter hepatocytes glucose metabolism by inhibiting the synthesis of the glycolytic key enzyme GAPDH.

Pancreatic Carcinoma Cell Motility and Metastatic Behaviour: A Possible Role of the Atypical Isoform of Protein Kinase C in Oncogenic Progression

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Background In most of epithelial tumours the oncogenic malignant progression to invasive phenotype, leading to metastatic dissemination, is accompanied by deep alterations of intracellular pathways that control cell adhesion and motility. Being a possible relationship between cell motility and prognosis of patients suffering from pancreatic carcinoma reported in a preliminary study, intracellular kinetics events involving in disregulated motility are further to investigate.
Aim For this purpose a new quantitative analysis of cell motility, based on time-lapse microscopy and digital imaging examination, was tested.
Methods Three different kinetics parameters, such as area change, plasma membrane remodeling and speed of linear movement, are quantified and combined in a single normalized value, defined Motility Score (MS).
Results Three separate non motile and as many motile clones from SUIT-2 cells were tested: the former showed an average MS of 16, 22 and 17, the latter of 93, 92 and 88 respectively. These results suggest that oncogenic progression in non motile clones affected the control of proliferation rate more than cell motility pathways; in motile clones whereas, being all the parameters involved, a different oncogenic progression implicating a complex alteration of control cell motility mechanisms is likely to occur. K-*ras*, mutated about in half of pancreatic carcinomas, is involved in cell proliferation pathways but also in the intracellular control of cytoskeleton dinamic through the activation of critical proteins, like protein kinase C (PKC). Further analysis of signal pathways regulating pancreatic carcinoma cell motility showed that atypical ζ, but neither classic nor novel isoform of PKC, plays an important role in maintaining a high MS level in motile clones. In order to verify this involvement we first used a specific (but not isoenzyme selective) PKC inhibitor, Chelerythrine chloride, that almost completely blocked the motility of these clones. Subsequently we exploited the ability of synthetic peptides with sequence corresponding to PKC pseudosubstrate region to inhibit the kinase activity of this enzyme. The peptides mimicking the pseudosubstrate region of classical and novel PKC isoform were unable to reduced any of MS components, while those corresponding to ζ PKC reduced all the parameters of MS in dose-depending manner.
Conclusion The atypical ζ PKC seems to play a regulatory role in the oncogenic progression of pancreatic carcinoma to metastatic behaviour.

Mutations of Pancreatic Secretory Trypsin Inhibitor and Cystic Fibrosis Transmembrane Conductance Regulator Genes in Patients with Pancreatitis

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Background and Aims An increased frequency of CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) gene mutations has been reported in sporadic pancreatic disease. In North American and German patients with chronic pancreatitis N34S mutation of Pancreatic Secretory Trypsin Inhibitor (PSTI) gene was reported. We examined in a group of Italian patients with different forms of pancreatitis the prevalence of N34S and CFTR mutations.

Materials and Methods In our study we included 76 patients followed in our unit: 15 chronic alcoholic (14 males and 1 females), 49 chronic idiopathic (30 males and 19 females), 12 acute gallstone-related (8 males and 4 females). N34S mutation has been detected by means of HindII restriction enzyme analysis and confirmed by sequencing the exon 3 from a PCR product. Screening for CFTR mutations was carried out in all idiopathic pancreatitis using Denaturant Gradient Gel Electrophoresis (DGGE) of all 27 exons as described by Ravnik-Glavac and samples presenting band shifts were directly sequenced.

Results Among 76 patients studied we identified 2 heterozygous for N34S mutation (4.1%) and 6 heterozygous for one CFTR mutation (W1282X, N187K, R75Q, 621+2T>G, deltaF508, R1162X) in the group of idiopathic chronic pancreatitis. We identified also 7 subjects heterozygous for T5 allele (5 idiopathic, 1 alcoholic and 1 acute forms).

Conclusions In our patients with chronic idiopathic pancreatitis we found both N34S and CFTR mutations. These data suggest a role of these mutations for the predisposition to chronic inflammatory disease of the pancreas.

Substance P (SP) Receptor Gene Expression in Chronic Pancreatitis

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Background Recent concepts have focused on the possible involvement of the nervous system and neuromediators in chronic pain and the inflammatory process in chronic pancreatitis (CP).

Aim In the present study was analyzed the expression and localization of neurokinin 1 receptor (NK-1R), which binds SP, and its association with pain and inflammation in CP.

Methods Pancreatic tissue was obtained from 31 patients with CP and compared with 9 normal pancreases. Quantitative PCR was used to determine the NK-1R mRNA expression levels and in situ hybridization and immunohistochemistry were used to localize expression sites of NK-1R mRNA and protein, respectively. We also analyzed whether an association exists between NK-1R

mRNA expression and pain and inflammation.
Results In CP samples, in situ hybridization and immunohistochemistry localized NK-1R mRNA expression and protein mainly in the nerves, ganglia, blood vessels, inflammatory cells and occasionally in fibroblasts. In patients with mild to moderate and strong intensity of pain, NK-1R mRNA levels were increased 14- and 30-fold over controls, respectively. There was a significant relationship between NK-1R mRNA levels and intensity of pain (r=0.46, P=0.03), frequency of pain (r=0.51, P=0.04), and duration of pain (r=0.46, P=0.01) in CP patients, but not with the degree of tissue inflammation.
Conclusions Our results suggest that substance P receptor gene is activated and involved in the pathophysiology of pain in chronic pancreatitis. The expression of NK-1R in inflammatory cells and blood vessels also points to an interaction of immunoreactive substance P nerves, inflammatory cells and blood vessels, and further supports the existence of a neuroimmune interaction in CP.

A Nutritional Approach with Herbal Remedy K-17.22 Delays the Onset of Spontaneous Chronic Pancreatitis

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Background Chronic pancreatitis (CP) is a progressive disease and to date no validated therapeutic options are available. Recently, it has been devised an herbal formula (Yojyo-Henshiko: K-17.22, Kyotsu Inc., Tokyo, Japan), obtained from selective control of the processing preparation and which has been shown in preliminary clinical tests to significantly decrease chronic viral liver disease activity.
Aim The aim of this study was to test the above preparation on the progression of a genetic model of CP.
Methods Four-week old WBN/Kob rats which were fed a specific MB-3 diet in order to promote CP within a further 12-week period. Rats were allocated into 3 groups: A) no treatment; B) K-17.22 50mg/kg-5% glucose; C) vitamin E 200mg/kg. The same schedules were applied "therapeutically" after the onset of CP (from 12th to 20th week). Rats were sacrificed at 12- and 20-week in the "prophylactic" and "therapeutic" group, respectively. Routine histology, blindly scored, was carried out. Total RNA was extracted from pancreatic tissue for PAP gene expression by RT-PCR method.
Results Unlike A and C groups, B rats pancreata didn't show any overt oedema/haemorrhage on macroscopic examination in the "prophylactic" group, but not on the "therapeutic" one. Either B and C rats preserved pancreas weight and lessened serum amylase ($P<0.05$ vs. A). Microscopic analysis showed that K-17.22 almost entirely prevented CP damage as compared to A and C rats ($P<0.001$) when used prophylactically while it significantly decreased fibrosis, inflammatory infiltrate, oedema and ductal hyperplasia in the "therapeutic" group ($P<0.05$). As compared to A and C group, B rats showed a complete suppression of PAP mRNA in the prophylactic group ($P<0.01$) and a significant decrease in the therapeutic schedule ($P<0.05$).
Conclusions The present preliminary data suggest that K-17.22 exerts powerful protective and therapeutic effect against the progression of experimental CP by mechanisms to be elucidated as yet. These might possibly involve effects such as antioxidative, microcirculatory-enhancement, gastric and pancreatic secretion suppression and cytokine regulation.

Gabexate or Somatostatin Administration before Endoscopic Retrograde Cholangiopancreatography in Patients at Risk for Post-Intervention Pancreatitis: A Multicenter, Placebo-Controlled Randomized Clinical Trial

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Aims a) To assess the efficacy of somatostatin, gabexate, or placebo on the occurrence of post ERCP pancreatic damage in patients whit risk factor. b) To determine factors predisposing to post- ERCP pancreatitis and hyperamylasemia.

Methods Somatostatin (750 μg, 183 patients), gabexate (500 mg, 197 patients) and placebo (saline, 199 patients) were given intravenously 30 minutes before endoscopy and continued 2 hours afterwards. Clinical evaluation of patients and serum amylase determination was scheduled at 4 and 24 hours after endoscopy. The development of pancreatitis and hyperamylasemia was related to patient, procedural, and operator related factors by both univariate and multivariate analysis.

Results Pancreatitis developed in 13 (6.5%), 16 (8.1%), and 21 (11.5%) of placebo-, gabexate-, and somatostatin-treated patients, respectively (P NS). At univariate and multivariate analysis, a sphincterotomy longer than 2 cm (P=0.0001), a higher than 3 pancreatic injection (P=0.01), and an unsuccessful cannulation (P=0.008) were predictive of post-ERCP pancreatitis.

Conclusion Short-term infusion of gabexate or somatostatin in high-risk patients is ineffective in preventing pancreatitis damage related to ERCP. Pancreatic injury was related to maneuvers of obtaining biliary access rather than to patients' characteristics or endoscopist's experience.

POSTERS - ORAL PRESENTATION

Primary Human Pancreatic Adenocarcinomas and Expression of Inducible Nitric Oxide Synthase and Cyclooxygenase-2

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Background Pancreatic ductal cancer remains one of the most difficult cancer to treat, as evidenced by little improvement in survival. The simple conclusion is that current detection and therapy are not satisfactory and an increased understanding of the molecular biology of pancreatic carcinoma is needed to develop new diagnostic and treatment approaches. Expression levels of inducible nitric oxide (iNOS) synthase and cyclooxygenase (COX) 2 were found to be frequently elevated in several types of human cancer and have also been directly linked to carcinogenesis.

Aim To investigate the role of COX-1, COX-2, and iNOS in pancreatic cancer, we evaluated these proteins expression in primary human pancreatic adenocarcinomas and matched normal adjacent tissue.

Methods Tissue samples were obtained at the time of resective surgery from patients with histologically demonstrated ductal pancreatic

cancer. Tissue samples were taken from a nonnecrotic area of the tumour and corresponding matched normal adjacent nontumorous tissue. The expression of COX-1, COX-2 and iNOS protein was evaluated by Western blot analysis.
Results COX-2 was marked expressed in all subjects with clinically diagnosed pancreatic cancer. When we compared levels of COX-2 protein, as determined by densitometry, they were consistently higher in cancer compared with paired normal pancreas. Immunoblot analysis indicate an approximately three/fourfold increase in the amount of COX-2 protein present in the malignant pancreatic tissue compared with paired normal sample. The iNOS protein was markedly expressed in pancreatic cancer whereas it was undetectable in the surrounding normal tissue. The expression of COX-1 was detected in both normal and cancerous tissue and the level was similar in all cancer and normal tissue. All patients with adenocarcinoma pancreas were positive for both iNOS and COX-2 protein.
Conclusions These results suggest that both iNOS and COX-2 are involved in pancreatic cancer and can have important clinical implications. The COX-2 and iNOS may prove as prognostic indicators for the adenocarcinoma and may form the basis for future novel therapeutic and/or preventive strategies using techniques to inhibit these genes, such as pharmacological antagonism, or antisense gene therapy.

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HLA-DRB1*04 Allele Contribute to the Genetic Susceptibility of Chronic Pancreatitis

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Background Chronic pancreatitis (CP) is characterized by irreversible morphological and functional alterations of the pancreas clinically presenting with upper abdominal pain as well as exocrine and endocrine insufficiencies. The disease involves genetic and immunologic factors and it is often associated with immunomediated disease such as sclerosing cholangitis.
Aim We investigated the Major Histocompatibility Complex (MHC) genes as a genetic background of CP.
Patients and Methods Allelic polymorphisms at the DNA level were investigated in the genes of MHC region (HLA DRB, DQB and polymorphism at position -308 of Tumor Necrosis Factor A, TNF A) with PCR based methodologies (PCR-SSP; PCR-RFLP) in 49 CP patients (40 male, 9 female) and 90 healthy normal controls (43 male, 47 female) of the same ethnical group. All patients and control gave their informed consent.
Results Among HLA-DRB1 genes, DRB*04 was significantly higher in CP patients than in controls (26.5% vs. 7.7%; $P<0.005$; RR=4.3). No association between CP and HLA-DQ and TNF A genes were found.
Conclusions These study supports a role of HLA-DRB*04 as susceptibility factor for CP.

Histopathologic Alterations of Pancreatic Slice after Glandular Section with the Harmonic Scalpel (Ultracision®)

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Background The use of harmonic scalpel in open and laparoscopic surgery, has been remarkably spread in these last years. The use of Ultracision® (UC) is interesting in pancreatic surgery where the least mechanical and thermic trauma of contiguity to tissues is combined with the reduction of lymphatic and blood losses. This peculiarity allowed the use of UC even for the section of the pancreatic gland.

Aim Retrospective evaluation of the alterations caused by mechanical energy of the UC and of the possible effects on the accuracy of the histopathologic diagnosis.

Methods The anatomo-pathologic findings of 15 cases of pancreatic resection with glandular section with UC have been analyzed. The pathology was in 12 cases ductal adenocarcinoma, in 2 cases a microcsystic cystoadenoma and 1 case of chronic pancreatitis. Ten pancreatoduodenectomies, 5 left splenopancreasectomies (3 laparoscopic procedures) were performed. The specimens have been fixed in 10% buffered formaline and included in paraffin. The 3-4 micron thickness sections have been colored with Haematoxylin-Eosin, PAS, Weigert for elastic fibres. The following antibodies: cytokeratins, vimentin, s 100, have been used for immunocytochemical study.

Results In every histological sections we can observe a damage of about 0.5 mm thickness of the necrotic-coagulative type, the surface layer of parenchyma appears frayed, intensely eosinophilic and amphophilic with several poured out erythrocytes and blocked capillaries. However it is always possible to underline small nervous structures in a clear way. Just under the surface layer, the glandular acini, even if wrinkled and with greatly eosinophilic cytoplasm, maintain the normal lobular architecture (when it is present), well underlined by histochemical coloring with PAS, and Weigert, which bring out respectively the basal membrane and the periacinal elastic fibres. The antigenic charge of acinal cells is often well preserved: the immunocytochemical coloring for the cytokeratin as a matter of facts results positive, even if weakly. Under 0.5 thickness there is a remarkable attenuation of the degenerative phenomena and, deeper, the tissues are not damaged. **Conclusions** According to our results we can conclude that the use of UC in the glandular resection doesn't reduce the possibility of histopathologic accuracy in the study of pancreatic slice. Indeed the coagulative damage spreads for less than 1 mm and in this thickness, also the tissutale structure is retained.

Pancreatic Fistula Definition as a High Risk Factor in the Complication's Development

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Background Despite in experienced hands the mortality rate related to pancreatic resections is acceptable, the pancreatic fistula (P.F.) development is regarded as a still frequent complication. The incidence of P.F.

is rather variable in high volume Centers also because of rather different applied definitions.
Aim The aim of this study is to present a comparison of different definitions present in recent literature and to demonstrate that the P.F. rate in the same group of patients treated in a high volume Center is strictly dependent upon definition applied.
Methods A Medline search was performed in respect of the last ten years literature about P.F. definition. To the reproducible definitions was assigned a score based upon two requested parameters: daily output (cc) and timing of fistulisation resulting by the sum between starting postoperative day and duration of the complication. The five summarizing definitions formulated have been applied to the same group of 242 patients undergone pancreatic head or intermediate resections with pancreatico-jejunal anastomosis in our between November 1997 and December 2000. The statistical analysis was carried out using the Chi-Square Yates correct test fixing the statistical significance at P value <0.01.
Results Among 25 different definitions identified, 13 were found suitable for the score application. Then we were able to formulate five final definitions summarizing the five current concepts on P.F.. The pancreatic fistula incidence is ranging between 9.9% to 28.5% according to the five different definitions applied to the 242 patients admitted to the study with highly statistical differences (P<0.00001 as most impressive result).
Conclusions P.F. rate after pancreatic resections is strictly dependent upon used definition. The general agreement for an universally accepted definition is urgently needed to correctly compare different experiences.