

ORAL COMMUNICATIONS

Islet-1 Expression in Human Pancreas and in Pancreatic Endocrine Tumors

Albarelo L, Andralojc K, Piemonti L, Capitanio V, Zerbi A, Di Carlo V, Doglioni C
Department of Pathology and Surgery, Scientific Institute Hospital San Raffaele. Milan, Italy

Background The LIM homeodomain protein Islet-1 is expressed in developing pancreas in rat and mouse. It is essential for the generation of pancreatic endocrine cells: targeted disruption of the *islet-1* gene results in an early arrest of embryonic development with abnormality of the pancreas anlage and complete absence of endocrine cells. Islet-1 expression in normal and neoplastic human pancreas has not yet been evaluated.

Aim To evaluate Islet-1 protein expression in developing and adult human pancreas and derived tumors.

Methods Normal samples of fetal (12w, 14w, 22w), pediatric (1y, 4y) and adult (25y, 55y), formalin fixed-paraffin embedded pancreatic tissues were evaluated for Islet-1 expression with an immunohistochemical technique. Two different monoclonal antibodies, raised against different epitopes of Islet-1 were utilized. Serial sections were immunostained for general neuroendocrine markers (chromogranin and synaptophysin). In order to evaluate coexpression, double immunostainings for either insulin or glucagon and Islet-1 were performed. A large series of previously characterized pancreatic endocrine tumors (PET), including benign (n=50), borderline (n=29), well differentiated (n=30) and poorly differentiated carcinomas (n=10) and pancreatic ductal adenocarcinomas (n=20) were also immunostained with anti-

Islet-1 antibodies.

Results Islet-1 was expressed in the nuclei of the majority of pancreatic endocrine cells from the beginning of endocrine differentiation in the fetal pancreas till in the adult life. All insulin and glucagon positive cells coexpressed Islet-1. Its reactivity was confined to the endocrine compartment (insulae and periductal endocrine cells); pancreatic acinar and ductal cells were negative. Both antibodies gave the same pattern of reaction and were equally effective in formalin fixed-paraffin embedded material. No Islet-1 immunoreactivity was observed in the ductal adenocarcinoma cases. Nuclear Islet-1 immunoreactivity was present in 87% of PET cases. Poorly differentiated endocrine carcinomas displayed a significant decrease in Islet-1 immunoreactivity with 70% of negative cases, but no relation with prognosis was observed.

Conclusions Islet-1 is expressed in developing and adult human endocrine pancreas, at variance with rodent pancreas where its expression is limited to the embryonic life. These antibodies are useful tools for the study of the complex array of transcription factors involved in endocrine differentiation of human pancreas. Islet-1 can be utilized as a sensitive marker for identifying pancreatic endocrine tumors.

Therapeutic Perspectives of Patients with Locally Advanced Pancreatic Cancer

Beneduce AA, Balzano G, Reni M, Zerbi A, Nicoletti R, Ortolano E, Villa E, Di Carlo V
Pancreas Unit, Radiochemotherapy and Radiology, San Raffaele H. Milan, Italy

Background 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). We used 42 R2 resections (macroscopic local residue) performed in the same period as control group.

Results From 1997 to 2004, 55 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. Twenty-seven patients (49%) had no response or progression, according to WHO criteria. Twenty-eight patients (51%) had partial response and were stratified in two subgroups: 9 patients (16%) were eligible for surgery with curative intent, whereas 19 patients (35%) had persistency of vessel invasion and continued chemotherapy. Of the 9 patients undergoing surgery, 8 were resected and one patient was not, because of

persistent vessel invasion. Of 8 resected patients, 4 had R0 resection, one R1 (microscopic margin involvement) and three R2 (macroscopic residue). One patient died because of haemorrhagic complications. Other two patients died of recurrence at 14 and 17 months. The remaining 5 patients are alive (range 10-75 months). Survival of 9 patients undergoing surgery (group 1) was compared with 19 patients who had partial response with no surgery (group 2) and with the control group of 42 patients with R2 resection. Median survival was not reached in group 1, it was 21 months in group 2 and 14 months in the control group. The survival curve of groups 1+2 was better than the control group ($P<0.05$).

Conclusions Patients with locally advanced pancreatic cancer may benefit of chemotherapy with PEFG regimen. Regression of vessel invasion can be expected in 16% of patients; in these cases a laparotomy with curative intent is indicated.

Reference

1. Reni M, Cordio S, Milandri C, Passoni P, Bonetto E, Oliani C, et al. Gemcitabine versus cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: a randomised controlled multicentre phase III trial. *Lancet Oncol* 2005; 6:369-76. [PMID 15925814]

No Pathological and/or Clinical Parameters Can Predict the Response to Somatostatin Analogues in Advanced Pancreatic Endocrine Well Differentiated Carcinomas

Bettini R¹, Falconi M¹, Butturini G¹, Mantovani W³, Capelli P², Boninsegna L¹, Festa L¹, Pederzoli P¹

¹Department of Surgery and Gastroenterology, ²Department of Pathology and ³Health Department, University of Verona. Verona, Italy

Aim To analyse the time to progression and the eventual prognostic factors which can predict, at diagnosis, the response to somatostatin analogues, as first line therapy.

Methods The study enrolled only consecutive patients suffering from advanced histologically proven non functioning

endocrine well differentiated pancreatic carcinoma with positive OctreoScan[®]. From 1999 to October 2004, 21 patients were treated with long-acting release octreotide 20 mg i.m. until tumour progression occurred. Clinical and pathological characteristics were correlated with the response to treatment.

Results Twelve patients (57%) developed a progression after a median of 14 months of treatment (IQR: 6-21.7 months). At the end of follow-up after a median of 38.4 months (IQR: 19-52.7 months) in the other 9 patients (43%) a stable disease was observed. Tumour progression did not correlate with any clinical (age, symptoms, tumour markers, resection of the primary tumour) or pathological

parameters (side, size, ki-67, presence of liver metastasis).

Conclusions In about a half of patients under study, octreotide seems to be able to stabilize the disease confirming its potential role in inhibiting tumour growth. None parameter, both clinical and pathological, is useful to predict the tumour response to treatment.

Mesenteric Portal Vein Resection during Pancreatectomy for Ductal Adenocarcinoma of the Pancreas: Is It Worthwhile?

Boggi U, Del Chiaro M, Croce C, Gremmo F, Sgambelluri AF, Cappelli C, Balzano E, Dinelli E, Mosca I, Signori S, Funel N, Campani D, Mazzeo S, Mosca F

Division of General and Transplant Surgery, Regional Referral Center for Pancreatic Diseases Treatment, University of Pisa. Pisa, Italy

Background Actual prognostic implication of infiltrated mesenteric portal vein (MPV) during pancreatectomies for ductal adenocarcinoma of the pancreas has not been defined completely yet and vein involvement often cannot be ruled out until transection of pancreatic neck.

Aim To analyze the prognostic implications of MPV infiltration in ductal adenocarcinoma of the pancreas and the short and long-term results of pancreatectomies associated to MPV resections.

Methods Six-hundreds and 85 pancreatectomies were performed in our Institution from November 1987 to May 2004. In 128 patients (18.6%) pancreatectomy was associated with vascular resection including 94 vein resection alone, 77 done for ductal adenocarcinoma of the pancreas (PC). Forty-eight patients (62.3%) underwent to pancreaticoduodenectomy, 23 (29.9%) to total pancreatectomy and 6 (7.8%) to distal pancreatectomy. There were 39 males and 35 females; mean age of the patients was 64.9 years, mean operative time 6.4 h, mean RBC transfusions 2.1 U, mean hospital stay 22 days.

Results The UICC stage of the disease after pathological analysis of the surgical specimen was: IIa in 14 (18.2%) cases, IIb in 59 (76.6%) cases, III in 1 (1.3%) case and IV in

3 (3.9%) cases. Sixty-three patients (81.8%) had positive lymph-nodes and 14 (18.2%) positive surgical margins (R1 resections). No patients received an R2 resection. Vascular infiltration was confirmed in 43 patients (43/77; 55.8%). The mortality and morbidity rates of the patients undergoing to pancreatectomies associated to MPV resection for PC were 2.6% and 33.6%, respectively. Seven patients (9%) required a re-laparotomy for complications. One-, 3- and 5-year actuarial survival rates were 55.1%, 16.5% and 10.2%, respectively. One-, 3- and 5-year actuarial survival rates of the patients undergoing to MPV resection for PC without histologically confirmed vascular infiltration were significantly higher on respect to the survival rates of the patients with histologically confirmed vascular infiltration (72.1%, 30.1%, and 20% vs. 47.7%, 5.6%, and 5.6%, respectively; $P < 0.05$).

Conclusions MPV resection during pancreatectomies is not associated with increase in morbidity or mortality rates. The long term survival rates of patients undergoing to pancreatectomies associated to MPV is similar to those undergoing to conventional pancreatic resections. Interestingly enough, lack of histological proof of tumor involvement is associated to statistically relevant survival benefit.

Angiogenesis Factors Are Likely Related to the Motility Behavior of Pancreatic Cancer Cell Lines

Bonora A¹, Mafficini A², Maraia G¹, Bassi C¹, Sorio C², Pederzoli P¹

¹Department of Surgical and Gastroenterological Sciences and ²Department of Pathology, University of Verona. Verona, Italy

Background The aggressive biology of ductal pancreatic cancer (DPC) appears to be related to the cell motile activity. Being cell motility a recognized pattern of invasive attitude, the identification of two different motile behavior subclones, derived from human DPC cell lines (SUIT-2), could lead us to better understand the mechanisms underlying the progression to malignancy.

Aim According to experimental findings these clones might differ in their angiogenesis supporting behavior. Therefore, we evaluated the expression of a number of related genes, in order to stress a possible relationship between angiogenesis factors and cell motility attitude.

Methods The two subclones, named motile (M) and non-motile (O) clone, were grown both in soft agar and matrigel, to analyze their growth attitude either in presence or in absence of extracellular matrix. A cell suspension of both clones was inoculated in two groups of ten nude mice respectively to evaluate the *in vivo* behavior. Then we evaluated mRNA expression of seventeen genes involved in angiogenesis and the *in vitro* release of related factors secreted by

DPC cells.

Results Both clones strongly grew in matrigel, while M failed to grow in agar, the need for extracellular matrix components suggesting a down-regulation of integrin-dependent signaling pathways. The pathological assessment showed a larger burden in O and a wider necrosis in M implanted tumors. The significant difference ($P < 0.01$) reached in median volume between O and M (2,812 vs. 17.5 mm³ respectively) is probably related to different expression of the genes involved in angiogenesis. As a matter of facts, VEGF and IL-8 were significantly up-modulated in O (1,053 vs. 676 pg/mL and 65 vs. 38 pg/mL, respectively), while an up-modulation of angiomodulin was found in M (10.5 vs. 4.4). The levels of other evaluated factors appeared to be similar in both clones.

Conclusions The different motility behavior of SUIT-2 subclones is associated with a different *in vitro* and *in vivo* growth pattern. More than the impairment of single factors, this finding is likely to be related to the imbalance of a complex pathway of integrin signals and angiogenesis factors.

Non-Functioning Endocrine Pancreatic Tumors: Factors Predicting Recurrence and Outcome

Capitanio V¹, Albarello L², Zerbi A¹, Balzano G¹, Rocchetti S¹, Beneduce AA¹, Varale R¹, Di Carlo V¹

¹Pancreas Unit and ²Department of Pathology, San Raffaele H. Milan, Italy

Background Only few data exist on long-term outcome and prognostic factors of pancreatic neuroendocrine tumors because of their low incidence, heterogeneous behaviour and different treatment modalities.

Aim to evaluate risk factors for recurrence and prognostic factors for long-term outcome

in non-functioning endocrine pancreatic tumors.

Methods Eighty-five patients with non-functioning endocrine pancreatic tumors were observed at our Institute in the period 1987-2004. In 67 of them (29 female and 38 male; mean age 54 years) complete data were

available to perform an univariate analysis, correlating recurrence and survival with clinical and histopathological factors. The following parameters were studied: age, clinical presentation (with or without symptoms), size of the primary tumor, presence of angioinvasion, adjacent organs involvement, synchronous or metachronous metastases, ki-67-index, surgical resection, medical therapy. Mean follow-up was 58 months (range 3-267 months).

Results Tumors were classified according to WHO 2000 system: 14 resulted benign neoplasm, 17 tumors with uncertain behaviour, 29 well differentiated carcinoma, 7 poorly differentiated carcinoma. 62 patients underwent surgical resection, whereas 5 did not. Eighteen patients showed a local or distant recurrence of disease (mean interval from diagnosis: 31.5 months; range 3-158 months): 4 tumors with uncertain behaviour, 10 well differentiated and 4 poorly differentiated carcinoma. Tumor size greater than 2 cm (odds ratio: 9.5; 95% CI: 1.172-78.55) and angioinvasion (odds ratio: 6; 95% CI: 1.5-24.01) were the strongest predictors of recurrence; mean time of recurrence was: 30

months in neoplasms greater than 2 cm in size, 54 months in neoplasms less than 2 cm, 30 months in patients with angioinvasion, and 47 months in patients without angioinvasion. Univariate analysis showed that lymph node status, proliferation fraction (ki-67-index) and surgical treatment displayed a significant correlation with overall survival. The results of analysis are showed in the Table.

	Hazard ratio	95% CI	Mean survival time (months)
Lymph node status	10.49	1.198-91.98	LN+: 114 LN-: 186
Ki-67index	7.74	1.2-46.86	Ki-67 >5%: 67 Ki-67 <5%: 152
Surgical resection	11.35	1.6-80.23	No resection: 103 Resection: 210
Synchronous metastasis	3.9	0.9-17.04	M+: 103 M-: 209

Conclusions Tumor size greater than 2 cm and vascular invasion were risk factors for recurrence; metastases to lymph nodes and ki-67-index greater than 5% were prognostic factors of an unfavorable outcome; surgical resection was related to a favorable prognosis.

Preliminary Results of a Phase II Trial of Dose-Intense PEFG (Cisplatin, Epirubicin, 5-Fluorouracil, Gemcitabine) in Advanced Pancreatic Adenocarcinoma

Cereda S, Dell'Oro S, Passoni P, Bonetto E, Viganò MG, Balzano G, Zerbi A, Staudacher C, Di Carlo V, Reni M

Department of Oncology and Surgery, S. Raffaele H. Scientific Institute. Milan, Italy

Background PEFG regimen was superior to standard gemcitabine in a phase III trial in advanced pancreatic adenocarcinoma (PA) [1]. This regimen was subsequently modified by increasing dose-intensity [2].

Aim To assess activity and feasibility of dose-intense PEFG regimen.

Methods 5-fluorouracil (FU) as continuous infusion at 200 mg/m²/day for the whole duration of chemotherapy (CHT), cisplatin and epirubicin both at 30 mg/m², and gemcitabine at 800 mg/m² were administered

every 14 days to patients with stage III or metastatic PA who were chemotherapy-naïve, less than 75-year-old, performance status (PS) greater than 50, and who had normal bone marrow, renal and liver function, till progressive disease or for a maximum of 6 months.

Results Between August 2003 and April 2005, 43 (27 or 63% metastatic) consecutive patients, median age 62 years, median PS 75, were treated with dose-intense PEFG at a single institution. Accrual is ongoing. Partial

response was yielded in 18 patients (42%). Among 33 patients with at least 6 months of follow-up, 18 were progression-free at 6 months from treatment start (PFS-6=54.5%) and median progression-free survival was 6.2 months. Three of 16 (18%) stage III patients became resectable after CHT. Radiotherapy concomitant to FU was administered at 10 stage III patients after the end of CHT. To date, 169 courses (range: 1-6; median: 4) of dose-intense PEFG were delivered. Main grade 3-4 toxicity consisted of: neutropenia in 9%, anaemia, stomatitis, nausea/vomiting in 3%, fatigue and diarrhoea in 2% of cycles. Dose intensity (mg/m²/week) was 13.5 for both epirubicin and cisplatin, 322 for gemcitabine and 1,053 for FU.

Conclusions Preliminary results of this study show that the outcome of PA patients treated

by dose-intense PEFG regimen is at least as good as that yielded by classical PEFG in terms of PFS (PFS-6: 54.5% vs. 42%; median PFS 6.2 vs. 5.4) and response rate (42% vs. 38.5%). Dose intensity for gemcitabine was increased by 26%, for cisplatin and epirubicin by 43%. Grade 3-4 haematological toxicity (neutropenia 9% vs. 43%; thrombocytopenia 0% vs. 28.5%) was consistently reduced.

References

1. Reni M, Cordio S, Milandri C, Passoni P, Bonetto E, Oliani C, et al. Gemcitabine versus cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: a randomised controlled multicentre phase III trial. *Lancet Oncol* 2005; 6:369-76. [PMID 15925814]
2. Dell'Oro S, Reni M, Bonetto E. Intensified PEFG regimen in stage III-IV pancreatic adenocarcinoma. *Ann Oncol* 2004; 15:242. [Abstract 919]

IgG Type 4 Are not Specific for Autoimmune Pancreatitis

Coato E, Frulloni L, Bernardoni L, Brunelli S, Vaona B, Bovo P, Faitini K, Bonzanini O, Prandelli C, Cavallini G

Department of Surgical and Gastroenterological Sciences, University of Verona. Verona, Italy

Background High serum levels of IgG type 4 (IgG4) have been proposed as a marker for the diagnosis of autoimmune pancreatitis (AIP).

Aim To evaluate whether the serum levels of IgG4 may be useful in the diagnosis of AIP.

Materials and methods We studied 27 patients suffering from AIP (13 males, 14 females, mean age 45.4±16 years). As control group, we studied 24 patients with a diagnosis of recurrent pancreatitis (RP), 46 of chronic pancreatitis (CP) and 34 of pancreatic cancer (PC). A commercial available immunonephelometric kit (Dade Behring, Marburg, Germany) was used to dose the serum levels of IgG and IgG subclasses. The normal serum IgG4 levels range in our laboratory from 0.07 to 0.64 g/L.

Results We observed an increase of serum levels of IgG4 subclass in patients suffering from autoimmune pancreatitis, but not statistically different from other groups of

pancreatic diseases (Kruskal Wallis test) (Table: value are expressed as g/L).

We did not observe differences in serum levels of total IgG and IgG subclasses in the different groups of patients. Nine out of 27 patients in AIP group (33%), 9 out of 24 in RP group (38%), 16 out of 46 in CP group (35%) and 15 out of 34 in PC group (44%), had serum levels of IgG4 higher than the upper normal limit.

Conclusions These data do not support the use of IgG4 in the diagnosis of AIP in an Italian population.

	AIP (n=27)	RP (n=24)	CP (n=46)	PC (n=34)
Total IgG	12.9±4.8	12.2±3.8	11.4±3.8	12.3±4.2
IgG I	7.7±3.1	7.2±2.2	6.7±2.3	7.6±3.4
IgG II	3.9±1.5	3.9±1.7	3.6±1.9	3.7±1.8
IgG III	0.51±0.3	0.53±0.3	0.51±0.3	0.54±0.3
IgG IV	0.84±1.2	0.56±0.5	0.64±0.6	0.61±0.5

Surgical and/or Conservative Management of Branch Duct Intraductal Papillary Mucinous Neoplasms: A Prospective Study on 118 Patients

Crippa S, Salvia R, Bettini R, Molinari E, Muselli P, Orciuoli M, Pederzoli P
Department of Surgery, University of Verona. Verona, Italy

Background Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas can be classified in two subtypes: main duct (MDTs) and branch duct tumours (BDTs). The latter group is reported to be less aggressive as compared with MDTs. Thus, a conservative non surgical treatment in particular cases has been proposed, but no prospective trial has been performed.

Aim To prospectively evaluate the conservative management of BDTs with no suspicion of malignancy and/or asymptomatic.

Methods From 2000 to 2004 all patients with BDTs underwent trans abdominal ultrasound, CWMRI with secretin and an accurate clinical and laboratory assessment. Patients who presented one of the following parameters (diameter greater than 3.5 cm, presence of nodules and thick wall, CA 19.9 elevation, a recent-onset or worsened diabetes, presence of symptoms) were addressed to surgery (Arm A). Previous informed consent, all the patients with asymptomatic disease and without any suspect of malignancy underwent conservative treatment according to a strict 6-month follow-up protocol (Arm B).

Results In the study period 118 patients with a diagnosis of BDTs (based on an evident communication between a cyst and the main duct in the absence of chronic pancreatitis) have been observed. They were 50 male and 68 female with a mean age of 63 years (range 31-81 years). Twenty two (18.6%) underwent

immediate surgery (Arm A) and final diagnosis was an IPMN in every case: adenoma in 10 cases (45.5%), borderline in 8 (36%), carcinoma in situ in 1 (4.5%), and invasive carcinoma in 3 (14%). Ninety-six patients (81.4%) underwent conservative follow-up (Arm B). The lesion was monofocal in 28 (29%) and multifocal in 68 (71%). The main lesion size was 1.7 cm in mean (range 0.7-3.5 cm). Median follow-up was 21 months (range 6-58 months). During follow-up, 5 patients (5.2%) of this group showed an increase in size of the main lesion (all greater than 4 cm) after a mean time of 18.4 months (range 12-25 months) and underwent surgery. A pancreaticoduodenectomy was performed in 3 case and left pancreatectomy in 2. Final diagnosis was an IPM adenoma and an IPM borderline in 3 and in 2 cases, respectively. No mortality was observed.

Conclusions BDTs are being observed with increasing frequency and they are often multifocal. Our data confirm their tendency toward an indolent biological behaviour. The combination of clinical-lab-radiological parameters adopted in this study seem to be reliable in order to chose between surgical treatment and follow up. In this latter group only few patients showed changes requiring subsequent surgery and in all of them the lesion was still benign. Longer follow-up is needed to confirm these data.

Pancreatic Cancer and Immunosuppression: Effects of Interleukin-2 on T-Lymphocytes Subpopulations in the Perioperative Period

Degrate L, Nobili C, Perego E, Franciosi C, Caprotti R, Romano F, Uggeri Fr
Department of Surgery, San Gerardo Hospital, University of Milano-Bicocca. Monza (MI), Italy

Background In pancreatic cancer patients, soluble factors produced by the tumor

environment are often distributed to the circulatory system where they effect a

generalized immunosuppression, resulting in reduced number and activity of T-lymphocytes subpopulations.

Aim To assess the effect of recombinant interleukin-2 (r-IL2), a cytokine with T-cell stimulating activity, on T-lymphocytes in pancreatic cancer patients.

Methods Twelve patients with resectable pancreatic adenocarcinoma received subcutaneous administration of r-IL-2 at high dose (12 millions IU/day) for 3 consecutive days prior to surgical radical resection (10 pancreaticoduodenectomies, one spleno-pancreatectomy, and one total pancreatectomy). We estimated the level of total T lymphocytes (CD3⁺) and their subsets (CD4⁺; CD8⁺; CD3⁺/CD16⁺CD56⁺) in peripheral blood before starting r-IL2 immunotherapy and on 1st and 7th post-

operative days.

Results After preoperative rIL-2 administration and radical surgery, we observed a significant increase of CD3⁺ T lymphocytes, CD4⁺ helper and CD8⁺ cytotoxic T cells both on 1st and 7th postoperative days (P<0.05, comparing to baseline data), while CD3⁺/CD16⁺CD56⁺ T lymphocytes reached a significant enhancement only on 7th day (P<0.002).

Conclusions The preoperative immunotherapy with high dose r-IL2 has been able to overcome the anergic state typical of pancreatic cancer patients, by expanding T-lymphocytes subpopulations. The high levels of T-cells obtained in these patients may strengthen their immune anticancer defense, reducing the dissemination of tumor cells in the peri-operative period.

Obesity and the Risk of Pancreatic Cancer: An Italian Multicenter Study

Fantini L, Pezzilli R, Morselli-Labate AM, Tomassetti P, Migliori M, Manca M, Gullo L
Department of Internal Medicine, Sant'Orsola-Malpighi Hospital, Alma Mater Studiorum.
Bologna, Italy

Aim The purpose of this work was to determine whether obesity is a risk factor for pancreatic cancer.

Subjects and methods We studied all consecutive patients having this tumor as well as controls matched for sex and age, from various Italian cities. A standardized questionnaire was used and it was compiled at personal interview, with particular attention to body weight at the time of the interview and, for those with the tumor, also their weight prior to onset of the disease. The body mass index (BMI) was calculated as the patients' weight in kilograms divided by their squared height in meters.

Results The study subjects were as follows: 229 (57.3%) were male, 171 (42.8%) female; the average age was 61.7 years, range: 22-79 years. The diagnosis of pancreatic cancer was based on clinical history and was confirmed by histology in 305 cases (76.3%), by surgery in 10 (2.5%), and by imaging techniques in

the remaining 85 (21.3%). For each patient, a control subject matched for sex, age (less than or equal to 5 years), social class, and geographic region was selected at random from the patients hospitalized at the same time in the same facility for acute nonmalignant disorders. The most frequent diagnoses were minor trauma (52%), abdominal hernias (9%), and transient disorders of the skin, ear, nose, or eye (39%). Patients with any type of cancer were excluded from controls, as were those with gastrointestinal disorders or with other conditions that could result in reduced oral intake or in weight loss. The risk of pancreatic cancer adjusted for smoking was 5-folds significantly higher (P<0.001) in patients with a BMI less than 23 kg/m² after diagnosis as compared to patients with a BMI ranging from 23 to 29.9 kg/m², while the risk in patients with BMI equal to or greater than 30 kg/m² was not significant (P=0.689). Taking

into account the BMI before diagnosis, smoking was confirmed as a significant risk factor (OR= 1.68; P=0.001) for pancreatic cancer, while no significant relationship was found between BMI classes and the risk of

pancreatic cancer (P=0.984).

Conclusions These findings indicate that obesity is not a risk factor for pancreatic cancer.

Preclinical Studies for the Development of Active Immunotherapy in Pancreatic Adenocarcinoma

Filipazzi P^{1,5}, Gavazzi F², Zerbi A², Albarello L³, Balzano G², Braga M², Dellabona P^{4,5}, Di Carlo V², Protti MP^{1,5}

¹Laboratorio di Immunologia dei Tumori, ²Chirurgia Generale II, ³Anatomia Patologia, ⁴Unità di Immunologia Sperimentale, ⁵Programma di Immunoterapia e Terapia Genetica dei Tumori Istituto Scientifico H. San Raffaele. Milan, Italy

Background Pancreas adenocarcinoma (PA) is the fifth most frequent cause of death from cancer. The natural history of the disease is brief and progressive with a 2-year survival of 28%. The disease is difficult to diagnose early and it is relatively resistant to standard treatment. Among these: surgery for a small percentage of eligible patients (5-20%), radio and chemotherapy, used after surgery or in metastatic tumors. New diagnostic and therapeutic strategies are needed. Immunotherapy represents one of the most interesting experimental approach for PA. We previously demonstrated that autologous dendritic cells (DCs) pulsed with the natural tumor peptides (NTPs), obtained by acid treatment of total tumor cells, successfully induce, both *in vitro* and *in vivo* in melanoma patients, CD8⁺ and CD4⁺ tumor-specific T cells, which recognize tumor associate antigens (TAAs) shared among allogenic melanomas [1 and unpublished results].

Aim Final goal is the development of a protocol of active immunotherapy in PA patients. Specific aims are to verify whether: i) shared TAAs exist in PA and if they are immunogenic, and ii) DCs pulsed with NTPs from allogenic PA induce anti-tumor T cells able to recognize the autologous tumor in PA patients.

Methods NTPs (mol wt 100-5,000 Dalton) were purified from a primary PA tumor cell line, established in our laboratory (DM), and two commercial primary (PaCa44) and metastatic (A8184) tumor cell lines. Autologous DCs pulsed with allogenic NTPs were used *in vitro* to stimulate CD8⁺ and CD4⁺ T cells from three healthy subjects and two PA patients (DM, BL). Activated CD8⁺ and CD4⁺ T cells were tested (proliferation, cytotoxic activity and cytokines release assays) to evaluate their tumor-specificity.

Results The results obtained demonstrate that NTPs from PA are immunogenic and strongly suggest the existence of shared TAAs among allogenic PAs. Most importantly, autologous DCs from the patients, pulsed with allogenic NTPs induced CD8⁺ and CD4⁺ T cells able to recognize and kill the autologous tumor.

Conclusions These data suggest that immunization with NTPs-pulsed DCs is a promising strategy to treat patients suffering from PA.

Reference

1. Imro MA, Manici S, Russo V, Consogno G, Bellone M, Rugarli C, et al. Major histocompatibility complex class I restricted cytotoxic T cells specific for natural melanoma peptides recognize unidentified shared melanoma antigen(s). *Cancer Res* 1999; 59:2287-91. [PMID 10344730]

Mitochondrial DNA (mtDNA) Mutations: New Insights for Pancreatic Cancer Diagnosis and Prognosis

Fogar P¹, Navaglia F², Basso D², Greco E², Sperti C¹, Zambon CF¹, Falda A², Stranges A², Pedrazzoli S¹, Plebani M²

¹Department of Medical and Surgical Sciences and ²Department of Laboratory Medicine, University of Padua. Padua, Italy

Background The D-loop region is the major control site for mtDNA expression because it contains the reading strand for origin of replication and promoters for transcription. Somatic D-loop mutations have implicated in the pathogenesis of cancers.

Aims 1) To compare germline and pancreatic cancer (PC) mtDNA D-loop sequence; 2) to verify whether in the germline mtDNA D-loop region there is any specific sequence correlated with PC diagnosis and outcome.

Methods Somatic (tumor) and germline (blood) mtDNA D-loop sequence was obtained from 24 PC and from blood of 12 age-matched healthy controls. mtDNA sequence was compared with the Cambridge sequence (<http://www.mitomap.org>).

Results Hot spot differences between tumor and germline mtDNA were found only in 3 patients. Among the numerous SNPs identified in our sequences, only 4 of them were unbalanced between PC and controls. These SNPs (CT16189, CT16519, AG73, CT152) were analysed by DHPLC in a larger

series of patients, including 100 PC, 41 chronic pancreatitis, 87 controls and 19 pancreatobiliary tract tumors. The haplotype T at 16189 and C at 16224 was correlated with pancreatic adenocarcinoma in non smokers ($X^2=4.8$; $P<0.05$), but not in smokers ($X^2=0.01$; P NS). In male, not in female patients with PC the mtDNA 16519 T allele was correlated with diabetes mellitus ($X^2=7.98$; $P<0.05$). PC patients without distant metastases and bearing this allele survived significantly lower (log rank test=9.74; $P<0.005$).

Conclusions 1) Somatic mtDNA mutations of the D-loop occur rarely in PC; 2) T16189-C16224 haplotype enhances PC risk in the absence of cigarette carcinogens exposure; 3) mtDNA 16519 T allele favors the onset of diabetes mellitus in PC supporting the role of mitochondria in the pathogenesis of this metabolic alteration; 4) the role of this allele in worsening metabolism is probably the basis of its association with a worse prognosis in non metastatic PC.

Intraductal Oncocytic Papillary Adenocarcinoma of the Pancreas

Franceschetti I¹, Parisi A¹, Gobbato M¹, Capelli P¹, Pecori S¹, Martignoni G², Zamboni G¹, Menestrina F¹

Pathology, ¹University of Verona and ²University of Sassari. Verona and Sassari, Italy

Context Epithelial cystic neoplasms represent 10% of pancreatic cysts and 1-3% of pancreatic carcinomas. Most of them are mucinous cystic neoplasms and serous cystadenomas. Pancreatic neoplasia mainly composed by oncocytic cells are rare; oncocytic features can be observed in some endocrine neoplasm and in some solid-pseudopapillary tumors. We describe a case of intraductal oncocytic papillary

adenocarcinoma with extension to the entire organ.

Case report A 71-year-old male patient had an important weight loss; radiologically, his pancreatic tissue was completely replaced by multilocular cystic formations; the greater one, in the body was 18 cm in diameter, with parietal solid projections inside. An intraductal papillary-mucinous neoplasm was suspected, and a radical spleno-

pancreatectomy was performed. At gross examination, the Wirsung was progressively dilated from the papilla of Vater to the body where it seemed to communicate with a voluminous cyst, which had a thin wall and an internal surface covered by mucinous material. The entire lumen of the Wirsung was occupied by multiple papillary projections. Surrounding pancreatic parenchyma was constituted by ectasic ducts with a cystic aspect, some with mucinous content and other occupied by papillary vegetations. At histological examination, cystic structures and papillary projections were covered by cylindrical cells with

oncocytic cytoplasm, forming a pseudostratified epithelium. Only with an extended sampling, microfoci of stromal infiltration were seen; extrapancreatic spread was not present. The patient is alive and well with a follow-up of 5 months.

Discussion Intraductal oncocytic papillary neoplasms are rare, they have macroscopic characteristics which are similar to the intraductal papillary-mucinous neoplasms and typically have an indolent clinical outcome. More studies are necessary in order to evidence the presence of distinctive clinical characteristics.

Characteristics of Pancreatic Fistula After Pancreatic Resections

Frasson M, Balzano G, Zerbi A, Cristallo M, Gavazzi F, Rocchetti S, Capitanio V, Di Carlo V
Pancreas Unit, San Raffaele H. Milan, Italy

Background pancreatic fistula is the most frequent and feared complication after pancreas surgery. In spite of this, guidelines worldwide accepted about definition and classification of pancreatic fistula are lacking.

Aims To describe: 1) the frequency of pancreatic fistulas after pancreatic resections; 2) the severity of fistulas, applying a clinical classification; 3) risk factors for the prediction of critical fistulas.

Methods A total of 728 consecutive patients undergoing pancreatectomy between 1995 and 2004 were retrospectively analysed: 486 pancreaticoduodenectomies (PD), 162 distal pancreatectomies (DP), 46 enucleations, 34 median pancreatectomies (MP). We defined 'pancreatic fistula' the presence in the drain of any quantity of fluid with amylase three times higher than serum. We classified fistulas considering the clinical implications for the patient, according to the classification proposed by Bassi: A: transient fistula, no clinical implication; B: fistula implying changes in patient's treatment; C: fistula causing an important extension of the hospital stay or relaparotomy or death. The risk factors for prediction of B-C grade fistulas were

evaluated by the squared-chi test.

Results Overall incidence of pancreatic fistula was 30.3% (221 patients). The fistula rate according to different resections was: PD 26.1% (A 42.5%, B 33.1%, C 24.4%), DP 32.1% (A 78.8%, B 21.2%, C 0.0%), enucleation 41.3% (A 63.2%, B 21.1%, C 15.8%), MP 67.6% (A 60.9%, B 34.8%, C 4.3%). If we exclude grade A fistulas, that do not implies variations on the clinical course, the incidence of B and C fistulas results: PD 15%, DP 6.8%, enucleation 15.2%, MP 26.4%. Fistula-associated relaparotomy rate was 12.2% (27 patients) and fistula-associated mortality rate was 4% (9 patients). Significant risk factors for B and C pancreatic fistulas after PD were Wirsung duct less than 3 mm ($P=0.02$) and soft pancreas ($P=0.05$), whereas the different treatment of the stump, malignancy, age and sex do not result to be significant risk factors.

Conclusions The incidence of fistula causing variation of patient's course is lower than the overall fistula rate, with a reoperation and mortality rate not elevated. Risk factors for critical fistulas were the small Wirsung duct and a soft pancreatic texture.

Laser Microdissection in Pharmacological Study of Pancreatic Cancer

Funel N¹, Giovanetti E², Campani D¹, Pollina LE¹, Mey V², Nannizzi S², Danesi R²,
Del Chiaro M³, Boggi U³, Del Tacca M², Bevilacqua G¹, Mosca F³

¹Division of Surgical, Molecular and Ultrastructural Pathology, ²Division of Pharmacology and Chemotherapy, ³Division of General Surgery and Transplantation and Regional Referral Center for Pancreatic Diseases Treatment. Department of Oncology, University and Hospital of Pisa. Pisa, Italy

Background Despite the knowledge of molecular pathology of pancreas cancer (PC), the systemic chemotherapy still relies on few drugs (gemcitabine and 5-fluorouracil). The rate-limiting step of gemcitabine activation is catalyzed by deoxycytidine kinase (dCK), whereas 5'-nucleotidase (5'-NT) and cytidine deaminase (CDA) inactivate the drug. Similarly, thymidylate synthase (TS) is the target enzyme of 5-fluorouracil, while polyglutamylation by folylpolyglutamate synthetase (FPGS) of intracellular 5,10-methylenetetrahydrofolate may enhance the cytotoxicity of 5-fluorouracil by allowing more efficient formation and stabilization of the inhibitory ternary complex involving thymidylate synthase and the 5-fluorouracil metabolite.

Aim In this work we compare, on samples microdissected and no-microdissected, RNA expression of key genes involved in pharmacological treatment of PC.

Methods One hundred and six cases of PC were collected in Pisa between December 2001 and June 2004 and RNA extraction was performed in all samples after laser microdissection (Leica ASLMD). In 17 cases RNA

extraction was also obtained from the whole tumor (comprising stroma, vessels, inflammatory cells). Quantitative PCR analysis was carried out for dCK, 5'-NT, CDA, TS and FPGS genes in both microdissected and no-microdissected samples.

Results Data obtained by no-microdissected were not so informative compared to microdissected specimens. In particular, in microdissected samples the quantitative analysis of the results showed an evident difference of mRNA expression of dCK (1.031±0.171), 5'-NT (0.932±0.166), CDA (0.959±0.154) and TS (1.088±0.189), and particularly for FPGS (0.609±0.399).

Conclusions As expected, laser microdissection is a valid tool for molecular analysis and this technique is much more valid in pancreatic carcinoma where the desmoplastic reaction can underestimate the molecular expression of epithelial component, the true target of chemotherapy. This suggests a possible stratification of patients on the basis of their genotype to create homogeneous groups with different likelihood to respond to gemcitabine or fluorouracil treatment.

Pharmacogenetics of Gemcitabine in Pancreatic Cancer

Giovanetti E¹, Mey V¹, Danesi R¹, Del Chiaro M², Funel N³, Boggi U², Orlandini C⁴,
Campani D³, Iannopolo M⁴, Nannizzi S¹, Ricci S⁴, Bevilacqua G³, Mosca F², Del Tacca M¹

¹Division of Pharmacology and Chemotherapy, ²Division of General and Transplant Surgery, ³Division of Pathology, ⁴Division of Oncology, Department of Oncology, Transplants and Advanced Technologies in Medicine, Regional Referral Center for Pancreatic Diseases Treatment, University of Pisa. Pisa, Italy

Background Although the first-line agent gemcitabine produces clinical benefits, the prognosis of pancreatic cancer remains dismal. Pharmacogenetics may guide clinical

management of this cancer, allowing the identification of responding patients.

Aim To define molecular markers influencing clinical response to gemcitabine treatment in

pancreatic cancer cells and characterize their expression pattern in specimens of pancreatic adenocarcinoma.

Methods From December 2001 to August 2004 a total of 105 patients (53 males and 52 females) with pancreatic cancer were evaluated. Sixty-two patients (median age 67.5 years) had radical surgery (3 after neo-adjuvant treatment) and 47 (75.8%) received adjuvant treatment with gemcitabine (1,000 mg/m²/day). Forty-two patients (median age 63.5 years) presented with metastatic disease and 36 (85.7%) received gemcitabine as palliative chemotherapy (3 after neo-adjuvant treatment). Neoplastic cells in frozen samples from 102 patients were isolated by laser microdissection and quantitative PCR was performed to study gene expression profile. Association between clinical outcome and gemcitabine determinant expression levels was estimated using Kaplan-Meier method. Moreover the role of drug transport and metabolism on gemcitabine cytotoxicity was examined with inhibitors of human equilibrative transporter 1 (hENT1), deoxycytidine kinase (dCK), 5'-nucleotidase (5'-NT) and cytidine deaminase (CDA) in three pancreatic cancer cell lines.

Results *In vitro* studies confirmed the key role of dCK, 5'-NT, CDA and hENT1 on gemcitabine sensitivity and their quantitative expression analysis in patients' samples demonstrated that these target genes were detectable in most surgical specimens with a variability that suggested a possible stratification of patients on the basis of their genotype to create homogeneous groups with different likelihood to respond to gemcitabine treatment. Indeed, a striking relationship was found between hENT1 expression and clinical outcome in all patients. In particular, overall survival was significantly longer ($P < 0.05$) both in the palliative and adjuvant setting in patients with higher hENT1 expression (median: 13.1 months; 95% CI: 12.2-13.9 months; and median: 28.0 months; 95% CI: 24.3-31.7 months; respectively), with respect to patients with lower hENT1 levels (median: 5.7 months; 95% CI: 4.6-6.9; and median: 13.2; 95% CI: 4.7-21.7 months; respectively).

Conclusions This study demonstrates the rationality of the choice of molecular determinants of gemcitabine activity to be examined in pancreas cancer, and provides the first evidence of a new strategy for its treatment optimization.

Effect of the Genetic Inactivation of Kinase Activity of Phosphoinositide 3-Kinase (Pi3k) Gamma in Experimental Acute Pancreatitis

Goffi A¹, Lupia E¹, De Giuli P³, Marengo S², Bosco O¹, Locatelli S¹, Dondi AE¹, Vlachou A¹, Hirsch E², Montrucchio G¹, Emanuelli G¹

¹Dipartimento di Fisiopatologia Clinica e ²Dipartimento di Genetica, Biologia e Biochimica, Università di Torino. Torino, Italy. ³Anatomia Patologica, Ospedale S. Lazzaro. Alba (CN), Italy

Background The G protein-coupled PI3Kgamma is an intracellular signalling molecule expressed in white blood cells and other tissues. In exocrine pancreas, PI3Kgamma regulates key pathologic responses to CCK hyperstimulation in isolated acini [1] and modulates the severity of acute pancreatitis (AP) *in vivo* [2]. Mice carrying a targeted mutation in the PI3Kgamma gene causing loss of kinase

activity (PI3Kgamma^{KD/KD}) have been recently described and showed to only partially reproduce the phenotype of PI3Kgamma^{-/-} animals [3].

Aim To define the role of PI3Kgamma kinase activity in experimental AP.

Methods AP was induced in wild-type, PI3Kgamma^{-/-}, and PI3Kgamma^{KD/KD} mice by supramaximal doses of cerulein (50 µg/kg i.p.). AP severity was evaluated measuring the

extent of acinar cell injury/necrosis, pancreatic edema, serum amylase, and neutrophil infiltration.

Results After 6 cerulein injections, PI3Kgamma^{-/-}, but not PI3Kgamma^{KD/KD} mice, showed a partial but significant reduction in acinar cell necrosis compared to control animals. Serum amylase levels, pancreatic edema, and neutrophil infiltration (although this was minimal) were not significantly different in the three groups. Prolonged administration of cerulein for 13 hours further increased all of the parameters of AP damage, with evident sequestration of neutrophils within the pancreatic tissue and the appearance of small foci of coagulative necrosis in the wild-type pancreata. Pancreatic necrosis and neutrophil infiltration resulted significantly reduced in PI3Kgamma^{-/-}, but not in PI3Kgamma^{KD/KD} mice, compared to wild-type animals.

Conclusions At variance from PI3Kgamma^{-/-}

mice, the severity of secretagogue-induced AP was not reduced in PI3Kgamma^{KD/KD} mice. Our results show that the protective effect observed in PI3Kgamma^{-/-} mice is not dependent on PI3Kgamma kinase activity and provide further information of the pathogenesis of experimental AP.

References

1. Gukovsky I, Cheng JH, Nam KJ, Lee OT, Lugea A, Fischer L, et al. Phosphatidylinositide 3-kinase gamma regulates key pathologic responses to cholecystokinin in pancreatic acinar cells. *Gastroenterology* 2004; 126:554-66. [PMID 14762792]
2. Lupia E, Goffi A, De Giuli P, Azzolino O, Bosco O, Patrucco E, et al. Ablation of phosphoinositide 3-kinase-gamma reduces the severity of acute pancreatitis. *Am J Pathol* 2004; 165:2003-11. [PMID 15579443]
3. Patrucco E, Notte A, Barberis L, Selvetella G, Maffei A, Brancaccio M, et al. PI3Kgamma modulates the cardiac response to chronic pressure overload by distinct kinase-dependent and -independent effects. *Cell* 2004; 118:375-87. [PMID 15294162]

Isolation and Characterization of Pancreatic Cancer (PC)

Diabetogenic Factor: A 14 Aminoacids Peptide Corresponding to the N-Terminal Sequence of a S-100 Calcium Binding Protein

Greco E¹, Basso D¹, Fogar P², Pucci P⁴, Flagiello A⁴, Baldo G², Giunco S², Navaglia F¹, Zambon CF², Falda A¹, Valerio A³, Pedrazzoli S², Plebani M¹

Departments of ¹Laboratory Medicine, ²Medical and Surgical Sciences, ³Clinical and Experimental Medicine, University of Padua. Padua, Italy. ⁴CEINGE Advanced Biotechnologies and Department of Organic Chemistry and Biochemistry, University of Naples. Naples, Italy

Background PC-associated diabetes is consequent to the action of a tumor peptide less than 10,000 Da.

Aim To identify the PC-associated diabetogenic peptide.

Methods Tumor homogenates from PC patients with (n=15) or without (n=8) diabetes, and normal pancreas homogenates (n=6) were subjected to 16.5% SDS-PAGE. After Comassie staining a band of approximately 1,500 Da was evidenced in tumor tissues only from diabetic PC. This band was cutted and sequenced by automatic Edman degradation.

Results The sequence obtained revealed a 14

aa peptide of 1589,88 Da, corresponding to the N-terminal sequence of an S-100 calcium binding protein. This peptide was synthesised and its effects on glucose metabolism were tested in cultured C₂C₁₂ myoblasts. These cells were cultured with different amounts (from 1 nmol/L to 2 mmol/L) of the 14 aa peptide. Glucose and lactate were measured in the supernatants after 24, 48 and 72 hours of incubation. In control myoblasts glucose concentration declined from 21.50±0.48 mmol/L (mean±SE) to 6.3±0.56, while lactate increased from 3.20±0.08 mmol/L to 34.50±1.24 after 72 hours of incubation. Fifty nmol/L 14 aa peptide caused a significant

reduction in glucose consumption and in lactate production after 72 hours of incubation with respect to control (Student's t test: $t=3.87$; $P<0.05$). At the same concentrations the 14 aa peptide caused also myoblasts phenotypic alterations (accumulation of cells at the periphery of culture wells, lack of differentiation in myotubes and presence of polynucleated cells).

Conclusions the N-terminal 14 aa peptide from an S-100 calcium binding protein is produced by PC causing diabetes mellitus; this peptide impairs glucose catabolism by myoblasts *in vitro* and this might determine hyperglycemia *in vivo*; its identification in patients' biological fluids might be helpful to diagnose PC when a recent onset diabetes mellitus occurs.

Common Bile Duct Strictures Due to Chronic Pancreatitis Managed by Self-Expandable Metal Stents (SEMS): Results of a Long-Term Follow-up Study

Iacopini F, Mutignani M, Tringali A, Familiari P, Spada C, Marchese M, Pirozzi GA, Riccioni ME, Costamagna G

Digestive Endoscopic Unit, Catholic University. Rome, Italy

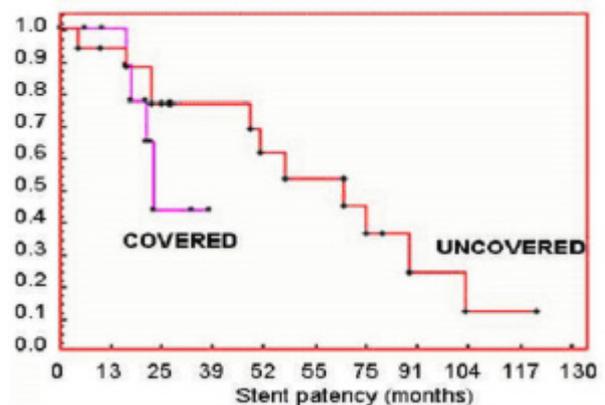
Background Common bile duct (CBD) strictures are reported as a complication of chronic pancreatitis (CP) in 3-23% of cases and when symptomatic, are an indication for derivative surgery. Patients at high surgical risk, with local contraindication (portal vein thrombosis) or that refuse surgery, need reiterated plastic stent placement. SEMS placement could be an alternative long-term treatment.

Aim To evaluate the long-term results of the management of CP-related CBD strictures by SEMS.

Methods From February 1990 to June 2004, 31 patients (29 M, mean age 49 years) with a symptomatic CP-related CBD stricture requiring plastic stenting with contraindication for surgery or refusing surgery, were treated by placement of a biliary SEMS at our institution. Thirteen (42%) patients had pancreatic calcifications. SEMS patency was assessed according to their characteristics.

Results Before SEMS placement all the patients had undergone a mean of 2.7 single plastic stent exchanges, every 7 months on average. In 15 cases SEMS clogged after a mean of 51 months (range 4-103 months), 15 patients have still a well functioning SEMS

after a mean of 34 months (range 6-121 months) and 1 patient died for unrelated causes after 28 months with a patent stent. Mean patency of nitinol and stainless SEMS was not significantly different (45 vs. 41 months, respectively). Mean patency of covered stents was 20 months (range 16-24 months) and mean patency of uncovered stents was 51 months (range 4-103 months) ($P=0.19$; see Kaplan Meier plot).



Conclusions Placement of SEMS in CBD strictures secondary to CP could be a valid alternative to surgery. According to these data uncovered SEMS have a longer patency than covered. Covered stents were placed only during recent years and follow-up is ongoing.

Old Done Idiopathic Chronic Pancreatitis Diagnosis: A Slippery Issue. Case Report

Landoni L, Falconi M, Riva F, Mascetta G, Tonazzo D, Armatura G, Pederzoli P

Department of Surgery and Gastroenterology, University of Verona. Verona, Italy

Context Recurrent upper abdominal pain associated with increased serum amylases and dilation of the Wirsung duct in a young male may suggest the diagnosis of idiopathic chronic pancreatitis (ICP). We report an interesting and slippery case.

Case report In 1982 a 25-year-old Caucasian male with familiar history neither for pancreatic diseases nor for alcohol abuse and biliary tract diseases was admitted at the Department of Surgery of our University. His medical history included several (approximately 10) recurrent episodes in a 3-year period of acute pancreatitis and signs of exocrine insufficiency. During previous admissions in other hospitals he was submitted to abdominal CT and ultrasound scan with evidence of a modest and homogeneous pancreatic enlargement. An ERCP showed a dilation of side branches ducts of the pancreatic tail. The patient underwent a left-pancreatectomy, with histological confirmation of sectorial CP. After surgery, the patient was asymptomatic for several years but from 1988 new episodes of pain occurred requiring several hospitalizations in Gastroenterological Units. A new ERCP was performed with evidence of dilation of the main pancreatic duct, a suspect of pseudocystic at the pancreatic body, and a delayed Wirsung emptying. In 1991, at the age of 34 years, the patient was submitted in our Institution to a second operation of pancreaticojejunostomy. Thanks to the

decompression of the pancreatic duct the following asymptomatic period was 13 years long. In the fall of 2004, when he was 47 years old, a new episode of pancreatitis occurs. A magnetic resonance colangiopancreatography showed a marked dilation both of the Wirsung duct and of the anastomized loop. An ERCP with brushing was performed but cytology was not diagnostic. Moreover, a revision of all the radiological pictures as well as of the previous resected specimen suggested the hypothesis that the diagnosis of ICP was wrong. In April 2005 a pylorus-preserving pancreaticoduodenectomy resulting in a totalization was performed. The histological examination of specimen showed the presence of an IPM carcinoma without infiltration of the stroma. The neoplasia involves the entire duct and the mucosa of the anastomotic loop.

Discussion Only in 1982 IPMNs are recognized by Kobashi as a subset of pancreatic exocrine tumours. They usually affect an elderly population and over the years they were also recognised as possible cause of chronic obstructive pancreatitis. The differential diagnosis between these two entities it is not always easy to do, above all at the beginning of the clinical history. This was particularly true when the diagnosis is of ICP. From this point of view this patient represents an interesting slippery case of misdiagnosis and teaches us that follow up is always mandatory.

Magnetic Resonance Cholangio-Pancreatography (MRCP) in Asymptomatic Hyperamylasemia

Malagò R¹, Manfredi R¹, Graziani R¹, Frulloni L², Patrizi F², Fantini K², Cavallini G²,
Pozzi Mucelli R¹

¹Department of Radiology and ²Department of Surgical and Gastroenterological Sciences,
University of Verona. Verona, Italy

Background Hyperamylasemia may be the first manifestation of undiagnosed pancreatic

disease, but may be also sustained by non-pancreatic causes, such as coeliac disease,

dyslipidemia, macroamylasemia, hepatitis C, renal failure.

Aim To assess the presence/absence of pancreatic abnormalities at MRCP imaging in patients with hyperamylasemia.

Materials and methods We prospectively enrolled from January to May 2005 all patients with asymptomatic hyperamylasemia, with at least 2 documented abnormally elevated serum levels of pancreatic amylase. Exclusion criteria were: pancreatic surgery and/or ERCP or general contraindication to MRCP (pacemakers or neurostimulators), alcohol consumption greater than 20 g/day. All patients underwent dynamic MRCP imaging before and after secretin stimulation.

Results We studied 12 patients (7 males and 5 females; mean age 50±15 years). Only 3 patients (25%) had normal MRCP imaging. The findings at MRCP before and after secretin stimulation are reported in the Table.

In 2/12 patients we observed a reduction in signal-to-noise of the pancreas greater than 15%, indicative of the presence of intracellular fat.

Conclusions Alterations at MRCP imaging are frequent in patients with asymptomatic pancreatic hyperamylasemia.

Findings	No.	%
Basal MRCP		
- Dilation	2	16%
- Cysts	1	8%
- Pancreas divisum (PD)	3	25%
- Normal	6	50%
MRCP after secretin stimulation		
- Diameter of Wirsung at 10 min > basal	2	16%
- 2 nd ducts dilation	4	33%
- Abnormal duodenal filling	1	8%
- Stenosis of the Wirsung duct	1	8%
- Santorinicele	1	8%
- Pancreas divisum	1	8%
- Normal	5	42%

A Study of the Relationship Between Idiopathic Pancreatic Hyperenzymemia and Dyslipidemia

Manca M, Migliori M, Salizzoni E, Calculli L, Serra C, Gaiani S, Casadei R, Pezzilli R, Gullo L
Institute of Internal Medicine, University of Bologna, S.Orsola Hospital. Bologna, Italy

Background One of us has recently described a new syndrome characterized by a chronic increase of serum pancreatic enzymes in the absence of pancreatic disease. It has been suggested by some investigators that this pancreatic hyperenzymemia may be due to pancreatic fatty infiltration secondary to hypercholesterolemia.

Aim We carried out the present study to see whether this hypothesis may be correct.

Methods Fifteen subjects with idiopathic pancreatic hyperenzymemia and hypercholesterolemia and 20 additional subjects with the same hyperenzymemia but without dyslipidemia were studied. In all these subjects pancreatic ultrasonography has been carried out; in those who had a hyperechogenic pancreas, magnetic resonance to establish whether they had signs of pancreatic fatty infiltration was carried out. In addition, in 25 of the subjects, 11 of whom

had hypercholesterolemia, serum pancreatic enzymes were measured for five consecutive days to study the diurnal pattern of the hyperenzymemia and to see whether there were correlations between this pattern and the dyslipidemia.

Results Of the 15 subjects with hypercholesterolemia, seven had a normal pancreas and eight a hyperechogenic pancreas at ultrasonography. Among the remaining 20 subjects with pancreatic hyperenzymemia without dyslipidemia 16 had a normal pancreas and four a hyperechogenic pancreas at ultrasonography. In the subjects with hypercholesterolemia, magnetic resonance did not show signs of fatty infiltration in the pancreas. In the 25 subjects in whom serum pancreatic enzymes were determined for five consecutive days, there have been marked diurnal variations, with frequent normalization of their levels.

Conclusion The results show that fatty infiltration of the pancreas does not exist in subjects with idiopathic pancreatic hyperenzymemia including those with hypercholesterolemia, suggesting that the chronic increase of pancreatic enzymes in

these subjects is not due to a fatty pancreas. The marked diurnal variations of the serum pancreatic enzyme levels further suggest that their increase is not dependent from an organic persistent pancreatic lesion such as fatty infiltration.

The Impact of Timing on the Efficacy of Foy in the Prevention of Acute Pancreatitis: A Randomised Study Comparing Prior vs. After-ERCP Administration

Manes G¹, Lombardi G², Pieramico O³, Bargiggia S¹, Bianchi Porro G¹

Divisione di Gastroenterologia, ¹Ospedale 'L Sacco', Milano, ²Ospedale 'A Cardarelli', Napoli, ³Ospedale 'Tappeiner', Merano. Milano, Napoli and Merano, Italy

Background and aim FOY administrated prior to ERCP reduces the incidence and severity of AP. Since FOY is expensive, selection of patients at higher risk to develop AP would optimise its use. Some factors associated to AP can be identified before ERCP (young age, female gender), but the majority are recognized only at the end of the procedure (multiple pancreas injections, pre-cut sphincterotomy, etc.). It is not known whether FOY administered at the end of ERCP is able to reduce the incidence of AP.

Methods Three-hundreds and 39 patients undergoing ERCP were treated with Foy 500 mg i.v. for 6 hours: 170 started the treatment within 1 hour before ERCP (group A) and 169 within 1 hour from the end of ERCP (group B). Incidence and severity of AP and hyperamylasemia were recorded, as well as

factors associated to the development of AP.

Results Incidence of AP was 5.9% (10/170) in group A and 6.5% (11/169) in group B (P NS). Only 1 patient in group B developed necrotizing AP. Hyperamylasemia occurred in 57 patients (33.5%) in group A and in 46 (27%) in group B (P NS). Female gender, difficult cannulation, acinarization, pancreatic duct injection and normal biliary tree were associated to the development of AP.

Conclusions Administration of FOY after ERCP protects from the development of AP similarly to FOY administered before. The majority of factors associated to the development of AP are recognized during ERCP. We suggest that FOY could be administered after ERCP, limiting its use only to those patients recognized to be at risk of developing AP during the examination.

A Prospective Comparison of Secretin Enhanced MRCP and EUS in Patients with Non-Alcoholic Non-Biliary Acute Recurrent Pancreatitis

Mangiavillano B¹, Mariani A¹, Arcidiacono PG¹, Giussani A¹, Curioni S¹, Rossi M¹, Zanello A², Castellaneta G¹, Testoni PA¹

¹Division of Gastroenterology and Gastrointestinal Endoscopy, and ²Department of Radiology, University Vita-Salute San Raffaele, IRCCS San Raffaele Hospital. Milan, Italy

Background MRCP and EUS are procedures comparable with ERCP in the diagnosis of bilio-pancreatic diseases, especially when combined with the i.v. administration of secretin (s-MRCP

and s-EUS) because of the increased visualization of the pancreatic duct system.

Aim No studies have compared these two procedures in patients with idiopathic acute

recurrent pancreatitis (IARP), which is the aim of this study.

Methods Consecutive patients with non alcoholic non biliary acute recurrent pancreatitis underwent, first, secretin-enhanced MRCP (s-MRCP) and EUS (s-EUS), then ERCP. 'Secretin test' both related to MRCP and EUS was performed to identify fibrosis of the main pancreatic duct (MPD) or sphincter of Oddi dysfunction (SOD). As a measure of agreement between s-MRCP and s-EUS for each categorical variables considered and for the final diagnosis, the Kappa coefficients and the 95% CI were calculated.

Results 19 patients were male, 21 female, with a mean±SD age of 48.7±16.4 years (range 19-74 years). Findings from s-MRCP and s-EUS in relation to the final diagnosis agreed in 14/40 patients (35%), corresponding to kappa=0.14 (poor agreement). Bilio-pancreatic ductal abnormalities were detected

by ERCP in overall 57.5% of cases (23/40 patients), in 62.5% (25/40 patients) by ERCP and s-MRCP: two patients with normal ERCP had suspected SOD. In patients with normal ERCP and s-MRCP, s-EUS detected in two cases gallbladder sludge and in one case IPMT: the final diagnosis by all the three procedures were done in 28/40 patients (70.0% of cases), in 35/40 (87.5% of cases) if three or more s-EUS parenchymal abnormalities (n=5 cases) and secretin MPD sclerosis (n=2 cases) were considered as diagnostic criteria of chronic pancreatitis.

Conclusions s-MRCP and s-EUS are both useful tools as first diagnostic step in the evaluation of patients with IARP but s-EUS seems the preferable procedure due to a higher accuracy for detecting biliary and both inflammatory and neoplastic pancreatic lesions. Further evaluations are needed to establish the diagnostic accuracy of these two procedures in patients with suspected SOD.

Prognostic Value of Ki-67 Expression in the Cytologic Identification of Pancreatic Endocrine Tumors: Preliminary Data

Manzoni MF¹, Franchi GM¹, Piani C¹, Cappelletti C¹, Arcidiacono PG², Albarello L³, Doglioni C³, Bosi E¹

¹Endocrinology, ²Gastroenterology and ³Pathology Units, San Raffaele Scientific Institute. Milan, Italy

Background Organ infiltration and distant metastasis are the only parameters that define the malignancy of pancreatic endocrine tumors. However, expression of proliferation markers, such as Ki-67, may be early predictors of the biologic behaviour of these tumors. Many studies in the literature demonstrate the prognostic value of Ki-67 expression in histological sections obtained from pancreatic endocrine tumors. We postulate that the expression of Ki-67 measured on fine needle aspiration cytology may provide pre-operative indications for the management of pancreatic endocrine tumors.

Aims 1) To examine the feasibility of measuring expression of Ki-67 on fine needle aspiration cytology; and 2) to compare the measurements of Ki-67 expression obtained on

fine needle aspiration cytology and histological sections from surgical removal of the tumor.

Methods We measured Ki-67 expression on endoscopic ultrasonography fine needle aspiration cytology and histological sections obtained after surgical removal of the tumor in six patients with pancreatic endocrine tumor.

Results Expression of Ki-67 was 20%, 15%, 1%, less than 1%, 1-2% in cytology and 15%, 19%, less than 1%, less than 1%, 2% in histology, respectively. One patients had a Ki-67 expression of 10% in histology, but unfortunately the Ki-67 expression in cytology could not be assessed for technical reasons.

Conclusions The results of this pilot study suggest that: 1) measurement of Ki-67 expression is feasible on fine needle aspiration cytology; and 2) there is a good

category agreement of Ki-67 expression between endoscopic ultrasonography fine needle aspiration cytology and histological sections of the tumor. If our results are confirmed in a larger study, the Ki-67

expression on cytology may help discriminate between low proliferative and medium/high proliferative tumors and thus could be used for prognostic and therapeutic pre-operative evaluation of endocrine pancreatic tumors.

A Second Look to Anti-TNFalpha Treatment in Acute Pancreatitis: Thumb Down?

Marotta F¹, Pavasuthipaisit K², Metugriachuk Y³, Tsuchiya J³, Lorenzetti A¹, Kuroi O³, Fesce E¹

¹Hepato-GI Unit, S. Giuseppe Hospital. Milan, Italy. ²Institute of Science and Technology. Mahidol, Thailand. ³Biokenkyusho Research Laboratory. Shizuoka, Japan

Background Anti-inflammatory drugs have a potential application in AP but anti-TNFalpha antibodies treatments remain conflicting, since worsening of pulmonary and pancreatic edema has been reported.

Aim To assess an anti-TNFalpha monoclonal antibody either in the prevention and treatment of experimental AP while also probing its effect on heat shock protein (Hsp)70-mediated protection, given its recent reported relevance.

Methods Specific pathogen free 8-week old mice were housed in a light/temperature controlled vivarium with *ad libitum* access to chow and water. AP was induced by hourly intraperitoneal injection of 50 µg/kg caerulein for 4 h. Group A mice received concomitant i.p. injections of anti-mouse TNFalpha mAb (25 µg/kg or 50 µg/kg); Group B as Group A but starting 1 h after last caerulein injections; Group C was administered anti-mouse IgG mAb (25 µg/kg) i.p. as IgG control; Group D served as disease control and given saline while Group E were healthy control mice given only sham saline injection. At sacrifice (4 h after the full blown AP) serum samples were obtained to test: routine blood tests, IL-

1beta, IL-6 and inducible Hsp. Histology of the pancreas and the lung was blindly assessed as well.

Results As compared to healthy control, either Group C and Group D showed significantly increased level of amylase, lipase and cytokines tested (C vs. E: P<0.01; D vs. C and E: P<0.01). These parameters were improved in both TNFalpha mAb regimens (P<0.01 but A vs. B: P<0.05). No dose-dependency was reported. The same picture among different groups applied when examining pancreas wet weight and necro-inflammatory scores. However, either pre- and post-treatment with TNFalpha mAb yielded comparable beneficial results. Hsp70 plasma level significantly decreased during AP (P<0.01) remaining unaffected by TNFalpha mAb, whatever the dosage employed.

Conclusions Within the limitation of an experimental study, the present data point out a significant beneficial effect of anti-TNFalpha treatment in AP even when applied soon after its onset. However, it is a matter of interest and concern that it does not seem to improve the protective stress response system.

Multidetector CT in Evaluation of the Retroportal Pancreatic Lamina: Correlation with Histopathological Findings

Mazzeo S, Cappelli C, Belcari A, Caproni G, Giannini A, Bertini R, Boggi U, Del Chiaro M, Croce C, Sgambelluri AF, Campani D, Funel N, Mosca F, Bartolozzi C

Department of Radiology, University Hospital of Pisa. Pisa, Italy

Background The neoplastic infiltration of the retroportal pancreatic lamina by adenocarcinomas of the pancreatic head or uncinata process corresponds to the infiltration of the retroperitoneal tissue and represents a critical factor in the tumor staging and in the surgical planning.

Aim The purpose of our study was to evaluate the role of multidetector CT in the assessment of the retroportal pancreatic lamina by correlating CT findings with histopathological results.

Methods The retroportal pancreatic lamina was evaluated in 34 patients affected by ductal adenocarcinomas of the pancreatic head or uncinata process, submitted to pancreaticoduodenectomy or total pancreatectomy. The suspicion of infiltration of the retroportal lamina arose at CT when the fatty

layer localized between the medial surface of the pancreatic head and uncinata process, the portal vein and mesenteric vessels appeared completely (macroscopic infiltration) or partially (microscopic infiltration) obliterated.

Results CT suggested infiltration of the retroportal lamina in 18/34 cases and absence of infiltration in 16/34 cases. At histopathology the presence of infiltration was confirmed in 16/18 (89%) cases and the absence of infiltration was demonstrated in 15/16 (94%) cases. Two false positive cases were caused by inflammatory findings of the peripancreatic fatty tissue. The sensibility of CT was 94%, specificity of 88% with an overall diagnostic accuracy of 91%.

Conclusions Multidetector CT is accurate in the assessment of the neoplastic infiltration of the retroportal pancreatic lamina.

Nosocomial Non-Biliopancreatic Infections in Acute Pancreatitis

Menchise A, Manes G, Bassano P, Balzano A, Rabitti PG, Uomo G

Departments of Internal Medicine and Gastroenterology, Cardarelli Hospital. Naples, Italy

Background Many studies are available on infection of pancreatic necrosis whereas little is known about the clinical relevance of extrapancreatic sepsis complicating the course of acute pancreatitis (AP).

Aim. This study was addressed to assess the incidence and clinical significance of nosocomial non-biliopancreatic (Nn-BP) infections in AP.

Patients and methods Data of all patients suffering from AP admitted in our institution from January 2002 to December 2004 were retrospectively reviewed. Two-hundreds and 52 patients were included into the study (mean age 59.4 years, range 19-81 years, female sex 62.9%, male 27%); 179 patients (71%) suffered from oedematous AP, 73

patients (28.9%) from necrotizing AP. All patients with necrotizing AP were treated with antibiotic prophylaxis; in oedematous AP antibiotic treatment was started following the clinical indications in each specific case. Nosocomial infection was defined in accordance with WHO criteria for nosocomial respiratory infections. Demographic data, clinical features, complications and outcome of the disease were analyzed.

Results Nn-BP infections were found in 27.4% of patients and were not related to demographic factors, comorbidities or etiology of AP. Of 69 patients affected, 42 presented oedematous AP and 27 necrotizing AP (P=0.04). Infected necrosis were found in 15 patients (20.5% of necrotizing AP) and

biliary sepsis in 9 patients (3.6%); deaths were 8, all in necrotizing group. Nn-BP infections did not influence the severity and outcome within the necrotizing and within the oedematous AP.

Conclusions In the present series Nn-BP infections are significantly more frequent in the severe group of AP patients and do not influence the prognosis that remains mainly related to multiorgan failure and infection of necrosis.

Pancreaticogastrostomy (PG) versus Pancreaticojejunostomy (PJ) after Pancreaticoduodenectomy (PD). A Prospective Randomized Study

Molinari E, Bassi C, Cavallini A, Crippa S, Serini P, Partelli S, Pederzoli P

Department of Surgery and Gastroenterology, University of Verona. Verona, Italy

Introduction while several techniques have been proposed for reconstructing pancreatico-digestive continuity after pancreaticoduodenectomy, only a limited number of randomized studies have been carried out.

Aim The present study has been addressed to compare the results of pancreaticogastrostomy versus pancreaticojejunostomy following PD in a prospective and randomized trial.

Methods A total of 151 patients undergoing pancreaticoduodenectomy with soft residual tissue were randomized to receive either pancreaticogastrostomy (Group PG) or end-to-side pancreaticojejunostomy (Group PJ).

Results The two treatment groups showed no differences in vital statistics or underlying disease, mean duration of surgery, and need for intra-operative blood transfusion. Overall, the incidence of surgical complications was 34% (29% in PG, 39% in PJ; P NS). Patients

receiving PG showed a significantly lower rate of multiple surgical complications (P=0.002). Pancreatic fistula was the most frequent complication, occurring in 14.5% of patients (13% in PG and 16% in PJ; P NS). Five patients in each treatment arm required a second surgical intervention; the post-operative mortality rate was 0.6%. PG was favored over PJ due to significant differences in postoperative collections (P=0.01), delayed gastric emptying (P=0.03), and biliary fistula (P=0.01). The mean postoperative hospitalization period stay was comparable in both groups.

Conclusions when compared to PJ, PG did not show any significant differences in the overall postoperative complication rate or incidence of pancreatic fistula. However, biliary fistula, postoperative collections and delayed gastric emptying are significantly reduced in patients treated by PG.

Endoscopic Management of External Biliary Fistula after Duodenopancreatectomy

Mutignani M, Tringali A, Spada C, Familiari P, Iacopini F, Marchese M, Perri V, Costamagna G

Digestive Endoscopy Unit, Catholic University. Rome, Italy

Background and aim ERCP is considered the treatment of choice for post-operative biliary leaks. Leaks after pancreaticoduodenectomy (DP) are difficult to treat endoscopically because of problems in

reaching the bilio-digestive anastomosis after surgical reconstruction.

Patients and methods Between May 1995 and March 2004, 7 patients (4 M, mean age 67 years, range 48-81 years) with post-

operative biliary leaks following DP underwent endoscopic treatment. ERCP was performed with a side viewing duodenoscope with the patient in the supine position. The afferent loop was identified, when necessary, under fluoroscopy using a guidewire and a guiding catheter.

Results Reason for DP were: bile duct cancer located in the middle/distal common bile duct (n=3), pancreatic cancer (n=2), ampullary cancer (n=2). Five patients had a pylorus preserving reconstruction (Traverso-Longmire) and 2 had gastric resection (Whipple). Five patients had an anastomotic leak, while 2 had a complete disconnection of the bilio-enteric anastomosis. The mean fistula output was 640 mL/day (range: 250-1000 mL/day). Patients with anastomotic leak were treated by placement of a 7 or 10 Fr naso-biliary drain connected with a continuous suction system. A 10 Fr naso-biliary drain was placed in the first patient with complete anastomotic disconnection but the fistula was still present 15 days later; two 10 Fr plastic stents were then inserted to

obtain closure of the fistula and to treat anastomotic substenosis; three months later the stents were removed without evidence of residual stricture. The second case of anastomotic disconnection was immediately treated by placement of 2 stents (8.5 and 10 Fr) and the fistula healed in 10 days. The fistula healed in all the patients after a mean time of 8 days (range: 2-20 days).

Conclusion Endoscopic management of anastomotic biliary leaks following pancreaticoduodenectomy is feasible even in cases with complete disconnection of the bilio-enteric anastomosis. The procedure can be performed with a duodenoscope which is more difficult to handle than a forward viewing scope, but allows easier identification of the anastomosis and treatment. Naso-biliary drain is useful in case of anastomotic leak because it allows suction and a check cholangiography to verify the healing, avoiding the need for a further ERCP to remove the stents. Patients with anastomotic disconnection can be treated by multiple stent placement to prevent stricture formation.

A Case of Pancreatic Heterotopy of Duodenal Wall, Intraductal Papillary Mucinous Tumour and Intraepithelial Neoplasm of Pancreas, and Papillary Carcinoma of Kidney in a Single Patient

Nobili C¹, Degrate L¹, Franciosi C¹, Caprotti R¹, Romano F¹, Perego E¹, Leone BE², Uggeri Fr¹

¹Department of Surgery and ²Department of Clinical Pathology, San Gerardo Hospital, University of Milan-Bicocca. Monza (MI), Italy

Case report We report a case of contemporaneous presence of pancreatic heterotopy of the duodenal wall, intraductal papillary mucinous tumour and intraepithelial neoplasm of the pancreatic head and papillary carcinoma of the kidney in a single patient. A 66-year-old man, for investigation of a 4-month history of urinary disorders, underwent ultrasound examination revealing a solid formation within the inferior pole of the left kidney. A computed tomography (CT) confirmed the presence of the 37 mm diameter hypovascular renal formation containing calcifications; but it appeared also

a 29 mm diameter heterogeneous mass within the pancreatic head; there was inflammatory enlargement of celiac lymph nodes; neither biliary ducts nor Wirsung were dilated and there was no atrophy of the pancreatic tail. Magnetic resonance revealed a multiloculated cystic component, with heterogeneous enhancement, of the pancreatic mass; renal lesion showed heterogeneous enhancement and hypovascular features; inflammatory enlargement of retroperitoneal nodes was found. One month later, a second CT confirmed the renal and biliary findings, but it revealed a modest enlargement of the

pancreatic mass, containing a bunch of little hypodense cystic areas, close to the mesenteric-portal axis without a cleavage layer. A resection of the left kidney inferior pole and a pylorus-preserving pancreaticoduodenectomy were performed. Histo-pathologic analysis of surgical specimen revealed mild differentiated papillary renal carcinoma; intraductal papillary mucinous adenoma of the pancreatic head; foci of intraepithelial pancreatic neoplasm (PanIN);

pancreatic heterotopy of duodenal muscular and submucosal layers.

Discussion The coexistence of several primaries and anomalies in one patient leads us to suppose a genetic predisposition to different lesions, even in absence of known familial genetic syndromes. The study of these cases is important because it may help in improving the investigation of molecular correlations and etiological factors of different solid tumours. Nowadays surgery is the only effective cure.

Role of Surgery in Pancreatic Metastases from Renal Cell Carcinoma

Ortolano E¹, Borri A², Zerbi A¹, Balzano G¹, Rocchetti S¹, Beneduce AA¹, Frasson M¹,
Di Carlo V¹

¹Pancreas Unit and ²General Medicine Unit, San Raffaele H. Milan, Italy

Background In the last years pancreas has been recognised as a possible site of metastasis from renal cell carcinoma (RCC).

Aim To better define the role of surgery in these clinical situations.

Methods We retrospectively analysed clinical records of 28 consecutive patients with diagnosis of pancreatic metastasis from renal cell carcinoma and treated at our Institution between August 1998 and May 2005. Patients were categorized into 3 risk groups (favourable, intermediate, and poor) according to the modified Memorial Sloan-Kettering Prognostic Factors Model [1].

Results Nineteen patients (67.9%) were male; mean age was 64.5 years at time of diagnosis of pancreatic disease. The interval between nephrectomy and the diagnosis of pancreatic localization was long up 23 years (median 8 years). Twenty of the 28 patients had surgery: 11 distal pancreatectomy (8 with splenectomy), 2 pancreaticoduodenectomy, 1 total pancreatectomy, 1 intermediate pancreatectomy, 5 enucleations. There was no peri-operative mortality. All operated patients resulted at favourable risk at time of diagnosis of metastatic RCC. Surgical treatment was excluded in 8 cases because of locally

advanced disease and/or general poor conditions. In this group 4 patients were at favourable risk, 3 at intermediate, 1 at poor risk. All of the not surgically treated ones received other therapies, as 80% of patients who underwent resection. In the group of patients undergoing surgery the 5-years Kaplan Meier survival rate was 85% with a mean survival time of 64.8 months; progression rate was 55%, with a mean progression time of 34.3 months. No pancreatic recurrence was observed. Patients who did not undergo surgery had a 5-year survival rate of 55%, with a mean survival time of 37.2 months.

Conclusion RCC is a systemic disease in which pancreatic metastases are possible localizations. Surgical resection in patients with pancreatic metastases from RCC, belonging to a favourable risk group, allows good local control and is related with high long-term survival.

Reference

1. Mekhail TM, Abou-Jawde RM, Boumerhi G, Malhi S, Wood L, Elson P, Bukowski R. Validation and extension of the Memorial Sloan-Kettering prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma. J Clin Oncol 2005; 23:832-41. [PMID 15681528]

Surgical Treatment of Non-Functioning Pancreatic Islet Cell Tumors

Pagogna S, Casadei R, Tomassetti P, Calculli L, Pezzilli R, Migliori M, Campana D, Zanini N, Minni F

Dipartimento di Scienze Chirurgiche e Anestesiologiche, Chirurgia Generale 'Minni',
Policlinico S.Orsola-Malpighi. Bologna, Italy

Background Non-functioning endocrine tumors of the pancreas (NFPTs) are islet cell tumors that are not associated with obvious signs or symptoms of hormone hypersecretion. They represent the most frequent pancreatic islet cell and because of their biologic heterogeneity, there is no standard approach to the management of NFPTs.

Aim Our aim is to evaluate the surgical treatment and its results in three different pancreatic groups of NFPTs: 1) solitary, benign, sporadic-non MEN1; 2) in the setting of MEN 1; 3) malignant NFPTs.

Methods Retrospective study that included 39 cases of patients with NFPTs observed in the period between 1985 and 2005. They represent the 52% (39/75) of all pancreatic islet cell tumors observed and were 16 males (41%) and 23 (59%) females with a mean age of 52 years (range 20-70 years). Group 1 includes 11 (28.2%) cases; group 2, 4 (10.3%) cases and group 3, 24 (61.5%) cases. In group 1, 4 were in the pancreatic tail, 4 in the body and 3 in the head; mean size was 3.5 cm (range 1.3-6.2 cm). Histologically, 4 were benign, 7 with uncertain behaviour. All cases were treated with pancreatic resection (resectability index=100%): 5 enucleoresections, 3 left pancreatectomies with splenectomy, 2 central pancreatectomies and, finally, 1 pancreaticoduodenectomy. In group 2, all patients presented multiple tumors, 3 in body-tail, 1 diffusely in the entire pancreas; maximum size was 9.8 cm, minimum few mm. Histologically, all were malignant and well differentiated; all cases were treated with

large pancreatic resections (resectability index=100%): 3 subtotal pancreatectomies with splenectomy, 1 total pancreatectomy. In group 3, 23 were solitary, 1 multiple; 2 were in the tail, 10 in body-tail, 11 in the pancreatic head and 1, multiple, involved the entire pancreas; mean size was 5.3 cm (range 1.4-13 cm). Histologically, 18 were well differentiated, 6 poorly. Eighteen out of 24 patients (75%) underwent large pancreatic resection with resection of other organs in 5 cases. All malignant tumors poorly differentiated were not resected.

Results Group 1: all alive and disease free with a mean follow-up of 10.2 years. Group 2: all alive, 2 disease free at a mean follow-up of 1 years, 2 with disease, 1 with local recurrence after 4 years and 1 with local recurrence and hepatic metastases after 3 years. Group 3: 11 (45.8%) dead, 7 for the disease (mean follow-up 21 months, range 4-41 months), 4 for other causes not related with the disease. 13 (54.2%) were alive (mean follow-up 77 months, range 7-120 months), 11 disease free, 2 with disease.

Conclusions Group 1: small, solitary, high resectability index, conservative pancreatic resections, good prognosis. Group 2: less frequent, multiple, low grade malignancy, high resectability index, large pancreatic resections, high frequency of recurrence but fair prognosis. Group 3: more frequent, good resectability index, large pancreatic resections, fair prognosis if well differentiated.

Neuroendocrine Tumor of the Pancreas and GIST: Is there a Correlation?

Pagogna S, Zanini N, Tomassetti P, Casadei R, Grottola T, Ricci C, Minni F

Dipartimento di Scienze Chirurgiche e Anestesiologiche, Chirurgia Generale 'Minni',
Policlinico S.Orsola-Malpighi. Bologna, Italy

Context Pancreatic endocrine tumors are uncommon neoplasms, their genetic

alterations are not well characterized. These tumors have site-specific differences in neuroendocrine characteristics, clinical course and genetic alterations. Gastrinomas are the most common functional, malignant pancreatic endocrine tumors. Gastrointestinal stromal tumours (GIST) are rare neoplasms originating from a primitive mesenchymal cell. Kit protein, a trans-membrane tyrosine kinase, is characteristically expressed by GIST. The incidence of neuroendocrine tumors and of GIST is 0.5 and 1-2 in 100,000 per year respectively. We report a very rare case of a pancreatic head gastrinoma associated with a jejunal GIST.

Case report A 83-year-old man was referred to our surgical department for an intestinal sub-occlusion with a 3-year history of pancreatic head cancer and multiple liver metastases. A gastroduodenoscopy showed a pyloric stenosis due to pancreatic mass compression. An abdomen US and CT scan confirmed the diagnosis of pancreatic head lesion and several liver metastases. A US-guided liver biopsy revealed neuroendocrine tumor metastases. Gastrin plasma level was higher than 10,000 pg/mL (reference range

13-115 pg/mL); plasma level of neuron-specific enolase was 17.6 ng/mL (reference range 0.0-12.5 ng/mL). A palliative gastrointestinal anastomosis (Roux-en-Y gastric bypass) was performed. During the operation two small nodules of a jejunal loop have been found and resected. Biopsies of the pancreatic mass revealed a neuroendocrine tumor. Immunohistochemistry showed low positive staining for chromogranin and high positive staining for synaptophysin and gastrin. Pathological studies on the jejunal resected nodules diagnosed two small gastrointestinal stromal tumors (0.4 cm in diameter); immunohistochemistry showed positive staining for c-kit, low positive staining for the marker S100, but was negative for desmin.

Discussion This is a very rare case of a neuroendocrine tumor of the pancreas associated to a jejunal GIST. Considering the macroscopic finding of the jejunal GIST, our surgical approach was justified. At a 6-month follow-up the patient is alive and well; he is under treatment with octreotide long acting release.

A Misleading Intrapancreatic Accessory Spleen Mimicking a Nonfunctional Neuroendocrine Tumor of the Pancreas

Panier Suffat L¹, Mazza L¹, Campra D¹, Farina EC¹, De Angelis C², Fronda GR¹

¹7th Division of General Surgery and ²Department of Gastroenterology, ASO S. Giovanni Battista, Molinette. Turin, Italy

Context Accessory spleen is found in 10% to 15% in autopsy case series. About 16% of these cases are intrapancreatic, more often located in the tail. Intrapancreatic accessory spleen (IPAS) may mimic a nonfunctional neuroendocrine tumor (Nf-NET) [1, 2].

Case report A 59-year-old man was admitted with a duodenal polypoid lesion found by upper endoscopy because of melena. At biopsy the lesion was a Nf-NET with immunohistochemistry positive for somatostatin. Hormonal status and neoplastic markers were within normal ranges, except for chromogranin A (1,398 U/mL).

OctreoScan[®] was negative. CT revealed an encapsulated hypervascular solid mass, about 1.5 cm in diameter, with smooth border, in the pancreatic tail and diagnosed as a further Nf-NET. An EUS showed the duodenal lesion and the pancreatic mass, referred to a multifocal Nf-NET. Contrast-enhanced EUS found a morphological pattern of Nf-NET untypically vascularized. A distal pancreatectomy with splenectomy was performed. The duodenal lesion was removed endoscopically in the same session. Histological features confirmed the duodenal Nf-NET with immunohistochemistry positive

for somatostatin, while the pancreatic mass was diagnosed as IPAS.

Discussion Advances in imaging modalities have increased the diagnosis of asymptomatic IPAS that are usually resected if they mimic a neoplastic lesion, about all a Nf-NET. The EUS is specific to identify pancreatic masses but there are no criteria for the differential diagnosis between IPAS and neoplasm. The diagnosis of suspected IPAS is confirmed by ^{99m}Tc-scintigraphy with heat damaged RBC.

Conclusion In the differential diagnosis of pancreatic Nf-NET, about all if in the tail, an IPAS, uncommon but non unusual cause of

misdiagnosis, must be considered. So unnecessary pancreatic resection might be avoided.

References

1. Lauffer JM, Baer HU, Maurer CA, Wagner M, Zimmermann A, Buchler MW. Intrapancreatic accessory spleen. A rare cause of a pancreatic mass. *Int J Pancreatol* 1999; 25:65-8. [PMID 10211424]
2. Brasca LE, Zanello A, De Gaspari A, De Cobelli F, Zerbi A, Fazio F, Del Maschio A. Intrapancreatic accessory spleen mimicking a neuroendocrine tumor: magnetic resonance findings and possible diagnostic role of different nuclear medicine tests. *Eur Radiol* 2004; 14:1322-3. [PMID 14615901]

Peripancreatic Vascular Anatomic Variations: Impact of Radiological Diagnosis with Multidetector Computed Tomography (MDCT) on Surgical Strategy

Pascali E¹, Calculli L¹, Casadei R², Amore B¹, Renzulli M¹, Fiscaletti M¹, Zanini N², Gavelli G¹

¹Department of Radiology, Radiology Unit III 'Prof. G.Gavelli', ²Department of Surgery 'Prof. F.Minni', S.Orsola-Malpighi Hospital. Bologna, Italy

Background The advent of multidetector computed tomography (MDCT), non invasive and extremely fast imaging technique, can be considered the diagnostic gold standard in study of abdominal vessels.

Aim To evaluate the impact that the diagnosis of peripancreatic vascular anatomic variations (including arteries and veins) can cause on surgical approach of patients with pancreatic cancer. The MDCT technique, using dynamic protocols, can help to detect the best surgical strategy.

Methods Sixty consecutive patients affected by pancreatic cancer (38 male, 22 female, average 65 years; dimensions between 2 and 5 cm) were scanned with MDCT with particular regard to abdominal vessels. The MDCT scans were performed with the triphasic technique at 0.75 mm during the arterial phase and at 1.5 mm during the other ones. We analyzed arterial, venous and venous Hendle's trunk vascular anomalies.

Results Arterial vascular district: 60 patients were examined: only 20 had vascular anomalies. In 2 patients the origin of common hepatic artery was aorta and in 4 was superior

mesenteric artery (AMS); in 7 cases the origin of right hepatic artery was AMS and in 2 the right and the left branch of hepatic artery originated from the celiac trunk but separately; in 2 studies the hepatic and the splenic artery had different beginning and in 2 the left branch of hepatic artery originated from the left gastric artery. One case reported an aneurismatic dilatation of an anomalous gastro-hepatic vessel. Venous vascular district: in 25 cases the inferior mesenteric vein led the splenic vein, in 3 the spleno-mesenteric confluence and in 2 patients the superior mesenteric vein. Hendle's trunk: was longer than 1 cm in 40 studies, smaller than 1 cm in 2 and the including vessels always run separated.

Conclusions The most important vascular anomalies concern the origin of hepatic artery from AMS and the anomalous confluence of VMI in mesenteric-portal trunk. The identification and the extension of Hendle's trunk are very important regarding a correct surgical approach on mesenteric-portal vessels.

Pancreatic Neuroendocrine Tumor Excision: 25-Year Experience

Pasquali C¹, Sperti C¹, Baratella P¹, Liessi G², Pedrazzoli S¹

¹Clinica Chirurgica IV, Università di Padova. Padua, Italy. ²Radiologia, Ospedale Civile. Castelfranco Veneto (TV), Italy

Background Neuroendocrine tumor excision (NTE) is considered a simple operation with low rate of complications. However data from laparoscopic surgery show a high incidence of pancreatic fistulas.

Aim Re-evaluation of our series of NTE.

Methods From 1980 to 2004, out of 109 patients who underwent surgery for neuroendocrine pancreatic tumor, 33 had a simple NTE. Patients with other associated pancreatic procedures were excluded. Seventy-two percent of cases were insulinomas. Age, sex, site and size of the tumor, associated diseases, hospital stay and complications were retrospectively reviewed by the clinical records.

Results Patients (12 males and 21 females) averaged 56.8 years, range 20-86 years. Mean size of the tumor was 1.7 cm and 54.5% were in the pancreatic head; 78.8% of cases had medical associated diseases. Hospital stay was 12 days (range 6-81 days) and mean period of gastric suction was 4 days. Sixty percent had a uneventful postoperative course. Complications were divided in early

(related to pancreatic surgery, general open surgery and medical) and late events. Complication related to pancreatic surgery were 6/33 (18%); 5 pancreatic fistulas (4 low output) and 1 acute pancreatitis, while 5/33 had a general surgery complication (2 leaking due to gastric and duodenal associated operations). Medical complications were recorded in 7 cases. Late complications occurred in 4 cases (2 incisional hernias, 1 pseudocyst, and 1 keloid). No patient was reoperated for pancreatic complications; 1 was reoperated for evisceration and 1 for hyper-parathyroidism in the early post-operative period. No mortality occurred. Re-evaluation of the clinical records in order to be submitted to laparoscopic surgery excluded 17/33 cases (51%) as candidate to laparoscopic approach.

Conclusions NTE is not related to a low complication rate even in open surgery, and major complications are due to associated surgical procedures. In the simple insulinoma excision we do not have fistulas since 1986 (17 cases).

The Quality of Life in Patients with Chronic Pancreatitis Evaluated Using the SF-12 Questionnaire: A Comparative Study with the SF-36 Questionnaire

Pezzilli R¹, Morselli-Labate AM¹, Fantini L¹, Frulloni L², Cavestro GM³, Ferri B², Comparato G³, Tomassetti P¹, Campana D¹, Gullo L¹, Corinaldesi C¹

¹Department of Internal Medicine and Gastroenterology, Sant'Orsola-Malpighi Hospital, University of Bologna. Bologna, Italy. ²Department of Surgical and Gastroenterological Sciences, University of Verona. Verona, Italy. ³Department of Clinical Science, Chair of Gastroenterology, University of Parma. Parma, Italy

Background There is the need to utilize a time-saving questionnaire to assess the quality of life in clinical practice.

Aims To establish the validity of the SF-12 questionnaire in chronic pancreatitis (CP) patients and to identify the predictors capable

of modifying the physical (PCS) and mental (MCS) component summaries in these patients.

Methods SF-12 and the SF-36 questionnaires were used.

Subjects One-hundred and 41 patients with

proven CP (116 males, 25 females; mean age 57.0±12.3 years, range 18-80 years) were studied. The mean age of onset of the CP was 42.0±15.3 years (range 8-77 years) and the mean time interval between diagnosis and admission to the study was 184.9±140.3 months (range 0-629 months). The etiology was alcohol abuse (more than 80 g/day for at least five years) in 109 patients (77.3%), due to other causes in 11 (7.8%) and unknown in the remaining 21 patients (14.9%). The BMI was 23.0±3.6 Kg/m² (mean±SD). The diagnosis of CP was made according to the criteria of Rome-Marseilles: 94 patients (66.7%) had pancreatic calcification, 58 (41.1%) had pseudocysts, and 104 (73.8%) had a dilatation of the Wirsung duct. Sixty patients (83.3%) had pancreatic insufficiency; 74 (52.5%) had diabetes secondary to pancreatitis and 62 (44.0%) had had pancreatic surgery. Fourteen (9.9%) patients underwent endoscopic pancreatic sphincterotomy for their disease. A histological diagnosis of CP was available in 62 patients (44.0%). Fifty-four patients

(38.3%) had pancreatic pain in the month prior to enrollment in the study. Seventy-six patients (53.9%) underwent non-pancreatic surgery and 88 (62.4%) had one or more comorbidities. The normative groups included 61,434 Italian subjects for SF-12 and 2,031 Italian subjects for SF-36.

Results CP patients had the SF-12 physical (PSC-12) and mental (MCS-12) component summaries significantly related to the PCS-36 and MCS-36 (P<0.001). The presence of pancreatic pain and non-pancreatic surgery accounted for 41.3% of the information in the formation of the PCS-36 score and 37.2% in that of the PCS-12 score, respectively. Gender, BMI, and pancreatic pain accounted for 15.3% of the information in the formation of the MCS-36 and for 14.7% in that of the MCS-12; using these clinical variables, the loss of information in applying the SF-12 instead of the SF-36 was very low (4.6% and 0.6% for the PCS and the MCS, respectively).

Conclusions The SF-12 is a good alternative to the SF-36 in assessing the quality of life in CP.

Intraductal Endocrine Tumour of the Pancreas: Report of Two Cases

Reghellin D¹, Bortesi L¹, Dalfior D¹, Capelli P¹, Martignoni G², Loss R¹, Zamboni G¹

Pathology, ¹University of Verona and ²University of Sassari. Verona and Sassari, Italy

Background Tumors of exocrine pancreas with an intraductal growth, such as intraductal papillary-mucinous neoplasm (IPMN) and the probably related oncocytic IPMN are well known entities. Recently, an intraductal acinar cell carcinoma has been described.

Aim We report two cases of endocrine tumors of the pancreas with a prevalent intraductal growth.

Methods We reviewed 167 endocrine tumors of the pancreas collected from the archives of the Department of Pathology of the University of Verona between 1974 and 2002.

Results Two cases showed a prevalent intraductal growth. Both patients were male, 48- (case 1) and 73-year-old (case 2), respectively. Imaging tests showed a solid mass in the head of the pancreas; in case 1 the

presence of a distinct mass bulging into the main duct suggested the diagnosis of IPMN. In both cases, a pancreaticoduodenectomy was performed. Grossly, case 1 showed a 4-cm solid mass growing into the Wirsung, with focal extension into the pancreatic parenchyma. In case 2 a 6-cm solid mass, involving the Wirsung and infiltrating the duodenum, was present. Microscopically, the two tumors involved the main pancreatic duct, which was dilated but lacked any metaplastic or dysplastic changes. The intraductal and parenchymal component of the tumors displayed a trabecular pattern and were composed by uniform, small or medium size cells, with round to oval nuclei with low/moderate atypia. Both cases showed angioinvasion, whereas case 2 presented also

with perineural invasion and regional lymph nodes metastases. Immunohistochemically, the intraductal, as well as the infiltrative tumor cells were positive for the endocrine markers: chromogranin A, PGP9.5 and synaptophysin, whereas were negative for acinar markers: trypsin, chymotrypsin, pancreatic lipase and alpha-amylase. The proliferation index was low in case 1 (Ki-67 less than 2%), whereas it was elevated in case 2 (Ki-67 greater than 5%). The final diagnosis (according to WHO) was: well differentiated

endocrine tumour, of uncertain behaviour (case 1) and well-differentiated endocrine carcinoma (case 2) and both patients are alive and well after 6 years and 1 year.

Conclusion Although intraductal endocrine tumours of the pancreas are rare, in our study we have found 2 cases out of 167, they have to be included in the differential diagnosis of intraductal neoplastic lesions of the pancreas. The lesion have to be clinically distinguished from IPMNs and histologically from intraductal acinar cell carcinoma.

A Mediastinic Mass of Unknown Origin

Rocchetti S, Balzano G, Zerbi A, Gusmini S, Nicoletti R, Frasson M, Di Carlo V
Pancreas Unit, Radiology San Raffaele H. Milan, Italy

Case report A 34-year-old Pakistan man came to our Intensive Care Unit for fever and a recruitment of respiratory distress that required invasive ventilation; a CT scan, performed in another hospital, showed multiple nodi and many hypodense lesions like abscesses and a similar abdominal, peripancreatic lesion. At the admission he was in bad clinical conditions, inflammatory index were much altered. A chest X-ray showed an extensive right pleural effusion with setti not drainable under US-guide. A thoracic drainage was placed: the output was 200 mL of a brown liquid. For the sequent increasing respiratory and septic distress the patient underwent a surgical toilette of the pleuric cavity (histological examination: inflammatory and necrotic tissue). A subsequent CT scan showed the presence of a sub-diaphragmatic fluid collection that was percutaneously drained. The measure of the amylase levels in the drained fluid was greater than 300,000 U/L: the hypothesis was a pancreatic mediastinic pseudocyst. The patient's conditions were worsening. In consideration of the supposed communications between the abdominal cystic lesion and the mediastinic lesion through the diaphragmatic jatus, the patient was operated. An explorative laparotomy was

performed without the finding of a real peripancreatic fluid collection and a trans jatal fenestrate surgical drainage was placed. Subsequent slow, progressive recovery of the respiratory distress was observed. Seven days after the procedure an active bleeding from the drainage was treated by partial resection of the mediastinic cyst. After some days the presence of air in the drainage was investigated with a radiological fistulography that showed a communication with the bronchial tree (low-posterior-medial bronchium of the right inferior lobe). A retrospective review of the CT scans showed the fusion of 3 dorsal vertebral somas; it was than proposed the diagnosis of esophageal duplication. The patient underwent surgical atypical lung resection of the right inferior lobe. Histological diagnosis: bronchial dysontogenic cyst secreting amylase. In consideration of this unsuspected finding another diagnostic hypothesis was mediastinic mature teratoma, found in the literature in another young similar Pakistan patient.

Discussion The patient is alive after ten months since the first clinical observation, is malnourished but the clinical conditions are improving. He still has a thoracic drainage with an output of 100 mL/day containing amylase.

EUS-Guided Puncture of Pancreatic Duct (PD) with Methylene Blue (MB) Injection for Localization of the Pancreatic Orifice after Ampullectomy

Rossi M, Diellou AM, Carrara S, Arcidiacono PG, Testoni PA

Division of Gastroenterology and Gastrointestinal Endoscopy, Vita-Salute San Raffaele University, San Raffaele Hospital. Milan, Italy

Context Endoscopic cannulation of the papilla may sometimes be difficult, in particular after surgical or endoscopic treatment of ampullectomy.

Case report This report describes the use of EUS-guided MB pancreatography for localization of PD orifice after an ampullectomy. A 56-year-old woman was hospitalized for recurrent acute pancreatitis. Two years before she underwent biliary sphincterotomy and surgical ampullectomy for a benign disease. During hospitalization laboratory tests evidenced hyperamylasemia; bilirubin and alkaline phosphatase were normal. MRCP showed a dilation of the main PD (5 mm) and of an accessory duct. At ERCP the day after the admission, the papilla appeared resected and, at its usual position, there was evidence of a stenotic biliary orifice while the pancreatic orifice was not

recognizable. We observed a stricture of the terminal common bile duct (CBD) and microlithiasis inside the CBD. Biliary orifice was cannulated and the CBD was dilated with a balloon. Following the patient underwent EUS that confirmed a dilation of PD with abrupt interruption at the duodenal wall. A guidewire was inserted through a 22 Gauge needle into the pancreatic duct under EUS-guide in order to pass through the pancreatic orifice but unsuccessfully. Then we administered MB through the needle into the pancreatic duct and we saw the flowing of it from the minor papilla. At ERCP minor papilla was easily localized; a sphincterotomy was performed and a pancreatic stent placed.

Discussion This report focused on the role of EUS-guided injection of MB for localization of pancreatic orifice in cases of difficult endoscopic cannulation.

CFTR, SPINK1 and PRSSI Genes Mutations in Patients Affected by Sporadic Chronic Pancreatitis

Salacone P, Arduino C, Salmin P, Brusco A, Bacillo E, Gaia E

S.C. Gastroenterologia, Ospedale San Luigi Gonzaga. Orbassano (TO), Italy. S.C. Genetica Medica, Ospedale San Giovanni Battista. Turin, Italy. Università degli Studi di Torino, Dipartimento di Genetica, Biologia e Biochimica. Turin, Italy

Background it is well known that three genes are involved in chronic pancreatitis: *CFTR* (cystic fibrosis transmembrane conductance regulator), *PRSSI* (cationic trypsinogen) and *SPINK1* (trypsin inhibitor).

Aims To determine the prevalence rate of *CFTR* and *SPINK1* gene mutations in our patients with chronic pancreatitis and to compare the clinical manifestations of the disease between patients carrying mutations and the ones who do not.

Methods We evaluated 128 patients with

diagnosis of chronic pancreatitis (19 with an alcoholic etiology). All patients were analyzed for all 27 exons of *CFTR*, 4 exons of *SPINK1* and 5 exon of *PRSSI* with DGGE (denaturant gradient gel electrophoresis) analysis. In 88 patients the clinical history, imaging, biohumoral and follow-up data were obtained.

Results We found 13 patients carrying mutations in the *CFTR* gene, 7 patients with *SPINK1* mutations and no patients with *PRSSI* mutations. No mutations were found

in patients affected with alcoholic pancreatitis. Among the 88 patients who were also clinically studied, 68 did not show mutations, 13 carried *CFTR* mutations and 7 *SPINK1* mutations. No statistically significant differences were observed between patients with and without mutations about the age at onset, the familiarity, the need for pancreatic surgery, the clinical manifestations of the disease (pain, dyspepsia) and the presence of pancreatic calcifications. In the subjects carrying a mutation in the *SPINK1* gene, the frequency of diabetes was higher than in the

other two groups.

Conclusion In our series the mutations of *CFTR* and *SPINK1* genes were found in about 15% of the subjects. In non familial cases of chronic pancreatitis it is not indicated to check for mutations of the *PRSS1* gene. We found no differences between patients carrying mutations and patients who do not for what concerns the onset and the clinical course. The diabetes is, instead, a frequent and early complication in chronic pancreatitis associated with *SPINK1* mutations.

Prognostic Factors for Resected Pancreatic Cancer: A Proposal for a Prognostic Score

Scaltrini F, Reni M, Bonetto E, Passoni P, Dell'Oro S, Zerbi A, Balzano G, Staudacher C,
Villa E, Di Carlo V

Department of Oncology and Surgery, S. Raffaele H. Scientific Institute. Milan, Italy

Background The results from the different studies about the cure for patients with pancreatic adenocarcinoma are troublesome to compare due to different selection criteria, follow-up duration, and inhomogeneous distribution of known and unknown prognostic factors. Whereas several experiences have investigated prognostic factors, the relevance of each variable is unknown.

Aim To identify independent baseline patient or disease related prognostic factors and to design a prognostic score significantly associated with survival for identification of risk groups among patients resected for pancreatic adenocarcinoma with curative intent.

Methods A retrospective series of 239 patients operated at a single institution between 1985 and 2002 analyzes the relationship between survival and patient-, tumor-, and treatment-related variables.

Results In both univariate and multivariate analyses tumor grade (1-2 vs. 3-4) and size (less than 3 cm vs. more than 3 cm), stage of disease (IA-IIA vs. IIB-III), preoperative CA19.9 value (less than 5- vs. more than 5-folds upper laboratory normal limit), and postoperative performance status (0-1 vs. 2-3)

were found to be independently predictive of survival. The combined analysis of these five variables resulted in a prognostic score (by assigning a value of either 0, if favorable, or 1, if unfavourable and adding for a final score), allowing to distinguish three different risk groups having varying survival. Risk group attribution was possible for 216 (90%) patients. Median, 2-year, and 5-year overall survival for 55 patients in low-risk group (patients with 0 to 1) were 28 months, 58%, and 21%, for 130 patients in intermediate-risk group (2 to 3) were 17.5 months, 32%, and 6%, and for 31 patients in high-risk group (4 to 5) were 9 months, 10%, and 0%. The differences between survival curves were statistically significant: low- vs. intermediate-risk $P=0.0002$; low- vs. high-risk $P<0.00001$; intermediate- vs. high-risk $P=0.00006$.

Conclusions Preoperative CA19.9, tumor size and grade, postoperative performance status, and stage were independently predictive of survival. The proposed score may allow identification of different patient risk groups, facilitate the comparative analysis of prospective trials, favor adequate assessment of new therapeutic strategies deserving further evaluation, and define stratification criteria for future phase III trials.

Recurrence Rate According to the Resection Pancreatic Margin Hystology in Intraductal Papillary Mucinous Neoplasm of the Pancreas

Serini P, Salvia R, Mascetta G, Landoni L, Valli L, Giardino A, Pederzoli P
Department of Surgery and Gastroenterology, University of Verona. Verona, Italy

Background Intraductal papillary mucinous neoplasms of the pancreas (IPMNs) which include different biological grade of dysplasia such as adenoma (IPMA), borderline (IPMB) and carcinoma (in situ, IPMCis, or invasive, IPMC), tend to growth along the ductal tree and often are multifocal. A complete surgical resection it is not always achievable, but with total pancreatectomy (TP).

Aim of this study was to retrospectively evaluate eventual local recurrences according to final diagnosis and pancreatic margin histology in patients who underwent a partial pancreatectomy for IPMN in our Institution.

Results From 1990 to 2004, 113 patients with IPMNs underwent a pancreatic resection for the disease. The Table shows resection margin histology according to the final

specimen pathological assessment. After a median follow up of 40.6 months (range 6-67 months), 6 patients (18.8%) developed a recurrence. The primary histology was an IPMC and an IPMA, in 5 cases and 1 case, respectively. The previous pancreatic margin showed a denudation in 2 cases, borderline dysplasia in other 2, it was negative in 1 and positive for carcinoma in an other patient who refused TP. The time to recurrence was 40.6 months in mean (range 6-67 months) and in 4 patients a second resection was possible.

Conclusions The results of this study confirm a low percentage of local recurrence after pancreatic resection for IPMNs which occurred both in case of negative margin and after border line dysplasia and denudation in 1.4%, 15.4%, 18.2% respectively. Moreover it is difficult to assess whether local recurrence depends on the margin status or is an expression of multifocality of the disease. Denudation seems to be particularly at risk, even if follow up is always mandatory.

Specimen	Resection margin (n=118)				
	Negative	Adenoma	Borderline	Carcinoma	Denudation
IPMA	21	4	0	0	1
IPMB	26	7	3	0	1
IPMCis	6	2	3	0	2
IPMC	21	4	7	3	7
Total	74 (63%)	17 (14%)	13 (11%)	3 (2%)	11 (10%)

Conventional Ultrasonography, Contrast-Enhanced Ultrasonography, and Contrast-Enhanced Computed Tomography in Dectection of Liver Metastases in Patients with Endocrine Tumors of the Pancreas: A Preliminary Comparative Study

Serra C, Mazzotta E, Piscitelli L, Calculli L, Campana D, Pezzilli R, Tomassetti P
Department of Internal Medicine and Gastroenterology, University of Bologna, Sant'Orsola-Malpighi Hospital. Bologna, Italy

Background Contrast-enhanced ultrasound (CEUS) significantly improves the diagnostic performance of ultrasonography in the assessment of focal hepatic lesions.

Aim To compare the diagnostic accuracy of conventional ultrasonography (US), contrast-

enhanced ultrasonography (CEUS), and contrast-enhanced computed tomography (CECT) in detecting liver metastases in patients with endocrine tumors of the pancreas.

Patients and methods Ten patients with

endocrine tumors of the pancreas (6 males and 4 females, mean age 59.8 ± 14.4 years, range 38-78 years). Eight patients had non-functioning pancreatic tumors and 2 had gastrinomas. All patients underwent to US, CEUS e CECT. The US and the CEUS were carried out using an US scanner (Philips HDI 5000) with a multifrequency convex probe (2-5 MHz); a contrast-specific software with pulse inversion technology was also applied. The SonoVue[®] (Bracco, Italy) was the US contrast medium utilized and the 2.4 cm³ of this substance was administered in bolus i.v. followed by 10 cm³ of saline solution. All patients also underwent somatostatin receptor scintigraphy.

Results US identified 95 liver lesions, CEUS 130, and CTA 100. US identified four different patterns: 40% of the lesions were hypoechoic, 50% hyperechoic (10% of which had an hypoechoic halo), and the remaining 10% were inhomogeneous. At CEUS all the

95 liver lesions had an enhancement during the arterial phase and were hypoechoic during the portal and parenchymal phases. This pattern is specific to hypervascular metastases and their particular behavior is not related to the US patterns. The CEUS enhancement in the late phases identified an additional 35 hepatic lesions of 5 ± 4 mm in diameter undetected by conventional US. Seventy-five of the 100 hepatic lesions detected at CECT (75%) were hypervascular, hyperdense during the arterial phase and hypodense in the subsequent phases. Twenty-five (25%) lesions were also hypodense during the arterial phase of acquisition. OctreoScan[®] showed a picture compatible with liver metastases in all patients.

Conclusions These preliminary data show that CEUS is the technique of choice in detecting hepatic metastases in patients with endocrine pancreatic tumors.

18FDG PET Is Very Useful in the Follow-up after Resection of Pancreatic and Periapillary Tumours

Sperti C¹, Pasquali C¹, Bissoli S², Fiore V², Scelzi E³, Mion M³, Lessi G⁴, Pedrazzoli S¹

¹Department of Medical and Surgical Sciences, Surgical Clinic IV, University of Padua. Padua, Italy. ²PET Center, Nuclear Medicine, ³Department of Oncology, and ⁴Department of Radiology, Castelfranco Veneto Hospital. Castelfranco Veneto (TV), Italy

Background Surveillance after resection of pancreatic and periapillary malignancies generally include abdominal ultrasonography (US) and/or computer tomography (CT), and CA 19-9 serum determinations. Unfortunately, the detection of tumor recurrence is often difficult because of post-therapy anatomic alteration and recurrent disease, when detected, is practically incurable.

Aim In this study we determined the accuracy and contribution to surgical decision making of FDG PET in recurrent pancreatic and periapillary malignancies.

Methods From January 1998 to December 2003, 45 patients underwent whole-body ¹⁸-FDG-PET during follow-up after resection for pancreatic (n=31) and periapillary (n=14)

cancers. All patients also underwent ultrasound and helical computer tomography, chest X-ray, and serum tumor markers (CEA and CA 19-9). Median follow-up period was 21 months (range 12-84 months).

Results A total of 28 patients experienced tumor's recurrence; serum CA 19-9 levels were high in 22 of them (79%). Sensitivity of ¹⁸-FDG-PET and CT scan in detecting tumor's relapse was 96% (27/28) and 57% (16/28), respectively. Twelve recurrences were detected only by PET (CT false negative); 9 out of 12 patients were asymptomatic. Six patients underwent surgical resection (three para-aortic lymph nodes, two liver and one colonic metastasis), 5 chemotherapy, and one radiotherapy. In three recurrence-free patients PET only

showed a second primary tumor that was successfully resected (one carcinoma of the lung and two colon cancers). A liver metastasis was detected only by CT scan (PET false negative); a single PET false positive result was explained by a local colonic inflammation. Fourteen patients are recurrence free. PET was negative in all; while three had transient elevation of CA 19-9 levels and three had CT findings equivocal for relapse. Overall, ¹⁸F-DG-PET modified the

treatment in 9/45 patients (20%), and allowed a wait and see policy, confirmed by further follow-up, in 6 patients (13%).

Conclusions ¹⁸F-DG-PET is very sensitive in detecting recurrent pancreatic and periampullary carcinoma even in asymptomatic patients. ¹⁸F-DG-PET allowed us to perform potentially radical surgery in several selected patients with localized, resectable recurrence or second cancer.

Non-Functioning Neuroendocrine Tumors (NFET): Role of CT in the Differential Diagnosis with Ductal Adenocarcinoma of the Pancreas

Tapparelli M¹, Graziani R¹, Manfredi R¹, Biasiutti C¹, Falconi M², Frulloni L², Patrizi F², Cavallini G², Pozzi Mucelli R¹

¹Department of Radiology and ²Department of Surgical and Gastroenterological Sciences. University of Verona. Verona, Italy

Aim To determine the CT criteria useful for the differential diagnosis between NFET and adenocarcinoma (ADK) of the pancreas.

Materials and methods Forty-three consecutive patients with NFETs and 46 patients with adenocarcinoma of the pancreas, were retrospectively enrolled. Forty-five patients were males and 44 were females. All patients underwent quadriphasic, contrast-enhanced CT, and surgical procedure (n=81) or pathologic examination (n=8), that represented the standards of reference. Image analysis was independently performed by two radiologists, blinded to the surgical data; discrepancies were resolved by consensus. Qualitative image analysis included: tumor margins (sharp/irregular), tumor density compared to adjacent pancreatic parenchyma (hypo-, iso-, hyper-dense), presence and site of calcification (single/multiple; central/peripheral), vascularization (hypo-, iso-, hyper-vascular), delayed retention/wash out, presence of upstream chronic obstructive pancreatitis. Quantitative image analysis included the tumor maximal diameter.

Results Tumor margins appeared sharp in 38/43 (88%) NFETs and irregular in 5/43 (12%); 46/46 (100%) ADKs showed irregular

margins. Seventeen out of 43 (40%) NFETs were hypodense compared to adjacent pancreatic parenchyma at NCECT and 26/43 (60%) were isodense. Thirty-seven out of 46 (80%) ADKs were isodense on NCECT and 9/46 (20%) were hypodense compared to adjacent parenchyma. Five out of 43 NFETs showed parietal calcification at NCECT, in 3/5 cases multiple; whereas none of the patients with pancreatic adenocarcinoma showed tumoral calcification. Twenty-eight out of 43 (65%) NFETs were hypervascular compared to adjacent pancreatic parenchyma, 11/43 (26%) were hypovascular and 4/43 (9%) were isovascular. Thirty-seven out of 46 (81%) ADKs were hypovascular compared to adjacent pancreatic parenchyma and 9/43 (19%) were isovascular. Twenty-five out of 43 (58%) NFETs showed delayed wash out, and 18/43 (42%) delayed retention. Thirty-two out of 46 (79%) ADKs showed delayed wash out, and 14/46 (30%) retention. Upstream obstructive chronic pancreatitis was observed in 17/43 (40%) NFETs and in 35/46 (76%) ADKs. Mean size of the NFETs was 5.9 cm (range 1-15 cm), of the ADKs was 3.7 cm (range 1.5-7 cm).

Hepatobiliary Scintigraphy (HBS) and Magnetic Resonance Cholangio-Pancreatography (MRCP) with Secretin Stimulation (MRCP+S) in Patients Suffering from Recurrent Pancreatitis (RP)

Tomba F¹, Vaona B¹, Frulloni L¹, Bovo P¹, Bernardoni L¹, Patrizi F¹, Biasin S¹, Katsotourchi A¹, Giorgetti PG², Cavallini G¹

¹Department of Surgical and Gastroenterological Sciences, University of Verona,
²Nuclear Medicine Unit of 'Maggiore' Hospital. Verona, Italy

Background Sphincter of Oddi dysfunction (SOD) may determine RP. However, in patients suffering from RP, the abnormalities of sphincter of Oddi contractility may relate to either the biliary or pancreatic portions of the sphincter, or both.

Aim to evaluate the integrated diagnosis of biliary SOD by hepatobiliary scintigraphy (HBS) and pancreatic SOD by MRCP with secretin stimulation (MRCP+S) in patients suffering from pancreatic or biliary diseases.

Materials and methods We studied 40 patients suffering from RP over a three-year period by HBS and MRCP (7 males, 33 females; mean age 46.3±15 years). Twenty-six patients (65%) underwent cholecystectomy and 16 (40%) endoscopic sphincterotomy (ES) before the study. HBS evaluated the hepatographic and biliary phases, and the transit to the duodenum of the HIDA. MRCP studied the morphological aspect of the biliary and pancreatic ductal system and the pancreatic functional response MRCP+S.

Results HBS was altered in 31/40 patients (77%) and MRCP in 20/40 (50%). Only 6 patients (15%) showed normal both MRCP+S and HBS, whereas 17 patients (43%) had

either MRCP+S or HBS pathologic and 17 patients (43%) had both investigations altered (Table).

Group	MRCP+S	HBS	No.	%
A	Normal	Normal	6	15%
B	Normal	Pathologic	14	35%
C	Pathologic	Normal	3	7%
D	Pathologic	Pathologic	17	43%

The frequency of altered HBS was higher in patients who underwent cholecystectomy than in those who did not (74% vs. 33%; P=0.033) or ES (100% vs. 65%; P=0.005) before the study, and with documented biliary lithiasis (77% vs. 44%; P=0.072). All 9 patients with normal HBS showed a normal aspect of biliary tree at MR cholangiography, whereas only 9 patients out of 31 patients with altered HBS showed a pathologic biliary tree at MR cholangiography.

Summary The frequency of biliary and pancreatic SOD is high in patients suffering from RP. Morphologic MR-cholangiography did not correlate with HBS. HBS is altered particularly in the presence of biliary lithiasis and in cholecystectomized patients.

Conclusions These data suggest the use of HBS in patients suffering from RP.

Increased Levels of Interleukin-18 Binding Protein in the Blood Circulation of Patients with Pancreatic Adenocarcinoma: A Potential Novel Mechanism of Tumor Immune Escape?

Tonel E¹, Bellone G¹, Carbone A^{1,2}, Novarino A³, Dughera L², Buffolino A¹, Scirelli T¹, Addeo A³, Bertetto O³, Emanuelli G^{1,2}

¹Department of Clinical Physiopathology, University of Turin, ²Department of Gastroenterology and Clinical Nutrition, and ³Department of Clinical Oncology, Azienda Ospedaliera San Giovanni Battista, Molinette. Turin, Italy

Background Interleukin-18 (IL-18) is a T helper 1 cytokine that induces interferon (IFN)-gamma production, Fas ligand

expression, and inhibits angiogenesis, but its bioactivity is regulated *in vivo* by its soluble decoy receptor, IL-18 binding protein (IL-

18BP). Recently, we observed that pancreatic carcinoma cell lines and primary tumors constitutively express IL-18, raising the issue of anti-tumor effects of a tumor-derived proinflammatory cytokine.

Aim This study was undertaken to determine levels of IL-18 and IL-18 binding inhibition in the blood of patients with pancreatic adenocarcinoma.

Methods Serum concentrations of IL-18 and its endogenous antagonist IL-18BP in 20 patients with histopathologically-confirmed primary pancreatic duct adenocarcinomas (stage III: n=4; stage IV: n=16) were compared by enzyme-linked immunosorbent assay (ELISA) with those in healthy controls. The biologically active mature protein of IL-18 was detected by Western blot analysis with a specific anti-IL-18 antibody. The inhibitory activity on IL-18BP was determined by inhibition assay using IL-18-responding PHA-stimulated T cells.

Results Concentrations of serum IL-18 were elevated in patients with pancreatic carcinoma

compared with those in healthy individuals (mean±SE: 350.7±41.7 pg/mL vs. 130.9±19.2 pg/mL; P<0.0001). No significant correlations were detected between the IL-18 level and stage. Specific ELISA and Western blot analysis revealed that serum samples from patients contained an 18-kDa polypeptide of IL-18, corresponding in size to the mature form. Moreover, serum samples from patients showed significantly higher levels of IL-18BP than in healthy donors (mean±SE: 3,617.2±1,156 vs. 2,535.4±182 pg/mL, P<0.001). Accordingly, the patient serum samples were able to significantly inhibit IL-18-induced IFN-gamma secretion from PHA-blasts.

Conclusions These data indicate that in pancreatic carcinoma patients, despite elevated systemic and local IL-18 levels, overproduction of IL-18BP may contribute to tumor development by the restriction on inflammatory activity of IL-18. These findings delineate a novel mechanism by which tumor may modulate anti-tumor cell-mediated immune responses.

Early Pancreatic Cancer and Peutz-Jeghers Syndrome: A Case Report

Zanini N, Casadei R, Brillanti S, Pezzilli R, Calculli L, Pagogna S, Minni F

Dipartimento di Scienze Chirurgiche e Anestesiologiche, Chirurgia Generale 'Minni',
Policlinico S.Orsola-Malpighi. Bologna, Italy

Context Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder characterized by hamartomatous polyposis of the gastrointestinal tract, pigmentation of the skin and mucous membranes, and an increased risk for pancreatic cancer. Herein we report a case of a 67-year-old woman affected by PJS and radiologically suspected cystic lesions of the whole pancreas. Our aim is to focus on the best diagnostic and therapeutic approach to this kind of patients.

Case report A patient with PJS linked gastrointestinal polyposis was referred to our institute because of a CT diagnosis of multiple cystic lesions of the pancreas. The diagnosis of PJS was made 22 years before after a colonoscopy biopsy. The patient had a medical history characterized by an hysterectomy for uterine fibroma, an

ileal segmental resection for intussusception, a lumpectomy for an in situ ductal carcinoma and a mucoid carcinoma of the breast and a recent diagnosis of hyperpigmentation of the conjunctiva. The patient was asymptomatic and a medical investigation was negative for any kind of pathological abdominal sign. Amylase and lipase serum levels were normal, an oral glucose tolerance test revealed an impaired glucose tolerance. Neoplastic serum markers (CEA, CA 19-9, CA 125) were normal. The patient underwent abdominal US, EUS, MR, and ERCP which showed multiple pancreatic cysts communicating with the dilated main pancreatic duct. A total pylorus-preserving pancreaticoduodenectomy was performed. There were no post-operative complications and the patient was discharged on post-

operative day 16. Histopathological examination showed: multiple mucinous cysts as intraductal mucinous neoplasia and well differentiated ductal pancreatic adenocarcinoma (histological diameter of the tumour was about 1 cm). Thirty-seven non-neoplastic nodes were found in the specimen. The patient is alive and disease free after 6 months.

Discussion PJS has been associated with different type of cancer, in particular with intraductal papillary neoplasia of the pancreas and with ductal adenocarcinoma. In our case the association between PJS and cystic lesions of the whole pancreas justified total pancreatectomy, so a curative resection was possible.

POSTER SESSION

Cytokeratin 19 Expression in Pancreatic Endocrine Tumors

Albarelo L, Capitanio V, Zerbi A, Di Carlo V, Doglioni C

Department of Pathology and Department of Surgery, San Raffaele Hospital. Milan, Italy

Background Pancreatic endocrine tumors (PET) are a heterogeneous group of neoplasms with variable clinical manifestations and biological behavior. There are no 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. Cytokeratin19 (CK19) expression has recently been proposed as a marker of malignancy in PET.

Aim To evaluate CK19 expression and clinicopathologic features of 126 PET surgically treated at San Raffaele Hospital.

Methods Immunohistochemistry for CK19 was performed on tissue microarrays consisting in 1 mm cores from 49 well differentiated endocrine tumors-benign (B), 35 well differentiated endocrine tumors-uncertain behavior (I), 31 well differentiated endocrine carcinomas (C) and 11 poorly differentiated endocrine carcinomas (P). CK19 expression was scored as negative or positive; the patterns of CK19 immunoreactivity was further classified as dot-like (DOT), perinuclear/cytoplasmatic (PN), diffusely cytoplasmatic (CYT), and membranous (ME). Pathological findings was compared with recurrence of disease and

death.

Results In benign and uncertain behavior tumor group (B-I) there were 48 CK19+ and 36 CK19- cases, with 1 recurrence of disease (ROD) in each group. In malignant PET (C-P) CK19 was expressed in 36 (85%); CK19 was negative in 6 malignant cases (15%); ROD and death were observed in 47% of CK19+ and in 66% of CK19- of malignant cases. CK19 positivity was more prevalent in malignant PET and this was statistically significant. CK19 expression in benign PETs, was not associated with a clinical aggressive course. The dot-like pattern of CK19 reactivity was observed only in benign and uncertain behavior tumors; none of these cases had ROD; the membranous pattern of CK19 immunoreactivity was observed mostly in malignant cases, as shown in the Table.

Table. Pattern of CK19 expression and histopathological classification.

	B	I	C	P
NEG	19 (39%)	11 (31%)	2 (6%)	2 (18%)
DOT	8 (17%)	6 (17%)	0 (0%)	0 (0%)
PN	5 (10%)	7 (20%)	7 (23%)	0 (0%)
CYT	9 (18%)	9 (26%)	14 (45%)	2 (18%)
ME	8 (16%)	2 (6%)	8 (26%)	7 (64%)
Total	49 (100%)	35 (100%)	31 (100%)	11 (100%)

Conclusions CK19 is not an absolute and reliable marker of biological behavior in PET. Different patterns of CK19 immunoreactivity could be of help in classifying PET.

Pancreas: Genes and Development

Amella C, Manca M, Sergi C

Institute of Pathology, Department of Pediatric Pathology, Medical University of Innsbruck.
Innsbruck, Austria

Background Pancreatic development is a complex process requiring a tight regulation by the expression of many genes some of which has been identified. Functional studies of the mutations occurring to these genes are allowing great advancement in the understanding of congenital pancreatic defects.

Aim For further enhancement in our understanding of the mechanisms behind normality and pathology in pancreas development it is necessary to critically organize actual knowledge and to depict future practicable research questions.

Methods A critical review of the current literature was performed.

Results Homeobox genes IPF-1 (13q12.1) are uniformly expressed in the early stages of pancreas development and when defective cause absence of the organ. In 1997 Stoffers *et al.* demonstrated a single nucleotide deletion in codon 63 causing, in homozygosity, pancreatic agenesis. PAX-4 (7q32) and PAX-6 (11q13) regulate pancreatic endocrine function differentiation

from endodermic elements. Sosa-Pineda *et al.* elegantly demonstrated in knockout mice the essential role of PAX-4 in the rising of beta cells and Sonder *et al.* presented biochemical and genetic assays' results demonstrating the key regulating role of PAX-6 on pancreatic insular hormones' genes transcription. Further Malecki *et al.* described heterozygotic mutations of NEUROD (2q32) associated with development of type II diabetes in their carriers, showing strong influences of development involved genes in adult diseases' natural history.

Conclusions During last years growing knowledge has stored up about genetic implications on pancreatic diseases. Nevertheless we are still far away from a concrete understanding of the refined mechanisms behind pancreatic functioning, missing a necessary background for the understanding of common and rare pathologies for the development of a unifying theory of pancreatic physiopathology and of rational prevention and therapeutic guidelines.

Characterization of Neuroendocrine Pancreatic Cancer with Multidetector Computed Tomography and Magnetic Resonance

Amore B¹, Calculli L¹, Tomassetti P⁴, Santini D³, Casadei R², Gavelli G¹

¹Department of Radiological Area 'Prof. G.Gavelli', ²Department of Surgery 'Prof F.Minni',

³Department of Pathology 'Prof. G.Martinelli', ⁴Department of Internal Medicine 'Prof. R.Corinaldesi', Sant'Orsola Hospital. Bologna, Italy

Background Neuroendocrine pancreatic cancer are neoplasms not so frequent and they are very difficult to diagnose and to differentiate from other solid pancreatic masses.

Aim To evaluate the multidetector computed tomography (MDCT) and magnetic resonance (MR) accuracy, using specific protocols, looking features of functioning and non-

functioning neuroendocrine tumors of pancreas.

Methods From 1990 till today, 72 consecutive patients affected by neuroendocrine pancreatic cancer were examined. The first patients analyzed were studied with angiography, the recent ones with MDCT and MR.

Results The study of the pancreas with

dedicate CT protocols and dynamic sequences is able to characterize neuroendocrine tumors and to differentiate them from other pancreatic cancer, based on the different contrast enhancement of the masses after infusion of iodate contrast agents. Neuroendocrine tumors are solid mass, well marginated, with expansive and not infiltrative growth and neoplastic vascular thromboses; sometimes they present signs of more aggressivity: necrotic or hemorrhagic degeneration and intralesional calcifications. The three-phasic study with MR after infusion of paramagnetic contrast agents can help to recognize pancreatic neuroendocrine tumor and sottoglissonian hepatic micrometastases

that are not visible with CT sequences.

Conclusions The gold standard for diagnosis of pancreatic neuroendocrine tumors is ¹¹¹In scintigraphy with octreotide. Neuroendocrine pancreatic metastases are well recognized by MDCT even if the micro and superficial foci in liver and the multiple foci in abdominopelvic region, suggesting for peritoneal carcinomatosis, were better showed by 18F-FDOPA PET. The above mentioned imaging techniques are useful for staging and sometimes for characterizing neuroendocrine tumors, even if clinical information is in any case very important. The pathologists, using immunohistochemistry are the only ones that can distinguish all the pancreatic masses.

Solid-Pseudopapillary Neoplasm of Pancreas: Casistic Review

Brighenti A¹, Capelli P¹, Canizzaro C¹, Zorzi MG¹, Martignoni G², Salvia R³, Zamboni G¹, Menestrina F¹

Pathology, ¹University of Verona and ²University of Sassari. ³Endocrinology Surgery, University of Verona. Verona and Sassari, Italy

Background Solid-pseudopapillary pancreatic neoplasm (SPT) are extremely rare, being 1-2% of all exocrine pancreatic tumours. The World Health Organisation classifies SPT as neoplasm of uncertain malignant potential or as malignant neoplasm. These latter are very rare and reported in literature only as case reports.

Methods In our study we considered 36 cases, 25 of these were from a single Surgery Department. In this Department 30% of neoplastic pancreatic resection were performed for cystic neoplasm. Between the cystic neoplasm 9% were SPT. In 30 cases we had complete clinical data, with an average follow up of 5.5 years.

Results Of the 36 cases, 33 were female, 3 were male. Mean age was 33 years (range 7-69 years). In 30 cases of known localisation of the tumour there was a preferential location for the body-tail region (body-tail: 21 specimens, head: 9 specimens). Macroscopically the tumours were solid in 42.5% of

cases, solido-cystic in 42.5% and cystic in 15%; mean diameter was 5.5 cm (range: 1.8-15 cm). One of 36 cases was malignant with synchronous liver metastasis and thrombosis of the splenic vein. Three cases had atypical characteristics, of uncertain meaning: two were characterised by local aggressiveness, one of these showed focal infiltration by direct extension into the splenic capsule and in a perivisceral lymph node; the other one had vascular invasion and features suggestive of vascular thrombosis. The third case presented strong atypia, even if focal. These latter 3 patients are still alive and disease free 5 months, 15 months, and 11 years after the surgical resection, respectively.

Conclusions This study proves that: 1) SPT are rare neoplasms, predominantly of young females; 2) these neoplasms are more frequent in the body-tail of the pancreas; 3) atypical features are rare and a longer follow-up is needed in order to understand their prognostic significance.

Vascular Thrombosis in Pancreas Transplantation: Multidetector CT in the Evaluation of Pancreatic Vessels and Parenchyma

Cappelli C, Mazzeo S, Pratali A, Belcari A, Caproni G, Giannini A, Bertini R, Vistoli F, Del Chiaro M, Boggi U, Bartolozzi C

Department of Radiology, University Hospital of Pisa. Pisa, Italy

Background Advances in immunosuppressive therapy, improvement in surgical techniques and post-operative imaging evaluation have allowed pancreas transplantation to become a successful elective procedure. However complications are still frequent, thus each patient needs a careful clinical and imaging follow-up.

Aim The purpose of our study was the multidetector CT evaluation of pancreatic vessels and parenchyma in patients submitted to pancreas transplantation, with arterial and/or venous thrombosis.

Methods Twenty-two patients submitted to pancreas transplantation were evaluated with multidetector CT, because of Doppler-US suspicion of vascular thrombosis. The multirow CT study was performed after the intravenous administration of contrast material, both in the pancreatic and the venous phases. To evaluate vascular structures, 3D reconstructions were performed. The pancreatic parenchyma was assessed by evaluating the morphology and the parenchymal enhancement.

Results We demonstrated 4 cases of arterial thrombosis, involving both the splenic and mesenteric branches, without venous thrombosis; in 3 chronic cases the transplanted pancreas resulted small and

inhomogeneous or completely atrophic and calcified; in one case of acute complete arterial thrombosis, the pancreatic parenchyma resulted normal. In three cases an arterial thrombosis of the mesenteric (n=2) or splenic (n=1) branch was found and the parenchyma resulted normal and a compensatory collateral circulation can be identified; such patients did not require treatments because of the absence of clinical alterations. When a partial venous thrombosis (portal vein: 1 case; splenic vein: 5 cases) was demonstrated, the pancreas resulted normal and the patients were successfully treated by means of systemic heparin. In complete venous thrombosis, isolated (n=3) or associated to arterial thrombosis (n=6), the parenchyma appeared enlarged and hypodense without enhancement, suggesting a parenchymal necrosis.

Conclusions Clinical surveillance of pancreatic allografts is difficult because of the lack of specificity of most clinical abnormalities; therefore imaging evaluation is often necessary. Multidetector CT, in association with clinical findings, can be useful in the therapeutic planning of patients submitted to pancreas transplantation complicated by vascular thrombosis.

EUS-FNA Accuracy in Patients with Biliary or Pancreatic Stents

Carrara S, Arcidiacono PG, Diellou AM, Mezzi G, Rossi M, Testoni PA

Endoscopic Ultrasonography Unit, Gastroenterology and Gastrointestinal Endoscopy Department, Vita-Salute University, San Raffaele Hospital, IRCCS. Milan, Italy

Background EUS-FNA has an elevated accuracy in diagnosis of pancreatic and biliary tumors. Some papers report that in cases of obstructive jaundice, when a stent has been previously placed in the common

bile duct (CBD) or in the pancreatic duct (PD), EUS-FNA accuracy and negative predictive value (NPV) decrease due to fibrosis and artifacts.

Aim In this retrospective single center study

we report our experience with EUS-FNA in patients with obstructive jaundice previously treated with biliary or pancreatic stent. The aim of this study is to assess the utility, adequacy and safety of EUS-FNA in these patients.

Methods Forty-nine patients with biliary or pancreatic stent underwent EUS between April 2001 and January 2005; 41 of them (25 males, 16 females; mean age 57 years) had also an EUS-FNA using a Pentax FG36UX echoendoscope and Wilson Cook 22 or 25 Gauge needles. A pathologist was present in the endoscopic room to assess the adequacy of the specimen. Data were entered into a spread-sheet (Excel, Microsoft Corporation) and reviewed.

Results Thirty-four patients had a plastic stent (2 migrated at the time of examination), 2 an external-internal drainage positioned by a radiologist, 5 a metallic stent. An average of

2.7 passes (range 1-7) was made into the lesion. No major complications were observed. The specimen was adequate in 33 patients (80%), scanty or suboptimal in 6 (14.6%), and non diagnostic in 2 (4.8%), one of which was suspicious. Four patients were lost at follow-up or still waiting for decision, but not operated yet. The EUS-FNA sensitivity, specificity, PPV, NPV were 83%, 100%, 100%, and 33%, respectively. The accuracy was 84%.

Conclusions ERCP with sphincterotomy and stent placement are known to cause edema, fibrosis and morphologic changes that interfere with endosonographic evaluation and FNA execution. Even though EUS-FNA should be performed before any other endoscopic approach for obstructive jaundice, it is safe and able to reach a final diagnosis in over 80% of ERCP-brush failures.

Celiac Disease: A Cause of Unexplained Elevated Serum Pancreatic Enzymes

Carroccio A¹, Di Prima A¹, Iacono G², Scalici C², Montalto G¹, Pirrone A¹, Morselli S¹, Soresi M¹

¹Internal Medicine, University Hospital of Palermo, ²Pediatric Gastroenterology, Di Cristina Hospital. Palermo, Italy

Background The frequency of elevated serum pancreatic enzymes in patients with celiac disease (CD) is unknown.

Aims To evaluate the serum levels of pancreatic enzymes in adult and pediatric CD patients.

Methods Serum pancreatic isoamylase and lipase were assayed in 90 adult and 112 pediatric consecutive CD patients at the diagnosis and after 12 months of gluten-free diet (GFD). Serum elastase and trypsin were assayed in a subgroup of adult CD patients. Pancreatic ultrasonography was performed at diagnosis and repeated in patients with elevated pancreatic enzymes after 6 and 12 months.

Results Twenty-six adult (29%) and 26 pediatric (23%) CD patients showed elevated values of serum pancreatic amylase and/or

lipase; trypsin was elevated in 69% and elastase in 19% of adult CD. Elevated serum pancreatic enzymes were observed with an almost identical frequency in patients with 'typical' and 'atypical' CD symptoms and in asymptomatic CD patients. Most of the elevated values were lower than two-folds the threshold limits. Elevated pancreatic enzymes were not associated with alcohol consumption, drug use, presence of abdominal pain or diabetes mellitus. Abdominal ultrasound scan showed no abnormal findings of the pancreatic region in any CD patients. After 12 months of GFD, pancreatic amylase was elevated in three cases and lipase in two cases: these patients had not strictly adhered to the GFD.

Conclusions We demonstrated about 20% frequency of elevated pancreatic enzymes

values in CD patients, including subjects without gastrointestinal manifestations and apparently asymptomatic subjects. The

finding of elevated serum amylase or lipase, in the absence of signs of pancreatic disease, would seem to advise assay for CD diagnosis.

Pancreatic Metastases from Renal Carcinoma

Croce C, Del Chiaro M, Dinelli E, Gremmo F, Signori S, Vistoli F, Sgambelluri AF, Mosca I, Balzano E, Funel N, Campani D, Boggi U, Mosca F

Università di Pisa, Divisione di Chirurgia Generale e Trapianti, Centro Regionale di Riferimento per la Cura delle Malattie del Pancreas. Pisa, Italy

Background Most pancreatic metastases (PM) are not suitable for surgery since they derive from high grade primary tumors, such as breast and lung carcinomas or melanoma, and are often associated to metastasis in other organs. On the contrary, PM from renal carcinoma (RC) are usually limited to the pancreas, occur many years after the treatment of the primary tumor, do not significantly benefit from currently available medical treatments and rarely recur after radical resection.

Aim To analyze a single-center experience with the surgical treatment of PM from RC.

Methods Out of a total of 744 pancreatic resections, performed between November 1987 and January 2005, 9 (1.2%) were done for PM from RC. There were 4 males and 5 females, ranging in age between 52 and 72 years (mean age: 61.8 years). PM were incidentally discovered in 4 patients and were clinically evident in the remaining 5. Mean interval of time between nephrectomy and diagnosis of PM was 12 years (range 3-21 years). There were 4 single PM (44.4%) and 5

multiple PM (55.6%), ranging in size from 8 to 2 cm (average diameter 4.1 cm). In 3 patients (33.3%) there were simultaneous metastases in the liver. One patient, a Jehowash's Witness, had already undergone a biliary by-pass to relieve obstructive jaundice.

Results Four patients underwent pancreaticoduodenectomy (44.4%), and 5 total pancreatectomy (55.6%). In three patients (33.3%) liver metastatectomies were performed at the time of pancreatectomy. There was no mortality, whereas post-operative complications occurred in 2 patients (22.2%). The median hospital stay was 13.3 days (range 11-18 days). After a mean follow-up period of 18.1 months, 4 patients were alive and disease free; 1 was alive with liver metastases and pancreatic remnant metastases. One- and 5-year survival rates are 88.9% and 44.4%, respectively.

Conclusions Pancreatic resection offers an opportunity of either cure or long-term palliation to patients diagnosed with PM from RC.

Solid Pseudopapillary Tumor of the Pancreas: Reports on 31 Consecutive Cases

Festa L, Salvia R, Sartori N, Denitto F, Boninsegna L, Barugola G, Pederzoli P

Department of Surgery and Gastroenterology, University of Verona. Verona, Italy

Background Solid pseudopapillary tumours of the pancreas (SPT), represent the most uncommon histotype (2-7%) of all exocrine neoplasms of the pancreas and prevail in young women.

Aim To consider the clinical presentation of SPT and evaluate treatment and biological behaviour in our own experience.

Methods The study population consist of 31 patients (27 females, 4 males; mean age of 34

years, range: 7-56 years) who underwent surgical resection at our Department from 1990 to 2004 with final histological diagnosis of SPT. All the aforementioned parameters, prospectively collected, were analysed.

Results The diagnosis was incidental in the majority of cases (17 patients; 54%). Whenever present, symptoms were abdominal discomfort in 10 cases (32%), jaundice in 2 (6.5%), weight loss in 6 (19%), vomiting in 5 (16%), and a palpable abdominal mass in 4 patients (15%). The neoplasm was localized in the pancreatic head in 11 (35%) patients and in the body-tail in 20. The main diameter ranged from 2 to 20 cm (mean 5.2 cm). At radiological make up the neoplasm was solid in 93.5% of the cases (29/31) and delimited by a capsule in 38.7% (12/31). An internal necrotic-hemorrhagic areas was present in 9 patients (29%). Calcifications were noticed in 2 patients and septa in one. None of the patients was metastatic at the time of diagnosis. All patients underwent surgery with radical intent. In 9 cases a pancreaticoduodenectomy was performed,

whilst 15 patients underwent a left-pancreatectomy (4 spleen preserving), 6 a middle pancreatectomy and one an enucleation. There was no mortality with an overall morbidity of 35%. At histological examination the presence of cellular atypia, vascular, neural and lymphatic infiltration, and the evidence of an expansive-infiltrating type were considered as parameters of possible malignancy. In this regard 7 patients (22.5%) showed at least one of these parameters. No patient underwent adjuvant treatment. At a median follow-up of 40 months (range 4-223 months), all the patients are alive without evidence of disease. Neither diabetes nor exocrine insufficiency was observed.

Conclusions SPT seems to be an indolent neoplasm with either benign or low grade aggressive biological behaviour. This attitude makes surgical treatment often possible despite the quite great size of the tumour at time of diagnosis. However the presence of aggressive histological parameters makes necessary long term follow up.

Pancreatic Cystic Tumor: Radiological Diagnosis with Multidetector Computed Tomography and MR

Fiscaletti M¹, Calculli L¹, Amore B¹, Casadei R², Gavelli G¹

¹Department of Radiology, Radiology Unit III 'Prof. G.Gavelli', ²Department of Surgery 'Prof. F. Minni', S.Orsola-Malpighi Hospital. Bologna, Italy

Background The diagnostic reliability of these CT parameters in study of pancreatic cystic tumors is still open to debate in literature because of the introduction of new clinical-anatomic-pathological entities.

Aim To evaluate multidetector computed tomography (MDCT) accuracy in diagnosis of pancreatic cystic tumor (PCT) considering the new anatomic-pathological findings.

Methods In a retrospective study we have examined the diagnostic accuracy of MDCT in a group of 60 PCT comparing radiological features with surgery and anatomic-pathologic findings.

Results In our study MDCT has demonstrated a good diagnostic accuracy (66.7%). A

correct diagnosis has been obtained in 31.3% of serious cystic tumors (SCT), in 62.5% of mucinous cystic neoplasms (MCN), and in 25% of solid-cystic papillary neoplasms. In the group of intraductal papillary-mucinous (IPMN) one case only was correctly diagnosed (1/7); the remaining cases were interpreted as mucinous tumors. Insular cell cystic tumor (ICCT) was diagnosed in 50% of cases. In a case of benign cystic lesion (hamartoma), MDCT was not able to obtain the correct diagnosis.

Conclusions MDCT is mainly used in pre-surgical diagnostic study of PCT. The common radiological parameters to identify PCT are the number (less than 6 or more than

6) and the dimensions of cysts (greater than 2 cm or less than 2 cm). Malignant transformation is recognised by irregularity of cystic wall and by presence of endolesional septa and parietal calcifications. Although MDCT is an valuable imaging technique in diagnosis of cystic lesions, in account of new

anatomic-pathological findings on PCT, the above-mentioned standard parameters (number and dimensions of cysts) have to be reconsidered. Thus, in order to obtain a correct differential diagnosis, CT findings have to be confirmed via MR cholangio-pancreatography and PET.

Differences in Clinical Manifestations in Patients with Chronic Pancreatitis and Mutations of *CFTR*, *SPINK1* e *PRSS1* Genes

Gaia E, Salacone P, Salmin P, Brusco A, Bacillo E, Arduino C

S.C. Gastroenterologia, Ospedale San Luigi Gonzaga. Orbassano (TO), Italy. S.C. Genetica Medica, Ospedale San Giovanni Battista. Turin, Italy. Università degli Studi di Torino, Dipartimento di Genetica, Biologia e Biochimica. Turin, Italy

Background The clinical pattern of the pancreatitis linked to mutations of *CFTR*, *SPINK1* e *PRSS1* genes is not well understood.

Aims We confronted the clinical characteristics of the disease in three groups of patients with chronic pancreatitis and mutations of *CFTR*, *SPINK1* *PRSS1* genes.

Methods Twenty-nine subjects affected by chronic pancreatitis, 7 carrying mutations of *SPINK1*, 13 of *CFTR* and 9 (all from the same family) of *PRSS1* gene were evaluated. The variables studied were: clinical onset, calcifications, diabetes, exocrine insufficiency, pancreatic surgery and family history of pancreatitis.

Results There were no significant differences in the age at onset between the three groups, but the clinical onset was earlier in the *PRSS1* mutated group (33 years vs. 38 years for *SPINK1* and 39 years for *CFTR*). The need for pancreatic surgery was higher in these patients (4% vs. 14% in the *SPINK1* group and 15% in the *CFTR* group), as the

frequency of calcifications. Diabetes was more frequent in subjects with *SPINK1* mutations (71% vs. 31% of *CFTR* and 11% of *PRSS1*). In the family carrying the *PRSS1* mutation, at least two subjects for each generation were affected, thus suggesting an autosomal dominant transmission. In the other groups the presence of an affected kindred was much lower (23% *CFTR* and 14% *SPINK1*), and the pattern of genetic transmission was not clear.

Conclusions chronic pancreatitis linked to *PRSS1* mutations show an earlier onset and a more sever illness, with a more frequent need for surgery. It is important to check for affected kindreds, normally found in more than one generation. On the contrary, the forms associated with mutations in the *CFTR* and *SPINK1* genes have a later onset, a more vague clinical course, and do not present an important familiarity. In the chronic pancreatitis linked to the mutations of the *SPINK1* gene, diabetes seems to be a frequent and early complication.

Microscopic Residual (R1) after Resection for Pancreatic Carcinoma Influences the Recurrence Type but not Prognosis: A Prospective Study on 88 Patients

Giardino A, Falconi M, Marcucci S, Muselli P, Barugola G, Valli L, Pederzoli P

Department of Surgery and Gastroenterology, University of Verona. Verona, Italy

Background and aim Given the absence of uniform data in literature, the aim is to

establish the clinical impact of microscopic residual (R1) on the margins after pancreatic resection for ductal carcinoma, on the progression of the disease; this on the basis of an accurate pathological study.

Patients and methods In 1977 we standardized a new protocol for the analysis of the specimens after pancreatic resection. From 1977 to 2002, 101 patients underwent resection for ductal carcinoma: 13 patients were excluded from the study (1 postoperative death, 12 R2). The remaining 88 patients were divided into two groups, according to the *status* of margins (R0 vs. R1) and subsequently assessed, according to site of the tumour, time to recurrence, survival, and antitumoral therapies.

Results The margins were found microscopically positive in 28 patients (31.8%). R0 and R1 are homogeneous in clinical characteristics, type of operation, and recourse to adjuvant therapies. The presence of angioinvasion was found to be the most

represented prognostic factor in R1 (R0 50% vs. R1 82%; P=0.005). The risk of local recurrence after 12 and 24 months is higher in R1 than in R0 (R1: 12 months 28%, 24 months 56%, vs. R0: 12 months 12.4%, 24 months: 19.3%; P=0.03), while the risk of liver metastasis and time of recurrence are equal. The median of survival in R0 and R1 is 42 months (95% CI: 14.8-69.1 months) and 21.5 months (95% CI: 20.6-22.4 months) (P=0.1), respectively. The multivariate analysis has shown nodal *status* to be the only independent prognostic factor both for recurrence, in any site, and survival.

Conclusions The presence of tumoral cells on the resection margins is associated with a significant risk of local recurrence. Nevertheless, the clinical impact is mitigated by the high number of hepatic recurrence and by the fact that the aggressiveness of the disease itself can be better interpreted considering the more classical pathological parameters of the specimen, like nodal *status*.

Evaluation of Pancreatic Neuroendocrine Tumors with Multidetector Computed Tomography (MDCT)

Gusmini S¹, Nicoletti R¹, Sgrazzutti C¹, Zerbi A², Di Carlo V², Del Maschio A¹

¹Department of Radiology and ²Department of Surgery, Vita-Salute University, San Raffaele Hospital. Milan, Italy

Background Pancreatic neuroendocrine tumours have long biological history; surgical approach increases the survival.

Aim To retrospectively evaluate MDCT in the detection, staging and assessment of surgical resectability of 7 pancreatic neuroendocrine lesions, subjected to surgery.

Methods We retrospectively evaluate 6 patients subjected to surgery for 7 pancreatic lesions (mean diameter: 31 mm), neuroendocrine at the histological examination: insulinomas (n=2), glucagonomas (n=3), few/barely differentiated neuroendocrine carcinomas (n=2). Typical symptoms of neuroendocrine carcinoma were in 4/6 patients. MDCT examination was performed with 16 slices technology (Aquilion 16, Toshiba), with triphasic technique (20, 40, 60

seconds, 120 kV, 250 mA, ScanTime: 0.5, TH: 1, HP/Couch Speed: 15, Ric.Index: 0.8), after administration of 750 mL of water, after injection of 2 mL/kg of iopamidol (Iopamiro 370, Bracco S.p.A., Milan, Italy), with 3.6-4.0 mL/sec flow. Axial acquisition and multiplanar reconstructions (MPRs: multiplanar reconstructions and CPRs: curved planar reconstructions) were analysed by two double-blinded radiologists that were veterans in pancreatic diseases.

Results Seven out of 7 lesions (100%) were correctly detected; 4 were hypervascular and 3 hypovascular. MPRs allow to identify a lesion (hypovascular insulinoma of uncinata process). Six out of 6 patients (100%) were correctly staged; hypervascular liver metastases (n=1) and hepatic hilar adenopathy

(n=1) were identified. MDCT, even with the support of MPRs and CPRs, correctly evaluated the surgical resectability in 6/6 patients. MDCT correctly demonstrated infiltration of venous (n=2) and arterious (n=1) spleen vessels and the presence of neoplastic thrombus in the portal vein (n=1), excluding involvement of other major peripancreatic vessels.

Conclusions In our limited experience, MDCT has shown to be a very accurate technique (100%) in the detection, staging and evaluation of surgical resectability. As used in the periampullary tumours, MDCT should get of common use in the diagnosis and preoperative analysis of pancreatic neuroendocrine tumours.

Mutations of the CFTR Gene in Idiopathic Pancreatic Hyperenzymemia

Manca M, Mantovani V, Migliori M, Pezzilli R, Gullo L

Institute of Internal Medicine, University of Bologna, S.Orsola Hospital. Bologna, Italy

Background Idiopathic pancreatic hyperenzymemia is a new syndrome that is characterized by a chronic increase of serum pancreatic enzymes in the absence of pancreatic disease. The etiology of this pancreatic hyperenzymemia is unknown, but the fact that it can occur in familial aggregates suggests the possibility that it is an expression of genetic alteration.

Aim To assess whether mutations of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene may have a role in the etiology of this hyperenzymemia.

Subjects and methods Seventy subjects with idiopathic pancreatic hyperenzymemia, 44 males and 26 females, mean age 48 years, range 8-74 years, in good health and without pancreatic or other digestive diseases, were studied in the period from February 2003 to June 2004. Of the 70 subjects studied, 13 had the familial form of pancreatic hyperenzymemia; they were members of six different families. The DNA was isolated from peripheral blood samples by using a spin column method. The mutation analysis of the *CFTR* gene was carried out using diagnostic commercial kits for the simultaneous

detection of 29 mutations and Tn polymorphism. The *CFTR* locus was examined for 30 mutations altogether that account for 69% of all such mutations in patients with cystic fibrosis in the Italian population. In subjects with *CFTR* gene mutations, sweat chloride analysis and nasal potential difference test were also carried out.

Results Among the 70 subjects studied, seven (10.0%) had *CFTR* gene mutations. These mutations were deltaF508 in one subject, 2789+5G>A in another subject, and T5 allele in the remaining five. All of these mutations were heterozygous, with the exception of one T5 allele that was homozygous in one subject. In all these seven subjects, the sweat chloride test and the nasal potential difference test were negative.

Conclusion The frequencies of the mutations of the *CFTR* gene found in the subjects studied are similar to the carrier frequencies in the general Italian population. We feel that idiopathic pancreatic hyperenzymemia is not a mild phenotypic expression of cystic fibrosis because, if it was, we would have seen a much higher frequency of *CFTR* gene mutations among our subjects.

High Frequency of Chronic Pancreatitis as Detected by Secretin Enhanced MRCP and EUS in Patients with

Non-Alcoholic Non-Biliary Acute Recurrent Pancreatitis

Mangiavillano B¹, Mariani A¹, Arcidiacono PG¹, Carrara S¹, Giussani A¹, Castellaneta G¹, Zanello A², Masci E¹, Testoni PA¹

¹Division of Gastroenterology and Gastrointestinal Endoscopy, ²Department of Radiology, University Vita-Salute San Raffaele, IRCCS San Raffaele Hospital. Milan, Italy

Background In the diagnostic investigation of patients with idiopathic acute recurrent pancreatitis (IARP), MRCP and EUS abnormalities are suggestive for the diagnosis of chronic pancreatitis (CP) in no more than 20% of cases. Secretin enhanced MRCP (s-MRCP) and EUS (s-EUS) are comparable with ERCP in the visualization of the pancreatic duct system limiting ERCP for therapy only.

Aim To prospectively compare s-MRCP and s-EUS in the detection of ductal and parenchymal abnormalities suggestive for the diagnosis of CP in patients with idiopathic acute recurrent pancreatitis.

Methods Consecutive patients with non-alcoholic non-biliary acute recurrent pancreatitis underwent, first, s-MRCP and s-EUS, then ERCP. The diagnosis of CP was established and graded according to the abnormal ERCP defined by the Cambridge classification. EUS features of CP were those described by Wiersema. As a measure of agreement between s-MRCP and s-EUS, the Kappa coefficient and the 95% CI were calculated.

Results A total of 40 patients, 19 male and 21 female, with a mean±SD age of 48.7±16.4 years (range 19-74 years) were studied. A poor agreement was observed from the

comparison of both main pancreatic duct (MPD) alterations ($\kappa=0.33$) and of side branches (IID) dilation ($\kappa=0.24$). Thirty percent of patients with non-alcoholic non-biliary RAP had three EUS ductal and parenchymal abnormalities and 12.5% from four to seven. In the evaluation of pancreatic ductal morphology, s-EUS had a higher sensitivity (100% vs. 75%) and specificity (94.4% vs. 88.8%) than s-MRCP in the detection of MPD alterations and a higher sensitivity (57.1% vs. 42.8%) but a lower specificity (78.8% vs. 93.9%) than s-MRCP as for side branches dilation. Agreement between s-EUS and ERCP was higher than that of s-MRCP both in early (57.1% vs. 42.8%) and moderate (100% vs. 75%) CP. In patients with normal ERCP, both s-MRCP and s-EUS identify ductal abnormalities suggestive for the diagnosis of early (n=2 for s-MRCP and n=7 for s-EUS) and moderate (n=3 for s-MRCP and n=2 for s-EUS) chronic pancreatitis.

Conclusions s-MRCP and s-EUS can diagnose CP in patients with idiopathic acute recurrent pancreatitis with a frequency higher than that reported in literature. Long-term follow-up studies are needed to confirm the accuracy of these two procedures for diagnosing CP in patients with normal ERCP.

Pancreaticopleural Fistula and Conservative Octreotide Treatment: Report of a Case

Mazza L¹, Panier Suffat L¹, Campra D¹, Farina EC¹, Emanuelli G², Montrucchio G², Fronda GR¹

¹7th General Surgery, ASO S. Giovanni Battista, Molinette. ²5th General Medicine, University of Turin. Turin, Italy

Context Pancreaticopleural fistula (PF) occurs in case of disruption of the pancreatic duct with leakage into the pleural cavity, due

to acute or chronic pancreatitis, abdominal trauma or surgery [1].

Case report A 32-year-old man was referred

for acute pancreatitis and recurrent pleural effusion after thoracentesis. Physical examination revealed bilateral pleural effusion, moderate dyspnoea and mild epigastric pain. Serum amylase and lipase were gradually decreasing. Chest X-ray and thoraco-abdominal CT confirmed bilateral, massive left-sided, pleural effusion, necrosis of the pancreatic tail with peripancreatic and retroperitoneal fluid collections. Pleural fluid amylase after thoracentesis was 16,500 IU/L. Octreotide was started at 100 µg s.c. tid. Clinical improvement and progressive reduction of the pleural effusion at chest X-ray were found. No further instrumental examinations (ERCP and MRCP) were performed. One week later, CT scan showed minimal pleural effusion and smaller abdominal collections. The patient was discharged with octreotide and one month later CT scan revealed no pleural effusion.

Discussion Clinical features of PF include massive, recurrent pleural effusion, cough, dyspnoea, chest pain with or without

abdominal pancreatitis-like symptoms. Diagnosis requires a high index of suspicion (history of pancreatitis, alcohol abuse, recurrent pleural effusion after drainage) and is usually made by thoracentesis (elevated pleural fluid amylase and lipase levels and high albumin content). ERCP may confirm the diagnosis and eventually play a therapeutic role with ES or pancreatic stent placement. CT and MRCP may complete the diagnosis. After medical failure (thoracentesis and/or tube thoracostomy with somatostatin analogue), therapeutic ERCP with pancreatic stenting is considered. Surgery remains the last-line of treatment.

Conclusion PF should be suspected in case of massive and/or recurrent pleural effusion in case of concomitant pancreatic inflammatory or post-traumatic diseases. First-line treatment should be conservative.

Reference

1. Dhebri AR, Ferran N. Nonsurgical management of pancreaticopleural fistula. JOP. J Pancreas (Online) 2005; 6:152-61. [PMID 15767731]

Vascular Involvement by Pancreatic Neoplasms: Correlation of CT Findings with Surgical and Pathologic Results

Mazzeo S, Cappelli C, Caproni G, Belcari A, Bertini R, Giannini A, Boggi U, Del Chiaro M, Gremmo F, Balzano E, Campani D, Funel N, Mosca F, Bartolozzi C
Department of Radiology, University Hospital of Pisa. Pisa, Italy

Background CT actually represents the elective diagnostic technique for the evaluation of pancreatic tumors, because it is able to detect and characterize lesions and also to stage them, thus defining the tumor resectability. For this reason it is fundamental to exclude the presence of some findings usually considered criteria of unresectability, and in particular the involvement of the vessels, even if recently some surgical institutions in selected patients have performed vascular resections.

Aim The purpose of our study was the multidetector CT evaluation of vascular infiltration by pancreatic neoplasms, by comparing CT findings with the intraoperative examination (surgical exploration

and intraoperative ultrasound) and the histopathological findings.

Methods We evaluated 37 patients with tumors of the pancreatic head, uncinate process or body, localized near to critical arterial and venous vessels (portal vein, superior mesenteric vein, celiac trunk, superior mesenteric artery) and submitted to pancreatic resection. The relation between neoplastic lesion and vessels were classified using the following grading: grade 0, no contact between lesion and vessel; grade I, focal contiguity without modification of the vessel caliber; grade II, lesion surrounding the vessel, without reduction of its lumen; grade III, cancer surrounding the vessel with reduction or obstruction of its lumen.

Results We evaluated 52 critical vessels with the following CT grades: grade 0 (4 cases); grade I (13 cases); grade II (17 cases); grade III (18 cases). Vascular resection was performed in 26/37 patients, with a total of 31 resected vessels. The intraoperative evaluation suggested the vascular infiltration in 3 vessels with grade 0, 5 with grade I, 15 with grade II, and 17 with grade III.

Histopathology excluded vascular infiltration in 4/4 cases with grade 0, and in 10/13 cases with grade I. Vascular infiltration was confirmed in 14/17 cases with grade II and 15/18 cases with grade III.

Conclusions Vascular infiltration is suspected when the neoplasm surrounds the vessel. The mere contiguity of tumor to vessel does not automatically signify vessel invasion.

State of Art in Diagnosis and Stadiation of Pancreatic Cancer with Multidetector Computed Tomography

Menetti F¹, Calculli L¹, Amore B¹, Casadei R², Gavelli G¹

¹Department of Radiology, Radiology Unit III 'Prof. G.Gavelli', ²Department of Surgery 'Prof. F. Minni'. S.Orsola-Malpighi Hospital. Bologna, Italy

Background New and dawned imaging techniques to study the pancreatic cancer are important because of the knowledge of new therapeutic strategies.

Aim Multidetector computed tomography (MDCT), associated with multiplanar reconstructions, is recognized as the gold standard in the study of this disease considering vascular infiltration, metastases and lymph nodes involvement (dimensions and location).

Methods A prospective study of 95 consecutive patients with pancreatic tumors underwent assessment with MDCT. We have evaluated tumor sizes (T), peripancreatic vascular infiltration (establishing a vascular grading), metastases (M) and size and location of lymph nodes associated with anatomico-pathological analysis.

Results In our study the MDCT reliability in pancreatic cancer stadiation was very high: sensitivity 98% and specificity 80%.

Conclusions Our findings suggest that metastases, vascular involvement and longitudinal extension of vascular infiltration are important parameters in order to exclude surgery. Until today it was evaluated only lymph node size (greater than cm 1.5=N+). In our study this parameter was not predictive of metastatic lymph node: 45.5% of lymph nodes less than 1 cm were N+ and 54.5% of lymph nodes greater than 1 cm were N-. MDCT is an important imaging technique for stadiation of pancreatic cancer and for demonstration of vascular infiltration but in order to recognize metastatic lymph nodes we hope to obtain better results using the new paramagnetic contrast agents.

Cystic-Solid Papillary Tumour: An Uncommon Neoplasm of the Pancreas

Navarra G¹, Bonomi S¹, Mitolo CI¹, Grassi A¹, Al Sahlani U¹, Ventrucci M², Virzì S¹

¹Department of Surgery and ²Department of Internal Medicine and Gastroenterology, Bentivoglio Hospital. Bologna, Italy

Background The cystic-solid papillary tumour of the pancreas is rare. It occurs predominantly in young women and generally

shows in most cases a benign behaviour. Since 1959, when the first case was described by Franz, until today, around 500 cases have

been documented in literature. Despite the large number of investigations, the pathogenesis of this tumour remains still unclear.

Case report We report a case of cystic-solid papillary tumour of the pancreas in a 16-year-old woman. The patient underwent abdominal CT that showed an apparently capsulated, solid, expansive mass originating in the retroperitoneal region. The tumour was identified by histopathology examination with immunohistochemical staining. The tumour was localized in the hooked process of the pancreas. It was adherent to the inferior cava vein, portal vein, common bile duct, duodenum and coeliac tripod, and it was capsulated. We performed a curative

resection. The patient was monitored during a follow-up period of thirty-six months without any evidence of disease recurrence and she is currently in good health.

Discussion The satisfactory outcome of this case supports the use of an aggressive surgical approach in all patients diagnosed with a cystic neoplasm of the pancreas. The tumour is rare and difficult to diagnose prior to surgery. The surgical approach is justified for the following reasons: 1) preoperative differentiation of a benign *versus* malignant tumour is very difficult; 2) potential adverse consequences on non resectional therapy are significant; 3) prognosis with curative resection is good.

Acute Pancreatitis: Prognostic Role of the Hemoconcentration

Neri V, Ambrosi A, Fersini A, Tartaglia N, Prete FP, Petito L, Valentino TP, Santacroce C

Division of General Surgery, Department of Surgical Sciences, University of Foggia, Polyclinic of Foggia. Foggia, Italy

Background Studies that associate the hemoconcentration with the development of necrotizing acute pancreatitis, are present in literature.

Aim To evaluate if the hemoconcentration is an early marker of necrotizing pancreatitis.

Methods The study was executed in patients admitted in the Division of General Surgery of Foggia University with diagnosis of acute pancreatitis in the period from January 1998 to June 2005. The prognostic Ranson's criteria were applied in all patients. Among the 60 patients admitted with diagnosis of acute pancreatitis (biliary pancreatitis in almost all patients), 24 were submitted to a CT-scan within 36-72 hours. Seven of the 24 patients had a necrotizing pancreatitis (Balthazar's score). The hematocrit (Hct) was retrospectively evaluated and associated with the CT-scan morphological data, as an early marker of pancreatitis severity.

Results The regression analysis showed an association between pancreatic necrosis, by means of CT evaluation, and the

hemoconcentration. Hematocrit more than 43% in the males and more than 39% in the females and/or a reduction of the Hct within the first 24 hours from the admission, were markers of severity and pancreatic necrosis (and organ failure). In 6 of the 7 patients with necrotizing pancreatitis there was critical value of Hct and only in 4 of the 17 patients with edematous pancreatitis there was a high value of Hct, showing the statistical significance of the proposed criteria ($P < 0.01$). The negative predictive value of the hemoconcentration was 94.7% for the evolution in pancreatic necrosis.

Conclusions The prognostic value of the hemoconcentration is comparable with the score of Ranson (48 hours of observation). So, it is an early and simple marker of the necrotizing evolution of the acute pancreatitis, because of its high negative predictive value: the patients with acute pancreatitis without hemoconcentration will rarely develop a necrotizing pancreatitis.

PanIN: Report of Two Cases with a Surgical Challenge

Nobili C¹, Franciosi C¹, Degrate L¹, Caprotti R¹, Romano F¹, Perego E¹, Leone BE², Uggeri Fa¹, Uggeri Fr¹

¹Department of Surgery and ²Department of Clinical Pathology, San Gerardo Hospital, University of Milan-Bicocca. Monza (MI), Italy

Case report We report two cases of PanIN not associated to invasive pancreatic ductal adenocarcinoma. A 77-year-old man presented with a 2-month history of several episodes of epigastric pain and dark urine. Trans-abdominal ultrasound revealed only a dilated common bile duct; laboratory data showed increased total bilirubin, gamma-GT and carbohydrate antigen-19.9. He has been affected of diabetes mellitus for 10 years. On admission, a CT evaluation revealed a choledochal stone and a mass within the pancreatic body-tail. A subsequent magnetic-resonance cholangiopancreatography found a dilatation of the common bile duct sustained by a lithiasic formation in the distal choledochus. Therefore, the patient underwent endoscopic retrograde cholangiopancreatography (CPRE) performing papillosphincterotomy and fragmentation of the stone. Endoscopic ultrasounds excluded peripancreatic vessels involvement by the mass, but showed another smaller choledochal stone. Patient underwent another CPRE and the day after a splenopancreatectomy was performed. Histopathologic analysis of surgical specimen revealed chronic pancreatitis with areas of

PanIN. The second was an 80-year-old man who complained a 6-weeks history of progressing jaundice, dark urine, colourless stools and weight loss. Abdominal CT showed a vegetation prominent into the duodenum around the papilla. The patient underwent CPRE to place a biliary stent. Subsequently a pylorus-preserving pancreaticoduodenectomy was performed. Histopathologic analysis of surgical specimen revealed high glandular intraepithelial carcinoma involving the duodenal peripapillary mucosa, the papilla and the ampulla; within the pancreatic head spread areas of PanIN.

Discussion PanIN is an asymptomatic lesion, usually incidentally discovered. Because of surgery is nowadays the only curative treatment for pancreatic cancer, in our opinion more efforts have to be made to recognize its preinvasive precursors, in order to increase the proportion of patient with resectable disease and to improve its dismal prognosis. Our cases support literature data. Characterization of early genetic changes in biosamples could allow an early diagnosis of this invasive cancer.

Role and Indications of Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) in Neuroendocrine Pancreatico-Duodenal Tumors

Pasquali C¹, Sperti C¹, Scappin S¹, Lunardi C¹, Chierichetti F², Liessi G³, Pedrazzoli S¹

¹Surgical Clinic IV, Medical and Surgical Science Department, University of Padua. Padua, Italy.

²Nuclear Medicine and ³Radiology, Castelfranco Veneto Hospital. Castelfranco Veneto (TV), Italy

Background Neuroendocrine pancreatico-duodenal tumors (NPDT) detection by imaging is a problem. Positron emission tomography (PET) provides biochemical and functional information on several tumors.

Few studies reported the ability of FDG-PET to differentiate benign from malignant NPDT.

Aim To evaluate the role of FDG-PET and to assess its indications in patients with NPDT.

Methods From 1994 to 2004, 70 patients 33

male and 37 female, (mean age 52.2 years, range 18-84 years) with NPDT (82.9% pancreatic) were investigated with FDG-PET. PET results were compared with CT-scan, MRI, and OctreoScan® scintigraphy and clinico-pathologic features of patients and survival.

Results Overall PET sensitivity was 55.7%; 79% of malignant tumors, and 17% of benign tumors were detected by FDG-PET. No duodenal tumor was detected by PET scan. Only 16% of primary less than 2 cm in size was localized. In 17.9% of cases PET scan provided new information able to change therapeutic management. In PET positive patients the additive information obtained by PET scan when compared with OctreoScan®, MRI, and CT scan were respectively 40.5% more, 21.7% more, and 25.6% more. In

malignant neuroendocrine tumors PET positivity was related to short survival. No patient with malignant tumor died for disease progression in the follow-up when PET was negative, while 13/30 PET positive patients died ($P < 0.03$).

Conclusions FDG-PET proved to be a second line technique in neuroendocrine pancreaticoduodenal tumors. PET results improve clinical staging of disease and is related to survival in malignant cases; in 17% of cases may change the therapeutic option. From our experience FDG-PET should be reserved for patients with suspected malignant tumor or pancreatic mass more than 2 cm or MEN I cases with at least one visible lesion. PET is not useful in duodenal tumors, benign insulinomas and small single pancreatic neuroendocrine lesion.

Double Pancreatic Lesion in Patient with Past Nephrectomy for Kidney Cancer: Case Report

Pasquali C¹, Morbin T¹, Scappin S¹, Vincenzi V², Parenti A³, Pedrazzoli S¹

¹Dipartimento di Scienze Mediche e Chirurgiche, Clinica Chirurgica IV, Univeristà di Padova.

²Medicina Generale, Ospedale Civile di Belluno. ³Anatomia Patologica, Università di Padova. Padua and Belluno, Italy

Case report Patient male, 65-year-old. Family history with IDDM. In the past story right nephrectomy for clear cells kidney cancer in May 2001 (stage T3 N0 M0). In the follow-up (June 2004) an abdominal ultrasound showed a peripancreatic cyst behind the head of the pancreas and a hypoechoic 16 mm lesion in the head of the pancreas. CT scan showed hypodense round 22 mm lesion behind the uncinate process and confirmed a solid hypervascular 16 mm lesion in the head of the pancreas. MRI showed a 20 mm cystic lesion in the uncinate process and within the head around nodule of 15 mm. 18 FDG-PET was negative. OctreoScan® scintigraphy showed uptake of the tracer in

head of the pancreas. Re-evaluation of CT scan of May 2001 showed the solid lesion already present (10-12 mm) at time of kidney surgery. No cystic lesions. Neuroendocrine markers and tumor markers were negative. Fecal elastase was normal. The patient underwent surgery in March 2005. Intraoperative ultrasound confirmed both the cystic and the solid lesion in the head of the pancreas. A pancreatic head resection with duodenal preservation was performed. Histology demonstrated solid metastasis of kidney cancer and intraductal papillary mucinous neoplasia (adenoma) of the uncinate process. At the follow-up the patient is alive and well, without disease.

Is there Any Role Left to Ultrasound-Secretin Test in the Magnetic Resonance Era?

Rigo L¹, Marangoni E¹, Manfredi R², Pozzi Mucelli R², Carbognin G², Bovo P³, Vantini I¹

Departments of ¹Internal Medicine, ²Radiology and ³Gastroenterology, 'GB Rossi' University Hospital. Verona, Italy

Background Ultrasound secretin test (US-S) was first proposed about 20 years ago as non-invasive test for pancreatic diseases studies, particularly for chronic pancreatitis, recurrent acute pancreatitis and Oddi's sphincter dysfunctions. The secretin-enhanced magnetic resonance cholangiopancreatography (S-MRCP) introduced in the 90s, proved to be an accurate technique for the non-invasive evaluation of the pancreatobiliary tract.

Aim To compare the results of US-S and S-MRCP in patients with symptoms suggestive of pancreatic disease and to evaluate the actual role of US-S test in the pancreatic morphologic and functional study.

Methods Between June 2002 and May 2005, 20 consecutive patients (7 men, 12 women, mean age 36.2 years, age range 11-64 years) with clinical findings suggestive of pancreatic disease underwent abdominal US (Esaote Megas 5-10 MH) and MR (single shot RARE 1.5 T technique) measurements of the main pancreatic duct before and after maximal stimulation with secretin intravenous bolus (Secrelux 1 U/kg). Final diagnoses were:

recurrent acute pancreatitis 10, history of acute pancreatitis 4, chronic pancreatitis 2, obstructive pancreatitis 2, autoimmune pancreatitis 1, non pancreatic abdominal pain 1.

Results Both US-S test and S-MRCP described morphologic aspects useful for the diagnosis of pancreatic disease, with an agreement in 13/20 patients. In the remaining cases, the US showed abnormalities not seen by MR in 6 cases while MR was abnormal and US normal in 1 case. The results of functional study are summarized in the following Table.

Conclusions Our results demonstrate a complete agreement between US-S and S-MRCP in 16/20 cases, partial agreement in 4/20, no cases of disagreement. The morphological study showed similar results in 13/20 patients, with US demonstrating alterations not seen by MR in 6 cases. Thus, the US-S test can be considered to be a valid alternative to MR in the study of pancreatic diseases, especially in patients with contraindications to MR or in the follow-up.

	S-MR normal	S-MR minor abnormalities	S-MR pathological
S-US normal	10/20 (50%)	0	0
S-US minor abnormalities	2/20 (10%)	2/20 (10%)	2/20 (10%)
S-US pathological	0	0	4/20 (20%)

Adjuvant Gemcitabine and Concurrent Radiotherapy in Operable Patients with Advanced Pancreatic Adenocarcinoma: A Phase II Study

Sainato A¹, Laliscia C¹, Pasqualetti F¹, Lencioni M², Boggi U³, Del Chiaro M³, Croce C³, Gremmo F³, Mosca F³, Cionini L¹

¹Department of Radiotherapy, ²Department of Oncology, and ³Department of Surgery, Pisa University. Pisa, Italy

Background Pancreatic carcinoma has a very poor prognosis: overall 5-year survival of about 5%. Gemcitabine (GEM) was proved clinically active and very effective

radiosensitizer in human pancreatic carcinoma cells. In phase I study we have determined at 300 mg/m² the maximum tolerated dose of weekly GEM with

concurrent radiotherapy (RT).

Aim To value the feasibility of adjuvant GEM and concurrent RT.

Methods Between February 1999 and May 2004, 53 patients with curative resection for locally advanced pancreatic cancer (T3-4, N0-1), were enrolled. Median age 59 years, males 52%. GEM 1,000 mg/m² days 1, 8, 15 every 21 days, for two courses, was given as an induction phase. The chemoradiotherapy phase consisted in weekly GEM at 300 mg/m², by 30-minutes intravenous infusion, administered at least 4 hours before RT. Fifteen MV photons were used with three-field technique to adequately cover the tumor bed and the lymphatic drainage. Patients received 40-50.4 Gy, 1.8 Gy/day, 5 days/week. The median time between surgery and induction phase was 58 days.

Results Forty-four out of 53 (83%) patients completed the planned induction phase and concurrent CT+RT course. The reasons for treatment interruption was: five (9.5%) early

disease progression (distant metastases), three (5.5%) G3 toxicity (in the induction phase), one voluntary interruption. Gastrointestinal symptoms (G1-2), neutropenia (G1-2) and cardiac toxicity (G2) observed in 58%, 37%, and 4% of patients, respectively. No G4 toxicity was observed. After a median follow-up of 21 months (range 6-62 months), 14/53 patients are still alive; the probability of survival at 12, 24, and 36 months was 75%, 49%, and 34%, respectively. Median survival was 22.5 months. The DFS at 12, 24, and 36 months was 64%, 34%, and 32%, respectively; median 16.3 months. Treatment failure: 27 (50.8%) distant relapse, 6 (11%) local and distant relapses, and only two local relapses (3.7%).

Conclusion After radical curative surgery for locally advanced pancreatic cancer, the combination GEM+RT was proved feasible with tolerable toxicity and satisfactory local control. Distant metastases remains the main problem for these patients.

Intraductal Papillary Mucinous Tumors (IPMTs) of the Pancreas: Contribution of 18-FDG PET to Surgical Decision Making

Sperti C¹, Pasquali C¹, Bissoli S², Fiore V², Liessi G³, Pedrazzoli S¹

¹Department of Medical and Surgical Sciences, Surgical Clinic IV, University of Padua. Padua, Italy. ²PET Center, Nuclear Medicine, and ³Department of Radiology, Castelfranco Veneto Hospital. Castelfranco Veneto (TV), Italy

Background Pancreatic IPMTs are increasingly being recognized, often in asymptomatic patients. Even with current imaging modalities, discrimination between benign and malignant tumor is still unreliable.

Aim This study was designed to evaluate the value of 18-fluorodeoxyglucose positron emission tomography (18-FDG PET) in identifying malignant lesions and the contribution of to surgical decision making of IPMTs.

Materials and methods From January 1998 to June 2004, 45 patients with suspected IPMTs were prospectively investigated with 18-FDG PET in addition to conventional imaging techniques (helical-CT and/or magnetic resonance cholangiopancreato-

graphy). 18-FDG PET was analyzed visually and semiquantitatively using the standard uptake value (SUV). Positivity was assumed when a focal uptake occurred with a SUV of at least 2.5. The validation of diagnosis was made by surgical operation (n=31), biopsy (n=3), or follow-up (n=11). Median follow-up time was 24 months (range 12-84 months).

Results There were 25 males and 20 females with a mean age of 64.3 years (range 37-80 years). Seventeen patients were asymptomatic. Thirty patients underwent pancreatic resection, 1 patient underwent palliative surgery, and 14 patients did not undergo surgery. An adenoma was diagnosed in 11 patients, a borderline tumor in 8, a carcinoma in situ in 4, and an invasive cancer

in 11 (in 11 patients the histology was undetermined). 18-FDG PET resulted negative in 11/11 adenomas and 7/8 borderline IPMTs, while resulted positive in 3/4 carcinomas in situ and in 11/11 invasive cancers. Positive 18-FDG PET findings influenced surgical decision making in 8 patients (18%): suggesting surgical resection in 6 patients (4 asymptomatic) without signs of malignancy on conventional imaging, allowing resection of unsuspected colon

cancer in 1 patient, and avoiding laparotomy in 1 patient with distant metastases. Furthermore negative 18-FDG PET findings allowed more limited resection in 6 patients and follow-up strategy in other 12 patients.

Conclusions 18-FDG PET is very accurate in distinguishing benign from malignant IPMTs, including non invasive carcinomas. 18-FDG PET is an alternative, non invasive, method useful to select the patients for surgical treatment or simple observation.

PET/CT Impact on Clinical Management of Patients with Pancreatic Lesions

Sperti C¹, Pasquali C¹, Bissoli S², Chierichetti F², Liessi G³, Pedrazzoli S¹

¹Department of Medical and Surgical Sciences, Surgical Clinic IV, University of Padua. Padua, Italy. ²Department of Nuclear Medicine and ³Department of Radiology, Castelfranco Veneto Hospital. Castelfranco Veneto (TV), Italy

Background Differential diagnosis of pancreatic masses remains difficult despite the introduction of several technologies. Positron emission tomography (PET) has an emerging role in the diagnosis and staging of different neoplasms, including pancreatic adenocarcinoma. However, an exact anatomic delineation of PET findings is often difficult. The integrated PET/CT scanner provides the advantage of image fusion in the same examination, improving the anatomic delineation of PET.

Aim To assess the impact of PET/CT on the management of patients with suspected pancreatic tumors.

Material and methods From January 2004 to January 2005, 103 patients underwent PET/CT examination for diagnosis and staging of suspected pancreatic neoplasm (n=77) or during the follow-up after resection for pancreatic cancer (n=26). All patients underwent also serum CA 19-9 assay and abdominal ultrasonography. PET/CT examinations were conducted according to standardized protocol following an injection of 350-450 MBq FDG. All PET/CT findings were confirmed by operation, biopsy or follow-up.

Results There were 46 males and 57 females

with a mean age of 60.5 years (range 37-80 years). In the group of patients with suspected pancreatic tumor, the lesions were located in the pancreatic head in 46, in the body in 16, and in the tail in 15 patients; in 25 cases there was a cystic lesion. In the final diagnosis, 41 patients had malignant tumors (40 adenocarcinomas and 1 lymphoma of the pancreas) and 36 a benign disease (12 serous cystadenomas, 8 chronic pancreatitis, 11 intraductal mucinous tumors, 3 endocrine tumors, undefined 2). Of the 42 PET positive pancreatic lesions, 41 were malignant (positive predictive value 97%) and none of the patients with PET negative lesions had cancer (negative predictive value of 100%). In 10 patients PET/CT showed distant metastases not seen by conventional examinations in 6 patients. Moreover PET/CT correctly identified as malignant 9 lesions with inconclusive findings on traditional imaging. Three patients required additional colic resection for simultaneous colon cancer not seen by conventional staging. Of the 26 patients studied in the follow-up after resection of primary tumor, recurrent disease occurred in 12 of whom 8 were only identified by PET/CT imaging (paraortic lymph nodes, liver, and local). In one

additional patient PET/CT correctly detected a second primary colon carcinoma. Finally, the management was changed in 21 patients (20%).

Conclusions The management of patients with suspected primary or recurrent

pancreatic cancer was changed in one fifth of patients, due to identification of malignancy, unknown metastases or associated disease. We suggest the use of PET/CT in the preoperative work-up or in the follow-up after resection of pancreatic adenocarcinoma.

Endoscopic Treatment of Chronic Pancreatitis in Pediatric Patients

Tringali A, Mutignani M, Familiari P, Spada C, Marchese M, Iacopini F, Pirozzi GA, Costamagna G

Digestive Endoscopy Unit, Catholic University. Rome, Italy

Background Chronic pancreatitis (CP) is a rare disease in the pediatric population, but can severely jeopardize the quality of life due to recurrent pain and relapsing attacks of acute pancreatitis leading to repeated hospitalizations. Endotherapy (ET) of severe CP with ductal obstruction has shown to be effective and safe in adults, however few data are available regarding children and adolescents.

Aim To review the immediate outcomes and the medium-term follow-up of ET in patients under the age of eighteen.

Patients and methods Between January 1991 and June 2003, 28 patients under the age of eighteen (12 males, mean age 12.6 years, range 2.5-18 years) underwent ERCP for CP at our institution. All patients had idiopathic CP. Purely diagnostic ERCP (n=7) was performed only before secretin enhanced magnetic resonance pancreatography (s-MRP) became available at our Hospital. More recently, therapeutic ERCP was performed only in case of abnormal s-MRP, showing obstruction of the main pancreatic duct (MPD). Overall, ET was attempted in 21 patients. Cholangiography was normal in all patients. According to pancreatographic changes and to Cremer classification, 8 patients had a Type I CP, 4 a Type III, 8 a

Type IV, and 1 a Type V. Stones and strictures of the MPD were detected in 7 and 4 patients, respectively. Medium-term results were considered 'excellent' when no further pain occurred, 'good' when pain decreased in frequency and intensity requiring only medical therapy or further ET, and 'poor' when patients eventually underwent surgery.

Results ET failed in two patients (9.5%) because of unsuccessful deep cannulation of the MPD. Pancreatic sphincterotomy was performed at the major papilla in 13 patients, at the minor in 5, and at both in one. Stones were always successfully removed, requiring preliminary ESWL in only one case. Stents were placed in 4 patients with MPD strictures. Complications occurred in 2 patients (10.5%): one mild pancreatitis, and one acute cholecystitis. There was no mortality. Follow-up was obtained in all patients. Mean follow-up was 59±42.5 months (SD). Results were 'excellent' in 11 patients (57.9%), 'good' in 7 (36.8%), and 'poor' in one (5.2%). Results were significantly better in patients without strictures (P<0.05).

Conclusions Endoscopic treatment of CP in children and adolescents is safe and effective, providing prolonged symptom relief and mostly avoiding surgery.

Persistent Elevation of Serum CA 19-9 without Evidence of Malignant Disease

Ventrucci M, Pozzato P, Cipolla A

Department of Internal Medicine and Gastroenterology, Bentivoglio Hospital. Bologna, Italy

Context Serum CA 19-9 is a marker widely used for digestive malignancies. However, in various benign diseases its elevation can also be observed; obstructive jaundice, liver disease, acute and chronic pancreatitis, diabetes mellitus, interstitial pulmonary disease and collagen vascular disease are such examples. We report a case of marked and persistent increase of serum CA-19-9 in a patient, currently in healthy conditions, who was admitted to our hospital because of severe diarrhoea.

Case report A 70-year-old woman was referred to our unit in 2002 for acute watery diarrhoea, lower left quadrant pain, vomit and fever. In her past medical history there was an episode of acute diarrhoea in 1960 and an endoscopic resection of a villous adenoma measuring 1.5 cm with low grade dysplasia in 1981. At admission, blood tests were normal except for C-reactive protein (17.5 mg/dL), haemoglobin (11.4 g/dL), albumin 2.2 g/dL, and CA 19-9 (514 U/mL). Abdominal ultrasonography, upper gastrointestinal series and endoscopy were negative. Abdominal CT-scan revealed normal liver and pancreas, but thickened wall of the right colon and a paracolic fluid collection. Colonoscopy showed lesions that were characterized by having a cobblestone surface, and exudative yellow plaques from the transverse colon to

cecum with hyperaemia and focal haemorrhage. Histology demonstrated the presence of chronic, non specific, inflammation of the lamina propria. Initial treatment with mesalazine and antibiotics was ineffective, while methylprednisolone, 60 mg i.v. dramatically ameliorated the symptoms within 2 weeks. The patient was discharged in apparently healthy conditions. Serum CA 19-9 was determined repeatedly: initially values fluctuated from 620 U/mL to normal values (in two sessions), but starting from 2003 levels were consistently elevated and a test performed in march 2005 showed markedly high values (1,331 U/mL). During follow up she underwent abdominal ultrasonographies, upper and lower GI endoscopies and CT scans which were always normal. A positron emission tomography performed in 2004 with 18F-FDG was also negative. At present, the patient is in an apparently healthy condition, her weight is stable, appetite is conserved and bowel movements are regular. Current blood tests are normal except for high triglyceride (264 mg/dL) and cholesterol (225 mg/dL) levels. Nitrites, leukocyte and bacteria are present in urine. Serum CA 19-9 value is 528 U/mL, while all the other tumour markers are normal. MRCP and endoscopic ultrasonography for the study of the pancreas will be performed in the near future.

The Surgical Treatment of Neuroendocrine Pancreatoduodenal Tumors in Multiple Endocrine Neoplasia Type 1

Zanini N, Casadei R, Tomassetti P, Calculli L, Pezzilli R, Migliori M, Campana D, Pagnogna S, Minni F

Dipartimento di Scienze Chirurgiche e Anestesiologiche, Chirurgia Generale 'Minni', Policlinico S.Orsola-Malpighi. Bologna, Italy

Background Multiple endocrine neoplasia type 1 (MEN 1) is an autosomal dominant inherited syndrome, with significant

variability in its clinical expression. It is classically characterized by tumors of the parathyroid glands, pancreatic islets and

anterior pituitary gland. About 35% to 75% of individuals with MEN-1 developed neuroendocrine neoplasms of the pancreas or duodenum. They are often malignant tumors and represent the most common MEN-1 related cause of death in MEN-1 kindreds.

Aim To evaluate our experience in the surgical treatment of neuroendocrine pancreaticoduodenal tumors in 12 cases of MEN-1 observed from 1985 to 2005.

Methods From 1985 to 2005, 12 cases of patients affected by MEN-1 syndrome, from 5 families, were observed in our Surgical Department: 11 (91.7%) were male, 1 (8.3%) female; in 12 out of 12 cases (100%) pancreaticoduodenal involvement was revealed at a mean age of 43 years (range 21-76 years). Tumors were multiple in 9 (75%) cases, single in 3 (25%) with a maximum size of 10 cm and minimum of few mm. In 8 (66.7%) cases the tumors were localized in the pancreatic parenchyma: 7 in body-tail, 1 in tail. In 4 (33.3%) cases pancreas and duodenum were involved: 2 duodenum plus pancreatic tail, 1 duodenum and pancreatic head and, finally, 1 duodenum and the pancreatic parenchyma diffusely. In 10 (83.3%) cases the histotype was single (6 non functioning, 3 gastrinomas, 1 insulinoma), in 2 (16.7%) multiple (non functioning plus

insulinomas plus gastrinomas and insulinomas plus gastrinomas). Nine (75%) patients underwent surgical treatment with 10 pancreatic resection: 8 subtotal pancreatectomies, 1 total pancreatectomy and 1 enucleoresection of the tumors.

Results Patients not surgically treated (n=3): 1 lost to follow-up; 2 alive with stable disease with medical therapy. Patients surgically treated (n=9): total recurrence 5 (55.5%) of which recurrence and no reoperation 4 cases, recurrence and operation 1 case. Eight patients are alive (median follow-up of 22 years and 6 months) of which 3 alive and disease free and 5 alive with disease (2 with pancreatic recurrence and hepatic metastases, 1 with duodenal gastrinomas and hepatic metastases, 1 with duodenal gastrinomas, and 1 with gastric carcinoids). One patient dead for the disease after 7 years and 4 months from the first operation.

Conclusion Pancreaticoduodenal tumors in patients affected by MEN-1 syndrome have to be treated as soon as possible to prevent hepatic metastases and the progression of the disease. The extension of the pancreatic resection have to be consider for the disease diffusion and the high frequency of the recurrences. We suggest large pancreatic resection until total pancreatectomy.