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KRAS and PT53 Mutations are Correlated with Lower Survival Rate in Resected Pancreatic Ductal Adenocarcinoma
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Context. Factor responsible for long-term survival of patients with pancreatic ductal adenocarcinoma (PDAC) underwent surgical procedure are poorly understood. Studies focusing on 5-year and 10-year survivors have shown that positive resection margins or tumor metastases to lymph nodes did not preclude long-term survival. Previous clinical study have shown that genes mutation can play a role in PDAC patients survival.

Objective. We have identified 15 patients out of 342 underwent surgery for PDAC who survived longer than 5 years after surgery (4.4%). Aim of the study was to clarify the clinical implication of the molecular status of KRAS, TP53, CDKN2A/p16 and SMAD4, and of other molecular markers, as IDH1 mutation gene, MSI and MGMT promoter methylation status in those long term survival.

Methods. Pathological specimen from 15 patients with PDAC that survived more than 50 months after surgery (“LS”) were analyzed for KRAS, TP53, IDH1, NRAS and BRAF mutational status using next generation sequencing. SMAD4 and CDKN2A/p16 expression was tested using immunohistochemistry. MGMT promoter methylation were also investigated. Molecular features of tumors from LS were compared with those of PDAC from a matched group of patients that died for PDAC related reason within 24 months from surgery (NLS).

Results. LS have a lower prevalence of KRAS and TP53 mutations and had more frequently SMAD4 retained expression, if compared with that of NLS (p=NS). Survival of patients with wild-type KRAS and wild type TP53 tumors was more than twice longer than that of patients bearing mutations in both KRAS and TP53 (90.2 vs. 41.1 months, p=0.032). Patients with tumors that were KRAS wild-type and that retained SMAD4 expression had a survival more than twice longer than cases with alterations in both genes (83.8 vs. 36.7 months).

Conclusions. Our data strongly support the fact that KRAS and TP53 mutations identify a subset of PDACs with worst outcome. The absence of KRAS, TP53 and SMAD4 genetic alterations may identify a subset of PDAC with better outcome, providing prognostic information for tailored treatment.

Screening/surveillance programs for pancreatic cancer in familial high-risk individuals: a proportion meta-analysis of screening results
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Background. Screening/surveillance programs (SSP) for pancreatic cancer (PC) in familial high-risk individuals (FPC-HRI) are becoming popular worldwide. They are the synthesis of the need to detect this fearsome cancer as soon as possible. We performed a meta-analysis of currently available data coming from screening/surveillance programs to evaluate the proportion of screening goals achievement (SGA), overall surgery and unnecessary surgery. Unnecessary surgery was provocatively considered as any final pathology not in line with SGA.

Methods. We searched MEDLINE, EMBASE and Cochrane library database from January 2000 to September 2016 to identify studies reporting results of SSP including cohorts of FPC-HRI. The main outcome measure was weighted proportion of SGA, overall surgery and unnecessary surgery among FPC-HRI cohort, using a random effects model. SGA was considered as any diagnosis of resectable PC, PanIN3 or high-grade dysplasia intraductal papillary mucinous neoplasm (HGD-IPMN).

Results. In a meta-analysis of 16 studies reporting on 1652 FPC-HRI, thirty subjects (1.92%), received a diagnosis of PC, PanIN3 or HGD-IPMNs. The pooled proportion of SGA was 1.1% (95% CI 0.6-1.7, I2=0%, p=0.0551). The pooled proportion of overall surgery was 5.7% (95% CI 3.7-7.7, I2=73.8%, p<0.001). The pooled proportion of unnecessary surgery was 64.5% (95% CI 38.3-90.6, I2=94.8%, p<0.001). A total of 104 surgical procedures (6.25%) was reported and among these distal pancreatectomy and total pancreatectomy were the most frequent (45% and 21% of cases, respectively). The overall number of diagnoses from specimens was 127 (7.6% of overall population of FPC-HRI, 1.2 lesion/subject).

Conclusions. The weighted proportion of SGA of SSP published so far is encouraging and justifies any attempt to pursue the goal of diagnosing early PC or pre-malignant lesions in asymptomatic FPC-HRI. The probability of receiving surgery during the SSP is not negligible and unnecessary surgery might be considered a possible price to pay.
Alcohol-related chronic exocrine pancreatic insufficiency: diagnosis and therapeutic management

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**Context.** To produce a guidelines for the treatment of patients with alcohol-related exocrine pancreatic insufficiency. Current estimates of the prevalence of chronic pancreatitis, one of the most common causes of exocrine pancreatic insufficiency, are in the range of 3–10 per 100 000 people in many parts of the world. Alcohol is a very important risk factor for exocrine pancreatic insufficiency and is involved in nearly half of all cases. The main hypothesis regarding the role of chronic alcohol consumption in pancreatitis is that there must be additional environmental or genetic risk factors involved for ongoing damage to occur.

**Aim.** Provide an overview of the pathogenesis of alcohol-related pancreatitis and to evaluate diagnostic issues and review current treatment options for this disease.

**Methods.** Current literature was reviewed using PubMed database.

**Results.** Treatment of patients with alcohol-related exocrine pancreatic insufficiency is complex, as the patient has two concomitant pathologies, alcohol-use disorder and exocrine pancreatic insufficiency/chronic pancreatitis. Alcohol abstinence is the starting point for treatment, although even this along with the most advanced therapies allow only a slowdown in progression rather than restoration of function. Treatment options for both exocrine pancreatic insufficiency and is involved in nearly half of all cases.

**Conclusions.** There is no doubt that PERT is indicated in patients with severe exocrine pancreatic insufficiency: this implies a significant improvement in the quality of life. Moreover, achieving alcohol abstinence is certainly the starting point for any further treatment. It is important to note that abstinence, and even the most advanced therapies, allow only a slowdown in progression rather than restoration of function.

Locally advanced pancreatic ductal adenocarcinoma: circulating microRNAs in extracellular vesicles as new dynamic biomarkers of response to FOLFIRINOX chemotherapy

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**Background.** FOLFIRINOX chemotherapy regimen is commonly used in neoadjuvant/palliative setting for locally advanced or metastatic pancreatic ductal adenocarcinoma (PDAC). Unfortunately, only one third of the patients display tumor downstaging, highlighting the necessity for seeking novel predictive markers for drug resistance/sensitivity. Within this context, a promising source of response-to-therapy biomarkers is constituted by circulating microRNAs (miRNAs). Therefore, the aim of our study was to identify differently expressed circulating miRNAs and to monitor their expression during FOLFIRINOX treatment in PDAC patients.

**Methods.** Fifty patients affected by locally advanced or metastatic PDAC were enrolled into our prospective, multicentre study. All patients received FOLFIRINOX chemotherapy as the first-line/neoadjuvant therapy. Circulating miRNAs were isolated from plasma and collected at several time points. The first “discovery cohort” consisted of eleven patients with short vs. long progression-free survival (PFS). Expression of circulating miRNAs were identified using a microarray panel. Emerging miRNAs were then validated in extracellular vesicles by RT-PCR in a second cohort of sixteen non-progressive patients (ie, those with partial response or stable disease).

**Results.** MiR-29a emerged as a potential predictive biomarker of response to FOLFIRINOX chemotherapy in the discovery cohort as well as in the validation group. In particular, it was significantly upregulated (2·36-fold change, p<0·0024) in extracellular vesicles after five cycles of FOLFIRINOX in non-progressive disease. Interestingly, the expression of miR-29a was significantly higher in extracellular vesicles than in circulating free miR-29a (p<0·0001).

**Conclusions.** Altered levels of circulating miR-29a in plasma and extracellular vesicles can anticipate radiologic progression of PDAC and guide more effective therapeutic strategies in particular in neoadjuvant setting.

Endoscopic ultrasound appearance of pancreatic serotonin-staining neuroendocrine neoplasms: a case series

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**Context.** The pancreatic localization of serotonin-staining neuroendocrine neoplasms (serotoninomas) is extremely rare. Overall, less than 350 cases have been reported in the world literature.
Objective. To describe a small series of 8 pancreatic serotoninomas in order to analyze the endoscopic ultrasound (EUS) appearance of this rare type of pancreatic neuroendocrine neoplasm (pNEN).

Methods. Between 2010 and 2016, all consecutive patients with histologically proven pancreatic serotoninoma who had undergone EUS were enrolled.

Results. 8 patients (6F, median age 68.5 yrs) had a diagnosis of pancreatic serotoninoma and underwent EUS examinations. Three had a G2 NEN, 5 had G1. Two patients had metastatic disease. Median diameter of the lesion was 10 mm. The nodal echotexture was hypoechoic in 7/8 cases. The most frequent localization was the pancreatic neck (4); in 3 cases, the tumor was located in the pancreatic head and in one in the body. In 7 cases the tumor caused a main pancreatic duct dilation; in 3 cases also the secondary ducts were dilated. In one case a dilation of the common bile duct was observed. At contrast-enhanced EUS (CE-EUS) no enhancement was observed. Elastography (2 patients) showed 2 rigid patterns of the lesion. One patient showed a full-blown carcinoid syndrome

Conclusions. From this case series a specific EUS appearance resulted for pancreatic serotoninoma, different from other types of pNEN. It appears difficult to differentiate it from both IPMN and pancreatic adenocarcinoma.

Effects of low-doses aspirin on clinical outcome and disease progression in patients with gastro-entero-pancreatic neuroendocrine tumors: results of a multicentric retrospective study

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Context. The chemopreventive effect of aspirin (ASA) has been observed in the setting of colorectal cancer. The impact of aspirin use on clinical outcome of patients with gastro-entero-pancreatic neuroendocrine neoplasms (GEP NEN) has not been evaluated yet.

Objective. To retrospectively evaluate the clinical outcome of GEP NEN patients treated with ASA

Methods. All the GEP NENs patients followed up in three European Centres, from January 2005 to September 2016, were retrospectively enrolled. The possible association between ASA and disease grading, staging, primary site, overall OS and PFS were evaluated.

Results. 253 patients were included (121 M, median age 64 yrs). The site of primary tumor was: stomach in 35, pancreas in 82 (pNEN), the small bowel in 83 (sbNEN), appendix in 27, colon in 19, unknown in 7. Grading was G1 in 154 patients, G2 in 64, G3 in 7; not available in 28. TNM staging was I in 99 patients, II in 16, III in 32 and IV in 86; not available in 10. No clear impact on OS or PFS was observed in patients taking ASA compared to those not taking it. Interestingly, in pNEN an inverse relation was observed between Ki67 and ASA intake (r=0.35, p=0.008). In sbNEN an inverse relation between lymphnodes involvement and ASA intake (r=-0.3, p=0.02) was observed. As expected, ASA intake was related with patients’ older age.

Conclusions. Even if ASA therapy seems not to have a direct clinical impact on OS or PFS in NENs, it is associated with lower Ki-67 values and less nodal involvement. Further studies are needed.

Can neutrophil-to-lymphocyte ratio (NLR) predict clinical outcomes of pancreatic neuroendocrine tumors (PanNETs)?

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Context. Pancreatic neuroendocrine tumors (PanNETs) are clinically ethergenous and may have metastatic potential. Histological grade is an accepted prognostic factor, even if noninvasive prognostic markers have not yet been identified.

Objective. This study assessed whether neutrophil-to-lymphocyte ratio (NLR) could predict clinical outcomes of PanNET patients.

Methods. 58 PanNET patients evaluated between 2010 and 2015 were retrospectively evaluated. The correlations between the preoperative NLR and clinicopathological parameters, including patient baseline clinical characteristics, overall survival (OS), progression-free survival (PFS), and postoperative oncological outcome were evaluated.

Results. NLR values were not significantly associated with overall survival (OS) and progression-free survival (PFS). At multivariate analyse only grading (i.e. G1, G2, G3) resulted as an independent predictors of OS (hazard ratio 6.01, p<0.01). Moreover grading showed a statistically significant correlation with diameter of the tumor (r=0.7130, p<0.001), TNM staging (r=0.599, p<0.001), whereas NLR did not. Finally NLR did not significantly change after surgery.

Conclusions. In this series of patient, NLR did not resulted an independent prognostic factor, differently from previously described.

Neoadjuvant therapy versus upfront resection for pancreatic cancer: the actual spectrum and clinical burden of postoperative complications

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Background. Neoadjuvant therapy (NAT) is increasingly used in case of borderline resectable or locally advanced pancreatic ductal adenocarcinoma (PDAC),...
showing promising results in terms of pathological outcomes. Little is known about its effect on surgical complications. We sought to determine whether NAT could affect the occurrence and the related clinical burden of post-pancreactomy morbidity.

**Methods.** We analysed 445 patients who consecutively underwent pancreatic resection for PDAC from 2014 to 2016 at the Department of Pancreatic Surgery – The Pancreas Institute, Verona University Hospital. The Modified Accordion Severity Grading System and resulting Average Complication Burden (ACB) were used to assess both the incidence and the related clinical burden of post-operative complications comparing patients treated with NAT and those who underwent upfront surgery (UFS).

**Results.** Of 305 pancreaticoduodenectomies (PD), those treated with NAT (n=99) had a lower incidence of pancreatic fistula (POPF, 9.1% vs. 15.6%, P=0.05), without cases of grade C. In case of grade B POPF, the ACB was higher (0.28 NAT vs. 0.24 UFS, P=0.05). Post-pancreactomy haemorrhage (PPH) rate was lower in the NAT group (9.1% vs. 14.6%, P=0.02), but the ACB was higher for grade B (0.37 NAT vs. 0.26 UFS, P=0.03) and C POPF (0.43 NAT vs. 0.29 UFS, P=0.05). Delayed gastric emptying (DGE) was higher in case of NAT (15.2% vs. 8.3%, P=0.04), with a higher ACB for grade C DGE (0.43 NAT vs. 0.29 UFS, P=0.03). Of 94 distal pancreatectomies (DP), NAT patients (n=26) developed more grade C POPF (11.5% vs. 1.5%, P=0.04) and DGE (11.5% vs. 2.9%, P=0.01), without differences in ACB. Of 46 total pancreatectomies (TP), those treated with NAT showed only an increased rate of pneumonia, but no difference in the ACB.

**Conclusions.** Patients undergoing PD for PDAC after NAT have a lower incidence of POPF and PPH, but a higher incidence of DGE if compared with patients treated with UFS. Among patients developing postoperative complications after PD, those receiving NAT are associated to an increased clinical burden.
are the two dominant phyla in the gut of tumor-bearing control mice. Proteobacteria (E. coli and A. hydrophila) and Verrucomicrobia (A. muciniphila) were the most represented phyla in the gut of drug-receiving mice.

Conclusions. Together with P. difficile (belonging to the Clostridium cluster XI), overgrowth of Enterobacteriaceae, to which E. coli belongs, is a frequent consequence of chemotherapies (Stringer AM 2009, Lin XB 2012). (Eckburg PB 2005). An overgrowth of Proteobacteria is known to be related to intestinal inflammation (Arthur J 2012 Science; Shin NR 2015), and a concomitant decrease in Firmicutes is associated with intestinal bowel diseases (IBD). In the light of all these observations, it appears clear that gemcitabine induces significant modifications in the intestinal microbiota composition, many of which may be detrimental for its own efficacy. Understanding chemotherapy side effects may explain the lack of activity or the chemoresistant processes helping to set up strategies to improve the effectiveness of therapy.

Results of an open-label phase II study of regorafenib (REOUND) in patients with refractory metastatic pancreatic cancer
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Context. Regorafenib is an oral multikinase inhibitor approved for treatment of colorectal cancer and GIST, but clinical activity was observed also in other cancers. Objectives: The primary endpoint was to evaluate efficacy of Regorafenib in refractory metastatic pancreatic cancer (mPC) in terms of progression-free rate (PFR) at 2 months (mos) (at least 8/19 patients (pts), 42%). Secondary endpoints included overall survival (OS), progression-free survival (PFS) and safety. Methods. This single arm, single-stage, phase II trial included patients with various types of metastatic cancers refractory to standard treatments. Here we present the results of the pancreatic cohort. Main inclusion criteria were: ≥1 measurable lesion per RECIST 1.1, ECOG PS<2,
adequate haematology, liver and kidney functions. Arterial/venous thrombosis within 6 mos before enrolment was an exclusion criterion. Pts received regorafenib 160 mg orally once a day, 3 weeks on/1 week off until disease progression or unacceptable toxicity. Response was assessed by CT scan every 8 weeks. Safety was assessed every 14 days for the first 8 weeks, then every 28 days.

Results. From January 2015 to January 2016, 20 pts were enrolled. 80% of them had received ≥2 lines of chemotherapy (range 1-3). 2-mos PFR was 25% (5/20 pts, all stable disease, SD). At a median follow-up of 5.3 mos, median PFS and OS were 1.6 mos (range 0.7-5.9) and 3.0 mos (range 1.1-6.1). Reasons for treatment discontinuation were disease progression (55%), adverse events (AEs) or clinical deterioration (45%). 35% of pts required dose reductions and 65% dose delays due to AEs. Main grade 3-4AEs were hand-foot skin reaction (20%) and hepatic toxicity (10%). Other common AEs were anorexia (60%), fatigue, anemia, diarrhea and fever (40%), hypophosphatemia and hypertension (30%).

Conclusions. Although the primary endpoint was not achieved, SD was observed in 25% of pts. Regorafenib failed to demonstrate activity in this cohort of pts. Clinical trial information: NCT01892527

Chemosensitivity in pancreatic cancer: a mechanobiology approach
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Context. A hallmark of pancreatic ductal adenocarcinoma (PDAC) is the remarkable stromal stiffness. This suggests that PDAC initiation and progression should be highly influenced by mechanical factors. However, the altered mechanobiology of PDAC might also play a key role in chemoresistance, through reduced drug permeability of tissue as well as indirect interference with oncogenic pathways.

Objective. This study aims to unravel the role of biomechanical aspects of tissue stiffening and force sensing in the chemoresistance to gemcitabine.

Methods. I tested the differential mechanical response of Panc-1 and Panc-1 resistant to (clinically relevant doses of) gemcitabine cell lines to matrix stiffness in 2D environments. I quantified cellular force generation by growing cells on soft (28 kPa) and stiff (140 kPa) elastic micropillar arrays coated with extracellular matrix components (i.e. fluorescently-labeled fibronectin and collagen). I simultaneously monitored cell spreading area, actin organization and Yes-associated protein (YAP) nuclear level by post-fixation immunostaining and confocal imaging.

Results. Panc-1 cells showed a significantly larger area of adhesion with respect to Panc-1 resistant, while the resistant phenotype was capable of exerting significantly higher forces in soft and stiff micropillars. In addition, the resistant phenotype showed significantly longer actin stress fibers and increased YAP nuclear translocation, suggesting higher contractility of cells resistant to gemcitabine. The mechanorecirocity was mostly altered when cells were adhering on collagen 2D substrates. Collagen type I is the common ligand for α2β1 integrins that are known to promote the malignant phenotype of pancreatic cancer and, more importantly, are significantly more expressed in Panc-1 resistant than in Panc-1 cells.

Conclusions. The differential mechanical response of chemoresistant PDAC cell lines suggests that a mechanobiology approach might lead to uncover an urgently needed novel strategy in PDAC treatment.

Multidisciplinary approach to familial pancreatic cancer. Two years experience
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Context. Familial pancreatic cancer (FPC) accounts for 4-10% of all pancreatic cancers (PC), and only 10% are associated with recognizable genetic mutations.

Objective. To better identify patients with FPC.

Methods. An interdisciplinary team was built up to keep a low suspicion threshold on patients with dreaded familiarity for PC. Patients were referred to a single-session, translational visit in gastroenterology and genetics, where clinical, anamnestic and pathological data were retrieved. Patients were stratified according to ESMO and ACG clinical guidelines. When indicated, patients were enrolled to undergo genetic analysis to assess the diagnosis of FPC by means of Next Generation Sequencing (NGS).

Results. 99 subjects were evaluated for suspected FPC. Of them, 51 (51.5%) met documented FPC clinical criteria. Twenty-five subjects (49.0%) had ≥2 relatives affected, of whom ≥1 was a first-degree (FDR). Ten of them (40%) were patients since they had a personal diagnosis of PC. Eight cases (15.7%) had ≥3 relatives affected (3 of them being patients). Fifteen (29.4%) had Lynch Syndrome (LS) (none personally affected by PC), 2 (3.9%) had hereditary pancreatitis (none affected by PC), 2 (3.9%) hereditary breast and ovarian cancer syndrome (none affected by PC).

Twenty-four (47.1%) of the clinical diagnoses were confirmed at the genetic level: 19 (37.3%) LS, 2 (3.9%) PRSS1, 2 (3.9%) BRCA2, 1 (2.0%) PALB2. Twenty-seven (52.9%) were negative at NGS analysis. Nine subjects showed 1 Variant of Unknown Significance (VUS), and four additional individuals harbored 2 VUS each (14 total subjects, 25.5%, for 17 total VUS).

Conclusions. The interdisciplinary model improves the identification of subjects with genetic PC susceptibility, properly selecting patients to be tested (47.1% vs. 10% positive results).
A splenic lesion mimicking a secondary lesion from a pancreatic body cancer
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Context. Splenic lesions synchronous to a pancreatic tail neoplasia are usually considered secondary lesions. We present a case of a pancreatic body mass with a splenic lesion in a 68-year-old woman.

Case report. In October 2016 a 68-year-old woman presented with abdominal swelling and weight loss (~8 kg b.w. over the previous 5 months), but no pain or other symptoms. Blood glucose was 114 mg/dl, HbA1c was 44 mmol/mol and Ca 19-9 was 102 U/ml. Abdominal US showed a 1.7 cm mass in the pancreatic body and a single 3.2 cm hypoecholic lesion in the spleen, both confirmed by a CT scan as hypodense lesions. 18FDG PET/CT showed uptake of the tracer in the body of the pancreas (SUV max = 6.0) and a similar gradient in an area of 2.5 cm at the lower pole of the spleen. In November, a new CT scan showed an increase in size of the body lesion up to 28x20 mm and distally a main pancreatic duct dilation (7 mm). Ca 19-9 was increased up to 290 U/ml. Despite the appearance of two synchronous neoplastic lesions, the suspect was of two different primaries. The patient underwent in November 2016 a left pancreatectomy and splenectomy. The postoperative course was uncomplicated and the patient was discharged on 8th p.o. day. Ca 19-9 returned to normal range within 20 days after surgery. Histology showed a poorly differentiated ductal adenocarcinoma of the body of the pancreas (5x1.2 cm), with metastasis in two peripancreatic lymph nodes (T3N1G3). In the spleen the nodular area of 2.8 cm with central necrosis was an inflammatory pseudotumor-like follicular dendritic cell tumor; immunohistochemistry was positive for CD35 and focally clusterin, and EBER positive (Epstein Barr Virus). A CT scan performed 2 months after surgery showed a pseudocyst (115x72 mm) which compressed the gastric antrum and the portal-mesenteric veins, still patent. A percutaneous drainage was performed to avoid portal vein thrombosis. The drain was removed after 15 days. No chemotherapy was administered. The patient is alive and well without recurrence 6 months after surgery.

Conclusions. In case of a pancreatic cancer and a single site extrapancreatic neoplastic lesion, a second primary tumor should be considered.

Clinical presentation, treatment and prognosis of neuroendocrine tumors of the ampulla of vater
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Background. NeuroEndocrine Tumors (NETs) of the ampulla of Vater are rare.

Methods. We reviewed our experience in ampullary NETs from January 2007 to December 2015 to identify clinical presentation, treatment and prognosis of these NETs. Follow-up (FU) to June 2017.

Results. Among 169 pancreatico-duodenal NETs observed in our Unit in the last 9 years, four were NETs of the ampullary region (2.4%). There were one man and 3 women, averaging 58.2 (range 51-64) years. None of the patients showed positivity of endocrine markers and hormones at preoperative blood examinations. Median tumor size was 1.5 cm (range 0.1-2.5), and only one patient had a lymph node metastasis. They underwent surgery: 2 pancreatico-duodenectomy (one performed in pancreatic cancer, with incidental finding of a non-functioning microNET), one ampullectomy and one enucleation. Two patients had a previous cholecystectomy, to an alteration of PKA signaling pathway. We report the first case of Carney complex with clinical features of chronic calcifying pancreatitis.

Case report. A 20 years old woman with a well-known history of Carney complex had an abdominal ultrasound in the follow-up of her disease with the finding of multiple hepatic adenomas and a 25 mm cystic pancreatic lesion and pancreatic head stones. A CT scan confirmed the pancreatic cystic lesion and stones and the hepatic lesions. She had been diagnosed with a giant cell hepatitis when she was a newborn; in the following years the patient underwent left adrenalectomy for a Cushing syndrome, surgical excision of a pituitary GH-producing adenoma and total thyroidectomy for multinodular goiter. Six years after the first abdominal US in another Center the patient underwent a liver resection of segments 5, 6 and 7 and in the same operation the pancreatic cyst was excised. A main pancreatic duct damage occurred. A percutaneous drainage was performed to relieve symptoms then Ethibloc injection was injected to seal the main pancreatic duct injury, and octreotide was used to reduce the pancreatic fistula flow; finally resulting in a 35 mm pseudocyst in the neck region. Eighteen months later the MRI showed a pancreatic duct dilation distal to the cyst and in our Unit the patient underwent a cyst-jejunostomy. Four years later a CT scan showed multiple pancreatic stones both in the head and in the body-tail of the pancreas and started a somatostatin analogue therapy to control GH hypersecretion. The patient did not develop a pancreatic insufficiency but as a result of octreotide administration had gallbladder stones and in 2015 underwent cholecystectomy. The patient is alive and well 14 years after the cyst-jejunostomy drainage operation.

Conclusions. In our knowledge this is the first report of chronic calcifying pancreatitis in a Carney complex.

Chronic pancreatitis in Carney Complex. A case report
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Context. Carney complex is a familial syndrome that includes myxomas of the heart, skin and breast; peripheral nerve schwannomas; spotty skin pigmentation; testicular, adrenal and GH-secreting pituitary tumors. This syndrome is due to gene PRKARIA mutations that lead

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and were discovered to be somatostatinomas at immuno-

staining; the others were non-functioning (NF) NETs. Two patients had a well-differentiated NET infiltrating surrounding structures or with lymph node metastasis (3/4 were G1), but none had a disease recurrence. All but one patient (who died for pancreatic cancer) are alive after a median FU of 102.5 months (range 23-122).

Conclusions. In our series, ampullary NETs seemed to be associated with a good prognosis, even if they were malignant NETs and an enucleation/ampullctomy could be performed.

Distal pancreatectomy for neuroendocrine tu-
mors. 35-year of experience in a single center
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Context. Pancreatic NeuroEndocrine Tumors (p-NETs) represent 2% of all pancreatic neoplasms. Distal pancre-
atectomy (DP) is the standard resective procedure for left-sided p-NETs, most of them non-functioning (NF), and often diagnosed when advanced.

Objective. We reviewed our experience in DP for body-
tail p-NETs in the last 35 years, to evaluate early and late results.

Method. From 1981 to 2015, 82 out of 307 p-NET pa-

tients observed underwent DP. They were enrolled in the study and evaluated in terms of type of operation, histology, early and long-term outcome and survival. SPSS software was used for statistical analysis.

Results. There were 48 M/34 F averaging 56 years, and 48 were NF p-NETs (58.5%), 34 functioning NETs (25/34 insulinomas). According to ENETS-TNM classification: 48% stage 1, 20% stage 4. Patients (62/82) were strati-
ted according to the grading: 53% were G1, only 3%

minute POPF developed in 20.7% of cases, all treated by inter-

ventional radiology. No relationship was found between risk of POPF and management of the pancreatic stump, or extension of pancreatic resection or splenectomy. Post-operative diabetes occurred in 19.5% of cases, and 21.9% of patients developed exocrine insufficiency, without any correlations with the extension of resec-
tion. Mean follow-up was 116 (range 1-312) months. Disease recurrence (including MEN-1) occurred in 8 (12.1%) patients with disease free survival of 14.6 mo. At diagnosis, 17 (20.7%) patients had liver metastases; after a R2 surgery they had a mean overall survival (OS) of 77.6 mo. After 5 years, 80% of metastatic patients were still alive. No difference in OS was found between G1 and G2 NETs, or NF and functioning NETs. Staging (p<0.02), and R0 vs R2 surgery (p<0.001) were factors related to OS.

Conclusions. DP for left sided p-NETs is a surgical procedure indicated even in liver disease, irrespective of functional status and R status. DP provides a long-
term OS and preserves a normal pancreatic function, but still has a relevant short-term complication rate such as POPF.

Major complications affect long-term survival in resected pancreatic cancer patients
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Context. Postoperative major morbidity has been asso-
ciated with worse survival in most gastrointestinal tumors. This association remains controversial in pan-
creatic cancer.

Objective. To analyze whether long-term survival in pancreatic cancer (PC) is affected by the occurrence of major surgical complications.

Methods. Records of all PC patients resected from 2007 to 2015 were included. Major morbidity was defined as any 30-day complication with grade 3-severity or higher (Clavien-Dindo Classification).

Results. Of 616 patients, 81.7% underwent pancreato-

duodenectomy (PD) and 18.3% distal pancreatectomy (DP). Major complications occurred in 18.5%; 19.1% after PD and 15.9% after DP (p=50). By univariate analysis, besides the conventional prog-
nostic determinants related to pathology and receipt of adjuvant treatment, major complications worsened long-term survival in proximal resections (median OS 26 months vs. 15, p=0.008). A difference was also seen at after distal pancreatectomy, but it did not reach sta-
tistical significance, likely related to small sample size (median OS 33 months vs. 18, p=189). In the multivari-
te model for pancreatoduodenectomy, major postop-
erative complications remained independently associ-
ated with worse survival [HR 1.38, 95%CI (1.01-1.87),
p=041], together with nodal involvement [HR 1.82,
95%CI (1.35-2.47), p<0.001], positive margins [HR 1.39,
95%CI (1.08-1.80), p=0.012], tumor size >3 cm [HR 1.43,
95%CI (1.11-1.85), p=0.006] and lack of adjuvant treat-
ment [HR 1.85, 95%CI (1.42-2.42), p<0.001].

Conclusions. In pancreatic cancer, major surgical com-

plications after pancreatic resection are associated with worse long-term survival. This effect is independent of the receipt of adjuvant treatment.

Changes in body composition during neo-

adjuvant treatment for pancreatic cancer
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SMAD4 related transfer through exosomes of glycolytic enzymes and miR-1260a underlies the reverse warburg effect in PDAC

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Context. SMAD4 related transfer through exosomes of glycolytic enzymes and miR-1260a underlies the reverse warburg effect in PDAC.

Objective. To verify whether SMAD4+ loss and related exosomes are involved in Warburg and reverse Warburg effects in PDAC, together with potential pathogenetic proteins and/or microRNAs.

Methods. BxPC3 (SMAD4+ HD) and BxPC3-SMAD4+ (BxPC3 stably transfected with SMAD4+) exo-enriched conditioned media (CM) were obtained following ultracentrifugation (4 days in 1% FCS). miRNAs expression and protein profiling of BxPC3 and BxPC3-SMAD4+ CM exosomes were performed (miRNA microarrays and SILAC). Human hsa-miR-1260a was transfected and silenced (miRIDIAN mimic and Hairpin inhibitor) in BxPC3-SMAD4+ cells. Glucose and lactate were measured in supernatants of pancreatic cancer cells and of PBMCs cultured in exo-enriched CM and non conditioned media (4 days).

Results. Analysis of SMAD4-associated exo-proteins identified glycolysis among the main de-regulated biological processes. One of the most SMAD4-associated de-regulated exo miRNAs was hsa-miR-1260a. BxPC3 cells had higher glucose consumption (p<0.01) and lactate production (p=0.01) than BxPC3-SMAD4+. PBMCs cultured in exo-enriched BxPC3 CM with respect to exo-enriched BxPC3-SMAD4+, had a higher glucose consumption and lactate production (p<0.05). hsa-mir-1260a mimics transfection of BxPC3-SMAD4+ lowered glucose consumption and lactate production with respect to hsa-mir-1260a inhibitor and non transfected cells. Exosomes from BxPC3-SMAD4+ transfected with hsa-mir-1260a mimic lowered lactate production of PBMCs with respect to hsa-mir-1260a inhibitor (p<0.05).

Conclusions. SMAD4 can stand among cancer-associated genetic alterations, which regulate the Warburg effect. SMAD4-related enrichment of glycolytic enzymes and of hsa-mir-1260a in cancer derived exosomes might underlie the reverse Warburg effect.

NR2F2 isoforms switch regulates epithelial to mesenchymal transition in pancreatic cancer

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Context. NR2F2 is an orphan nuclear receptor transcription factor associated to low overall survival, enhanced cell invasion and alteration of stemness in Pancreatic Ductal Adenocarcinoma (PDAC). NR2F2 exhibits two isoforms, known as V1 and V2, with V2 lacking the DNA binding domain and whose function is currently substantially unknown. Whereas V2 is localized in the nucleus and the cytoplasm, V1 expression is limited to the nucleus. There is sounding scientific evidence that this receptor might regulate the epithelial to mesenchymal transition (EMT) a process linked to chemoresistance and metastatization in PDAC.

Objective. Our aims are: (1) the characterization of NR2F2 isoforms contribution to EMT and tumor progression; (2) the role of V2 cell localization in the regulation of EMT in PDAC.

Methods. NR2F2 expression, localization and regulation of EMT were evaluated by WB, IHC, IF, and time-lapse microscopy in in vitro experiments. Resistance to chemotherapy was studied treating PDAC cells with gemcitabine. The study of tumor growth in vivo was performed on an orthotopic xenograft mouse model. Proteomic analysis was carried out by 2D-DIGE followed by GO and Reactome classification with Cytoscape.

Results. NR2F2 isoforms are overexpressed in primary tumors. PANC-1 cells expressing NR2F2_V1 or V2 show...
an altered phenotype that is predominantly mesenchymal in V2 overexpressing cells, as demonstrated by IF and WB. Consistent with this observation V2 cells are more resistant to gemcitabine and are more tumorigenic in vivo. Proteomic analysis identifies a central core of modulated proteins implicated in TGF-β signaling. Forcing V2 localization in the nucleus reduces the aggressiveness of cancer cells.

**Conclusions.** Our results suggest that NR2F2 isoforms differentially influence PDAC progression with V2 isoform acting mainly on EMT; interestingly, regulation of EMT by V2 is influenced by its cell localization. Given its association to PDAC, the modulation of the receptor isoforms might result in novel therapies.

**PD1+ cells accumulate in highly metabolic tumors in pancreatic adenocarcinoma**

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**Context.** The pathways that regulate immune cell function and metabolism in cancer are tightly linked and metabolic dysfunction can severely impact on the efficiency of the anti-tumor immune response.

**Objective.** Here we investigated the association of tumor metabolic activity and immune infiltration in Pancreatic Ductal Adenocarcinoma (PDAC), a micro-environment characterized by profound metabolic deregulations and a strong immunosuppression.

**Methods.** Pancreatic juice from 30 patients with pancreatic pathologies surgically operated at Humanitas Clinical and Research Center was analyzed by Nuclear Magnetic Resonance to investigate the metabolomics. Immunohistochemical evaluation of metabolic and immune infiltrate markers was performed in a cohort of 40 PDAC patients. Tumor glycolysis was targeted in a murine PDAC cell line by knocking down the gene encoding for Phosphofructokinase (PFK). Glucose metabolism and tumor infiltrating leukocytes (TILs) were analyzed by multicolor flow cytometry comparing PFK deficient tumors and control tumors.

**Results.** Metabolomic analysis of pancreatic juice indicates a metabolic signature that discriminates among ductal pancreatic tumors and other pancreatic pathologies. In human PDAC sections, a higher density of PD1+ TILs correlates with tumors expressing higher levels of GLUT-1. Furthermore TILs accumulate in highly glycolytic tumors. In a preclinical model, PDAC tumors obtained from cell lines with different metabolic consumptions were differently infiltrated by T cells, with PD1+ CDB-TILs accumulating in highly metabolic tumors.

**Conclusions.** Both in human and preclinical models of PDAC, tumor cell glycolysis impacts on the type of immune cell infiltration, underlining a key interplay between glucose metabolism and the antitumor immune response.

**Differential regulation of IL-6 production in KRas-transformed pancreatic cells displaying epithelial or mesenchymal phenotype**

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**Context.** Oncogenic KRas in human pancreatic adenocarcinoma causes the constitutive activation of the transcription factor NF-kB and the switch-on of an inflammatory program, which further fuels NF-kB and STAT3 activation.

**Objective.** We addressed the role of oncogene-triggered inflammation in tumor progression, using specific sub-lines of the recently KRas-transduced pancreatic HPDE cell line (KRas-HPDE) selected for distinct epithelial or mesenchymal features (E-Cadherin, Vimentin, TWIST, ZEB, SNAIL, SLUG).

**Methods.** Four epithelial and 4 mesenchymal cloned sub-lines of the original KRas-HPDE cell line were characterized for production of inflammatory mediators and in vivo growth in immune deficient mice, after treatment with pharmacological inhibitors of IL-1 or IL-6 signaling (IL-1R antagonist, anti-IL-6 mAb).

**Results.** Inhibition of IL-1 signaling by Anakinra had profound effects in KRas-HPDE cells pancreatic sub-lines with epithelial features: it reduced the production of inflammatory mediators; inhibited in vivo tumor growth in mice and the inflammatory stroma; significantly reduced NF-kB p65 and STAT3 phosphorylation in cancer cells. In contrast, pancreatic sublines with mesenchymal phenotype were completely resistant to IL-1 inhibition and showed preserved inflammation. In these cells, the epithelial-to-mesenchymal (EMT) transcription factor TWIST actively transcribed IL-6 and CXCL8, thus bypassing the IL-1 block. Pharmacologic targeting of mesenchymal pancreatic tumors in vivo with anti-IL-6 mAb successfully reduced tumor growth and inflammation.

**Conclusions.** Our results indicate that tumor cells which have undergone EMT transition, early occurring in pancreatic ductal carcinoma, are resistant to IL-1 inhibition, because the EMT-related transcription factor TWIST sustains an IL-6-associated inflammation. These results bear relevance for the correct design of therapeutic strategies aimed at targeting cancer-related inflammation in pancreatic cancer, and suggest that inhibition of IL-6 may prove successful also in neoplastic cells with EMT features. (Funded by AIRC 5x1000 n. 12182)

**The MUST score and pancreatic exocrine function are not associated with extra-pancreatic events during the follow-up of chronic pancreatitis patients**

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**Background.** The majority of deaths (60–75%) in patients with chronic pancreatitis (CP) are due to extra-
pancreatic consequences of the disease like cardiovascular events, osteoporosis, and infections. Data are lacking regarding the risk of such events and their relation with exocrine (EPI) or endocrine pancreatic insufficiency and the nutritional status during the FU. Recent guidelines recommend the use of the MUST score to assess the nutritional status of CP patients.

**Aim.** To evaluate the incidence of extra-pancreatic events in patients with CP during the follow-up and their association with CP features, pancreatic function and nutritional status.

**Methods.** Retrospective analysis of a single-centre cohort of CP patients prospectively enrolled and followed-up. Epidemiological data, risk factors, new hospitalizations were recorded at the diagnosis and at FU visit. EPI assessed by fecal elastase, MUST score evaluated as a nutritional tool. The occurrence of death and of extra-pancreatic events was recorded. Differences in terms of clinical features, risk factors and nutritional factors analysed by fisher and t-test. Logistic regression analysis used to identify association of investigated variables with events of interest.

**Results.** 100 patients (65% male; mean age 60) enrolled with a mean FU of 56±12 months. 54% had a toxic aetiology and 46% had EPI. 11% of patients had severe CP and 27.5% had a MUST score ≥2 at diagnosis. During the FU, 2 patients died for cardiovascular events and 15.4% needed endoscopic/surgery treatment. 30% needed hospitalization, in 35% for extra-pancreatic events. Toxic aetiology had a two-fold risk of new hospitalization (OR 2.3; 95%CI 0.94-6; p 0.06). Patients with severe disease had a higher risk of hospitalization (OR 6.2; 95%CI 1.2-35 p 0.02) and extra-pancreatic events. There was no association between EPI or MUST score≥2 and extra-pancreatic events. Toxic aetiology had a two-fold risk of new hospitalization (OR 2.3; 95%CI 0.94-6; p 0.06). Patients with severe disease had a higher risk of hospitalization (OR 6.2; 95% CI 1.2-35 p 0.02) and more often needed endoscopic/surgery treatment (50% vs. 11% p 0.01).

**Conclusions.** Some 27% of patients were at high risk of malnutrition at diagnosis, and 30% of them were hospitalized during the FU, often for extra-pancreatic events that caused death in 2%. Toxic aetiology and severe disease are associated with hospitalization, but EPI and MUST score do not seem to be useful in predicting these events.

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**Percutaneous transhepatic laser lithotripsy: a feasible option for the treatment of complex biliary stones**

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**Context.** Most biliary calculi are successfully removed with endoscopic retrograde cholangiopancreatography (ERCP). Percutaneous intervention is a feasible option after failed ERCP. Nevertheless, complex biliary calculi may need open surgery; moreover, patients with biliary anastomosis are usually not amenable to endoscopy.

**Objective.** We describe three cases of patients with biliary stones resistant to standard treatments successfully treated with percutaneous transhepatic laser lithotripsy (PTLL).

**Methods.** All patients presented with cholestasis. After failed ERCP, patients required percutaneous interven-

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**Contrast enhancement of pancreatic neuroendocrine neoplasms: is it correlated with tumor grade?**

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**Context.** Pancreatic neuroendocrine neoplasms (pan-NENs) are usually described as solid hypervascular lesions; nevertheless, hypovascularity or inhomogeneous enhancement are not uncommon. It is still to be completely understood whether enhancement is correlated with the biological behavior of panNENs.

**Objective.** The purpose of this study is to compared panNENs enhancement and tumor grade.

**Methods.** Consensus retrospective analysis of pre-operative magnetic resonance (MR) examinations performed between January 2015 and January 2017 was conducted by two radiologists. Enhancement was compared with tumor grade using Fisher’s exact test. Size was compared between hypo-, iso- and hyperenhancing tumors using Kruskall-Wallis H test. Enhancement heterogeneity was analyzed with the histogram analysis technique. Pearson’s product-moment correlation test was conducted to test correlations between histogram-derived metrics and tumor size. Histogram-derived
parameters were compared with tumor grade using Mann-Whitney U test. P values <.05 were considered significant.

**Results.** 42 patients were included. The mean tumor size was 32.6 mm (10-105 mm), 18 G1 panNENs (26.6 mm; 10-83 mm), 21 G2 panNENs (33.8 mm; 13-80 mm) and 3 G3 tumors (60.3 mm; 26-105 mm) were included. No significant differences were found regarding the relative proportions of hypo-, iso- and hyperenhancing lesions between tumor grades. Hypovascular tumors were significantly larger than hypervascular panNENs (45.7±9.3 vs. 32.5±21.76 mm, p=.009). Positive correlations were found between enhancement heterogeneity, expressed in terms of arterial and portal kurtosis, and tumor size (r=0.40 and .439, p<.004).

**Conclusions.** PanNENs enhancement is not correlated with tumor size. Hypovascular tumors and lesions with inhomogeneous enhancement are larger compared to their counterparts, independently from tumor size.

| Table 1.—Fisher. No significant differences between tumor signal intensities were found between tumor grades (p>.05). |
| --- | --- | --- |
| | G1 | G2-3 | P |
| Hypo | 16 (43.2%) | 21 (56.8%) | 6.99 |
| Iso | 2 (50%) | 2 (50%) | 580 |
| Hyper | 0 (0%) | 1 (100%) | 571 |

| | G1 | G2-3 | P |
| Hypo | 4 (36.4%) | 7 (63.6%) | 4.43 |
| Iso | 9 (52.9%) | 8 (47.1%) | 348 |
| Hyper | 5 (35.7%) | 9 (64.3%) | 742 |

| | G1 | G2-3 | P |
| Hypo | 4 (57.1%) | 3 (42.9%) | 4.58 |
| Iso | 6 (37.5%) | 10 (62.5%) | 750 |
| Hyper | 8 (42.1%) | 11 (57.9%) | 714 |

**Kruskall Wallis:**
- .257 PRI
- .093 PORT
- .194 ISO
- .34 PRI
- .093 ISO
- .093 IPO

**Methods.** Moderate to weak significant correlations (.20<r<.590) were found between tumor size and the following parameters: **T1fs**: Skewness, Uniformity, Kurtosis, Delayed. No significant correlations (p>0.05) were found between other histogram-derived parameters and tumor size.

Moderate to weak significant correlations (.20<r<.590) were found between tumor size and the following parameters: T1fs, Arterial, Portal, and Delayed. No significant correlations (p>0.05) were found between other histogram-derived parameters and tumor size.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>r</th>
<th>p</th>
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<tbody>
<tr>
<td>T1fs-skewness</td>
<td>543</td>
<td>.001</td>
</tr>
<tr>
<td>T1fs-kurtosis</td>
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<td>.023</td>
</tr>
<tr>
<td>Arterial-kurtosis</td>
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<td>.001</td>
</tr>
<tr>
<td>Portal-kurtosis</td>
<td>439</td>
<td>.004</td>
</tr>
<tr>
<td>Delayed-kurtosis</td>
<td>-312</td>
<td>.044</td>
</tr>
</tbody>
</table>

No significant differences were found between G1 and G2-3 tumors regarding size-unrelated histogram-derived parameters.

**Conclusions.** Enhancement is not correlated with tumor grade in panNENs. Intratumoral heterogeneity on pre-contrast, arterial and portal phase, expressed in terms of histogram-derived kurtosis, is positively correlated with tumor size.

**Histogram analysis of MR images: new prognostic biomarkers for pancreatic neuroendocrine neoplasms**

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**Context.** Few studies investigated heterogeneity in pancreatic neuroendocrine neoplasms (panNENs) through the analysis of imaging data. Histogram analysis explores heterogeneity by examining the distribution of gray levels within a region of interest.

**Objective.** To correlate the results of histogram analysis of magnetic resonance (MR) imaging data with the biological behavior of panNENs.

**Methods.** 42 pre-operative MR examinations were retrospectively analyzed. Histogram-derived parameters were correlated with histopathological features using Mann-Whitney U test. ROC curves were constructed to determine optimum thresholds for each histogram-derived parameter, and sensitivity and specificity were assessed. P values <.05 were considered statistically significant.
Results. The entropy of the apparent diffusion coefficient (ADC) distribution was significantly higher in G2-3 than in G1 tumors (7.9±1.55 vs. 5.9±2.34, p=0.005); sensitivity and specificity were 85.3% and 61.1%. ADC kurtosis was significantly higher in panNENs with vascular involvement, nodal and hepatic metastases compared with less aggressive tumors (5.58±2.95 vs. 3.54±2.37, 4.84±3.36 vs. 3.08±1.22, and 6.94±4.75 vs. 3.26±1.27; p=0.008, .021, and .008, respectively). Sensitivity and specificity of ADC kurtosis were: 85.7/74.3%; and 100/62.8%.

Conclusions. Histogram analysis of ADC values can explore heterogeneity in panNENs. ADC entropy and ADC kurtosis are the most accurate histogram-derived parameters for the identification of panNENs with malignant behavior.

Phosphorylated Histone H3 (PHH3) is a novel, interesting prognostic marker in GEP-NETs

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Context. Neuroendocrine tumors are rare neoplasms which often originate from the gastro-entero-pancreatic tract. Despite their relatively indolent nature GEP-NETs have an heterogeneous prognosis depending mainly on tumor stage and grade as measured by the proliferation index Ki 67. However, this method has some limitations and is time-consuming. Some recent studies suggested that the mitotic count based on immunohistochemistry (IHC) for the phosphorylated histone H3 (PHH3) could be an alternative, useful and effective proliferation marker in pancreatic NETs. This new prognostic biomarker, however, has rarely been evaluated in NETs of other primary sites.

Objective. to evaluate the accuracy of PHH3 as prognostic marker of overall survival and progression-free survival, in GEP-NETs in comparison with Ki 67.

Methods. Clinicopathologic data and paraffin-embedded tissues were evaluated for GEP-NETs patients whose tumors were resected between 2007 and 2017. Mitotic counts were analyzed on PHH3-stained slides and compared with Ki67 results. Survival probability was calculated with the Kaplan-Meier curve and Cox analysis employed to calculate hazard ratios (HR). A p<0.05 was considered statistically significant.

Results. 45 GEP-NETs patients were included (57.8% men; median age 58.9 years, range 17-79). Primary tumour sites were stomach (6, 13.3%), pancreas (15, 33.3%), and midgut/colorectal (24, 53.3%). The median follow-up period was 43 months (range 3-168 months). 30 tumors were stage III-IV, 15 stage I-II. 26 tumors were G1, 18 were G2 and only 1 was G3 according to Ki67; there were no G5 cases according with PHH3 mitotic count. The median time for evaluation of a PHH3-stained slide was 2 minutes, compared to 8 for Ki67. PHH3 and Ki67 values had a good linear correlation (Spearman R=0.65; p<0.0001). There was no difference among pancreatic and GI tract NETs in terms of Ki67 values (mean 2.3 vs. 6.5; p=0.2) while PHH3 mitotic count was significantly lower in pNETs (0.67 vs. 4; p=0.01). Both Ki67 (HR 1.24 x increasing unit; p=0.005) and PHH3 (HR 1.23; p=0.008) predicted OS, both none of them PFS.

Conclusions. PHH3 seems a promising biomarker, being less time-consuming than Ki67. The two markers show a good correlation and similar accuracy in predicting overall survival in GEP-NETs, while in this series, possibly due to the relatively low number, they were not associated with progression free survival.

Presentation symptoms and risk factors are associated with diagnostic delay and disease stage but not with survival of patients with pancreatic cancer

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Context. One of the reasons for PDAC low survival rate is delayed diagnosis as symptoms are often unrecognized. Data on the association between presentation symptoms, diagnostic delay, disease stage and survival are, however, limited and heterogeneous. Furthermore, the association between risk factors for developing PDAC, such as smoking, obesity, alcohol intake, diabetes and family history and diagnostic delay has not been explored.

Objective. to investigate the association between presentation symptoms, diagnostic delay, risk factors for PDAC, stage at diagnosis and survival.

Methods. the above mentioned data were recorded in a dedicated single-centre database of prospectively evaluated PDAC patients. Fisher test and Student’s t-test were used to analyze categorical and continuous variables. Survival probability was calculated with the Kaplan-Meier curve and Cox analysis employed to calculate hazard ratios (HR). A p<0.05 was considered statistically significant.

Results. in 447 consecutive PDAC patients (mean age 68, 51% male) the mean diagnostic delay was 3.9 months (95% CI 3.58-4.37). Jaundice was the leading presentation symptom in 75 (16.3%), weight loss in 169 (37.8%), pain in 112 (25%), new-onset diabetes in 44 (9.8%). Diabetes was incidental in 25 cases (5.6%) or related with undetermined complaints in 24 (5.4%). The diagnostic delay was significantly shorter in patients with jaundice (mean 1.1 months) compared to all other presentations (p<0.001): pain 3.4, new-onset diabetes 5.4 and weight loss 5.9. PDAC family history, smoking and previous diabetes were not associated with presentation symptoms or delay, but obese patients (4.3 vs. 3.3 months; p=0.01) and those drinking alcohol (4.4 vs. 3.6 months; p=0.05) had a longer delay. The mean diagnostic delay was of 4.4 months in patients with distant metastases, 4.0 in locally advanced and 3.3 in resectable disease (p=0.02
Recurrence after resection for pancreatic cancer: is there a place for surgery?
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Context. Currently the treatment of recurrent pancreatic cancer remains a challenge for the advanced stage of the disease and the limited therapeutic role of chemotherapy and radiotherapy. Only few studies have been published on the surgical approach for recurrent pancreatic cancer or second tumors.

Objective. To report our experience of intensive follow-up after resection for pancreatic cancer and the role of surgery for recurrent or second neoplasms.

Methods. Patients who had undergone surgical resection for pancreatic cancer from January 2000 to December 2013 were prospectively followed up for a median time of 28 months (17-108). Patients underwent, every three months for the first two years and then every six months, clinical evaluation, biochemical tumor marker assay (CA19-9), abdominal US and/or helical-CT, whole-body PET scan (from January 2004, PET/CT) one year after surgery or when clinically indicated. All patients were treated with adjuvant chemotherapy after primary resection. Indication for surgery was given in accordance with oncologists. Validation of recurrence diagnosis was made histologically or radiologically.

Results. 195 patients who underwent surgery with curative intent for PDA developed a recurrent disease. There were 25 local, 26 local and liver, and 144 metastatic recurrences (101 liver, 31 peritoneum, 11 lung, 1 bone). Thirty-five patients underwent surgical treatment: 20 resection, 14 exploratory laparotomy (2) or surgical palliation (13). Median overall survival (OS) in the group of patients who underwent resection was 20 months, better than OS in patients treated only with chemo-radiotherapy or supportive therapy (respectively 6 and 3 months) (p<0.02). During the follow-up, 9 patients developed a second cancer that was successfully resected in all.

Conclusions. In selected patients, a re-resection of recurrent pancreatic cancer is feasible. Survival after tumor's recurrence was better in patients who underwent radical resection compared with patients treated with palliative surgery or chemotherapy alone. A close follow-up allowed to diagnose a second cancer in 9 patients: in some of these, surgical resection may prolong survival. Many efforts have to be invested in the recognition of localized recurrence in order to improve the outcome of these patients.

Multimodality treatment for borderline resectable and resectable pancreatic cancer: clinical outcomes after surgery, neo/adjuvant chemotherapy and adjuvant IMRT-based chemoradiation
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Context. Survival in pancreatic cancer remains poor and surgery is the potential curative therapy. Multimodality treatment in adjuvant and neo-adjuvant setting can improve relapse free (RFS) and overall survival (OS) of these patients.

Objective. To evaluate clinical outcomes of sequential surgery, neoadjuvant/adjuvant chemotherapy (CT) and adjuvant IMRT-based chemoradiation (CRT) in patients with resectable (RPC) or borderline resectable pancreatic cancer (BRPC).

Methods. We retrospectively analyzed patients with resected pancreatic cancer treated with adjuvant 5-fluorouracil-based CRT between 2011 and 2016. Neoadjuvant CT was administered in patients with borderline resectable pancreatic cancer. Patients with resectable disease were treated with adjuvant CT. Treatment efficacy was evaluated in terms of OS, RFS, and local recurrence free survival (LRFS). Toxicity was scored according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

Results. Adjuvant IMRT-based CRT was administered at Humanitas Cancer Center to 51 resected patients (12 BRPC, 39 RPC), median age 52 yrs (46-82), M/F 29/22. Neoadjuvant poli-CT was administered to 12 BRPC patients for a median of 4 months (3-6). 34 out of 39 patients (90%) with RPC received adjuvant CT for a median of 4.8 months (2-6). 5 patients were unsuitable for CT due to age and comorbidity. 50 patients had T3 tumors (98%) and 1 patient had a T4 tumor (2%). N1-2 disease, according to TNM v. 8, was observed in 42 patients (42%) and R1/resection in 47 patients (92%). Median IMRT dose was 50.4 Gy (45-56 Gy) delivered in 25-28 fractions. Median follow-up was 46 months (12-85). Median OS from diagnosis was 25 months. OS rates at 1-3-4 years were 88%, 39% and 19%, respectively. At univariate analysis, NO-1 stage (p<0.01), CT (p<0.006) and absence of systemic progression (p<0.001) was correlated with better OS. Median LRFS calculated from surgery was 53 months, with a 1-3-4 years LRFS rates of 88%, 66% and 60% respectively. Median RFS was 9 months.
CRT-related toxicity was acceptable, with G3 acute toxicity rate of 8% and only 1 case of G3 gastrointestinal late toxicity.

**Conclusions.** Combined multimodality treatment with surgery, CT, and CRT is an effective therapeutic option for selected patients with resectable and borderline resectable pancreatic cancer. In particular, adjuvant IMRT-based CRT represents a well-tolerated and promising option, characterized by low toxicity and encouraging LRFS rates.

**Stereotactic body radiation therapy for unresectable locally advanced pancreatic cancer: clinical outcomes on 100 patients**

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**Context.** Pancreatic adenocarcinoma is characterized by a poor prognosis. Surgery is the gold standard of care, however more than 50% of patients are unresectable at the time of diagnosis. In patients with locally advanced pancreatic cancer (LAPC), the integration of chemotherapy (CT) and chemo-radiation treatment (CRT) is the current therapeutic option, associated with a significant toxicity rate and with a disappointing overall survival (OS). In the last years, the role of stereotactic body radiotherapy (SBRT) in the treatment of LAPC was investigated. Higher local control related to the high doses employed, short overall treatment time and sequential integration with systemic therapy, represent the crucial advantages of SBRT over conventional CRT.

**Objective.** To assess the efficacy of SBRT in patients with inoperable LAPC.

**Methods.** Patients with unresectable LAPC with maximum tumor diameter ≤ 5cm, without limph node disease and without distant metastasis were treated with SBRT, after multidisciplinary board evaluation. Prescription dose was 45 Gy in 6 fractions. Primary end-point was freedom from local progression (FFLP). Secondary end-points were overall survival (OS), progression-free survival (PFS), and toxicity. Local control (LC) was defined according to RECIST v1.1 criteria. Acute and late toxicity was scored according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

**Results.** Between January 2011 and December 2016, 100 patients (44 male-56 female) with LAPC were treated with SBRT at Humanitas cancer Center. Median age was 71 years (range 41-88 years). 57 patients (57%) received CT before SBRT, for a median time of 5 months (range 3 - 10 months). In 44 patients (77%) gemcitabine-based CT was administered (4 gemcitabine alone, 21 GEMOX, 9 PEX-G, 10 gemcitabine-nab paclitaxel), whereas 15 patients (33%) received FOLIRINOX. Median follow-up was 86 months (range 2-88 months). FFLP was 82% and 76% at 1 and 2 years, respectively. At univariate (p<0.05) and multivariate analysis (p<0.001), lesion size was significant for LC. Median PFS was 7 months (95% CI 4.76-8.23). Median OS was 12 months (95% CI 8.76-13.21). CT administered before SBRT (p < 0.005) and FFLP (p<0.002) were significantly correlated with OS. Grade 3 gastrointestinal toxicity was detected in 2% of patients.

**Conclusions.** SBRT is an effective and safe local therapy for selected patients with LAPC. Our results suggest that the stereotactic treatment may be a promising therapeutic option in the multi-modality treatment of these patients.

**A novel insight into the anticancer mechanism of metformin in pancreatic neuroendocrine tumor cells**

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**Context.** The antidiabetic drug metformin displays anticancer properties in several neoplasms, including neuroendocrine tumors (P-NETs). In P-NETs, aryl hydrocarbon receptor-interacting protein (AIP) acts as a tumor suppressor and is up-regulated by the somatostatin analog octreotide.

**Objective.** Aim of the present study was to evaluate the effect of metformin on P-NET cell proliferation and its interaction with octreotide; apoptosis was evaluated by flow cytometry and colony images by bright-field microscopy. The involvement of the AIP pathway in these events was evaluated by western blot and siRNA trasfection.

**Methods.** Brdu incorporation assay was used to investigate the effect of metformin on P-NET cell proliferation and its interaction with octreotide; apoptosis was evaluated by flow cytometry and colony images by bright-field microscopy. The involvement of the AIP pathway in these events was evaluated by western blot and siRNA trasfection.

**Results.** In P-NET cells, metformin inhibited cell proliferation (-62±15% p<0.001 vs. basal at 10mM), without any additive effect when combined with octreotide, reduced colony formation and cell number (66±6% p<0.001 vs. basal) and increased apoptosis (+389±170% p<0.01 vs. basal). Both octreotide and metformin up-regulated AIP expression (+111±31% p<0.05 and +140±20% p<0.01 vs. basal, respectively). AIP silencing abolished the antiproliferative and proapoptotic effects of metformin. Moreover, metformin decreased HSP70 expression, increased Zac1 and AHR expression; these effects were abolished in AIP silenced P-NET cells.

**Conclusions.** We showed for the first time that metformin exerts its anticancer effects through AIP complex modulation. These findings provide a novel insight into the antitumorigenic mechanism of metformin and the molecular rationale for its use in the clinical setting for P-NET treatment.
Tumor size correlates with grading in non-functioning pancreatic neuroendocrine tumors and is not age-dependent

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Results. Excluded from survival analysis. Multiple logistic regression and Cox’s regression to evaluate possible correlation between continuous variables. Multiple logistic regression and Cox’s regression analysis was performed. Patients with R2 resection were excluded from survival analysis.

Objective. To evaluate a possible correlation between age, tumor size and grading in patients with NF-PanNET and its impact on disease free survival (DFS).

Methods. Patients who underwent surgery for sporadic NF-PanNET (excluding G3) were retrospectively analysed. Linear regression analysis was performed to evaluate possible correlation between continuous variables. Multiple logistic regression and Cox’s regression analysis was performed. Patients with R2 resection were excluded from survival analysis.

Results. 235 patients were enrolled. Median age was 61 years. Tumors were PanNET G1 in 138 (59%) cases. Median radiological and histological diameter was 25 mm for both. Age was correlated neither with tumor size nor with Ki67 value. Conversely, tumor size was significantly associated with Ki67 value (r: 0.273, P<0.0001). On multivariate analysis, predictors of tumor grade were tumor size (OR: 3.72, P=0.0001) and microvascular invasion (OR: 6.94, P<0.001). A tumor size cut-off of 27 mm accurately predicted PanNET G2. At a median follow-up of 59 months, 192 patients were alive with no evidence of disease, 32 patients (14%) had recurrence and 9 patients (28%) eventually died of disease. On multivariable analysis, predictors of DFS were tumor size > 27 mm (HR: 3.40, P<0.036) and the presence of perineural invasion (HR: 5.27, P<0.0001).

Conclusions. Tumor size correlates with grading and it is a strong predictor of recurrence after surgery for NF-PanNET. Tumor size is not associated with increasing age suggesting that natural evolution of these neoplasms is not time-dependent, supporting the safety of a surveillance policy for small asymptomatic NF-PanNET.

Laparoscopic distal pancreatectomy: what factors are related to conversion. Lessons learned from 68 consecutive procedures in high volume pancreatic center

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Methods. A retrospective study of a prospective database of 68 patients scheduled for a laparoscopic distal pancreatectomy was conducted. Pre-, intra- and postoperative data were collected. Patients who underwent a standard LDP were compared with those who needed a conversion to open approach as regards demographic, clinical, radiological and surgical data. Uni-multivariate analyses were carried out. All the procedures were performed at a high-volume center by pancreatic surgeons experienced with laparoscopic surgery.

Results. Univariate analysis suggested that the site of the lesion, the extension of pancreatic resection and the requirement for an extended procedure to adjacent organs were significantly associated with the risk of conversion to open approach. Multivariate analysis showed that only the extension of pancreatic resection (subtotal pancreatectomy) was significantly related to the odds of conversion (OR 19.5; 95% CI 1.1-32.3; P=0.038). The preoperative suspicion of malignancy differed between the two groups; however, this difference did not reach the statistical significance (P=0.095).

Conclusions. Despite the limitations of the study, the extension of pancreatic resection seems to be the main factor related to conversion during laparoscopic distal pancreatectomy.

Intraductal papillary mucinous neoplasms: the bologna experience. Lessons learned from 357 cases observed in a tertiary care center

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Methods. A retrospective study on a prospective database of 357 patients observed at our institution from January 2004 until January 2016 was conducted. Pre-, intra- and postoperative data were collected. Patients managed conservatively were compared with those who underwent surgery as regards demographic, clinical data, radiological work up, features of the cysts and overall survival (OS). Multivariate analyses were carried out in order to assess factors related to patients’ management as well as those related to OS.

Results. Multivariate analysis showed that the factors strongly related to surgery were: location in the tail of the pancreas (OR 4.48; P=0.011), presence of mural nodules (OR 15.39; P<0.001), Wirsung size > 5 mm (OR 8.55; P<0.001), Wirsung size ≥ 10mm (OR 13.75; P<0.001), a positive citology (OR 19.81; P=0.008) and acute pancreatitis (OR 16.7; P=0.001); conversely, age was independently related to the follow-up strategy (OR 0.93; P=0.001). Furthermore, parameters that significant-
ly influenced OS were: age (HR 1.07; P<0.001), jaundice (HR 7.67; P<0.001) and the presence of mural nodules within the cyst.

Prevalence of incidental discovery of intraductal papillary mucinous neoplasm: Bologna experience

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Context. Several studies evaluated IPMN prevalence using selected patients: CT or Colangio-Wirsung Magnetic Resonance (CWRM) and EUS populations. The "true" prevalence of incidental IPMN still remain unknown.

Objective. To evaluate the prevalence of IPMN in a non-selected population and its correlation with other diseases.

Methods. Data from 6,357 ultrasonography (US) performed from 2012 to 2015 were collected. The inclusion criteria were: age > 18 years and absence of pancreatic disease. All patients with suspected IPMN were further investigated with CWRM. The prevalence of IPMN was calculated. The association with others disease were studied with multivariate analysis.

Results. A total of 240 pancreatic cystic lesions were detected. CWRM confirmed that 224 (93.5%) were IPMN. The prevalence of IPMN was 3.5% (224/6357): IPMN type II and type I/III had a prevalence of 3.3% and 0.2% respectively. At univariate analysis, IPMN were more frequent in female patients (P<0.001), age between 40-50 years (P=0.007) as well as cirrhosis (P=0.011), non cirrhotic liver disease (P<0.001) or inflammatory bowel disease (P=0.007) as well as cirrhosis (P=0.011), non cirrhotic liver disease (P<0.001) or inflammatory bowel disease (P=0.003). Multivariate analysis showed that the only factors related to IPMN were female gender (OR 2.3; 95% CI 1.5-3.3; P<0.001) and age between 40-50 years (OR 2.1; 95% CI 1.5-3.0; P<0.001).

Conclusions. The prevalence of IPMNs in a non-selected population was 3.5%. The only factors related to this prevalence were female gender and age. No association with chronic or neoplastic disease was found.

Is surgery the best treatment for reducing years of life lost due to sporadic small (<2 cm) non-functioning pancreatic neuroendocrine tumors? A single center experience

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Context. There is currently substantial controversy regarding the best management of nonfunctioning pancreatic neuroendocrine tumors (NF-PNETs) <2 cm.

Objective. To evaluate whether the surgical approach is the best treatment for sporadic small NF-PNETs.

Methods. Retrospective study involving 102 surgically treated patients affected by NF-PNETs. Patients having small tumors (<2 cm) and those having large tumors (>2 cm) were compared regarding demographics, clinical and pathological factors, evaluating the risk of malignancy and relation to survival times such as overall survival (OS), disease free survival (DFS), years of life lost (YLL), years lost due to disability (YLD) and disability adjusted life years (DALY).

Results. Small tumors were T3-4 in 11% and G2-3 in 36.6% of cases; lymph node and distant metastases were present in 31% and 8% of cases, respectively. When small and large tumors were compared, significant differences were found in relation to the presence of symptoms (P=0.012), tumor status (P>0.001), grading (P<0.001) and YLD (P=0.002). Multivariate analysis predicting malignancy and survival times showed that tumor size was related only to grading (P<0.001). The YLL and DALY were influenced by age at diagnosis (P<0.001) and presence of symptoms (P=0.039), while YLD was only related to grading (P=0.036).

Conclusions. Tumor size alone did not seem to be reliable in predicting malignancy. In fact, small tumors could present nodal or distant metastases and could be G2-3 in a non-negligible percentage of cases. Secondly, their risk of malignancy and survival time are similar to larger tumors. Additional parameters should be considered in order to reduce YLL of patients with small tumors, such as age at diagnosis, presence of symptoms and grading.

Minimally invasive pancreaticoduodenectomy: which is the good “way”? Systematic review and network meta-analysis of non-randomized comparative studies

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Context. Many mini-invasive pancreaticoduodenectomy (MIPD) techniques are reported, but their advantages respect to the open one (OPD) and between each other are unclear.

Objective. To evaluate which is the safest way to perform MIPD.

Methods. A systematic literature search of studies comparing different types of MIPD: laparoscopic-assisted (LAPD), totally-robotic (TRPD), totally-laparoscopic (TLPD) or totally-laparoscopic-robotic-assisted (TLPD-RA) to OPD. Primary endpoint was postoperative mortality. Secondary endpoints were intraoperative, postoperative and oncological outcomes. A network analysis was performed to compare the different techniques.

Results. A total of 240 pancreatic cystic lesions were detected. CWRM confirmed that 224 (93.5%) were IPMN. The prevalence of IPMN was 3.5% (224/6357): IPMN type II and type I/III had a prevalence of 3.3% and 0.2% respectively. At univariate analysis, IPMN were more frequent in female patients (P<0.001), age between 40-50 years (P=0.007) as well as cirrhosis (P=0.011), non cirrhotic liver disease (P<0.001) or inflammatory bowel disease (P=0.003). Multivariate analysis showed that the only factors related to IPMN were female gender (OR 2.3; 95% CI 1.5-3.3; P<0.001) and age between 40-50 years (OR 2.1; 95% CI 1.5-3.0; P<0.001).

Conclusions. The prevalence of IPMNs in a non-selected population was 3.5%. The only factors related to this prevalence were female gender and age. No association with chronic or neoplastic disease was found.
meta-analysis (NMA) was built to generate direct, indirect and mixed estimates effects, between different approaches, for each variable. Effects were reported as pairwise comparisons and hierarchical ranking that each approach could be the best or the worst for each outcome, expressed by the surface under the cumulative ranking curve (SUCRA).

Results. Nineteen studies were identified, involving 2640 patients: 1777 OPDs; 81 LAPDs; 420 TRPDs; 226 TLPDs; 136 TLPD-RAs. No differences regarding post-operative mortality were found in pairwise comparison. LAPD had high probabilities of being the worst approach, while TRPD had high probabilities of being one of the best. Regarding secondary endpoints, OPD resulted the best for operative time and postoperative bleeding, but the worst for blood loss and wound infection. TRPD or TLPD-RA seemed the best for delayed gastric emptying, length of hospital stay, harvested lymph nodes and postoperative morbidity. TLPD often resulted the worst approach, especially for overall and major complications, postoperative bleeding and biliary leak.

Conclusions. The safest MIPDs are those involving a robotic system, which seems to have a promising role in order to ameliorate the outcomes of OPD, especially if compared to a pure laparoscopic approach.

Surgical management of peritoneal carcinomatosis in a patient with pancreatic neuroendocrine tumor: a case report
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Context. Pancreatic neuroendocrine tumors (PNETs) are a heterogeneous group of neoplasms usually associated with slow growth but a high rate of distant metastases, including peritoneal carcinomatosis (PC). The case of a 43-year-old woman who had been diagnosed with a neuroendocrine tumor of the pancreatic tail, 30 mm in size, with metastatic spread to the ovaries, the peritoneum and to the neck lymph nodes is herein reported to discuss the prognostic impact of PC on life expectancy and a possible treatment strategy.

Case report. After a bilateral ovariectomy the diagnosis of a G2 metastatic neuroendocrine tumor was made. The patient thus underwent PET-Ga DOTANOC scan, CT scan, endoscopic ultrasound (EUS) with fine needle aspiration, contrast enhanced ultrasound (CEUS) and finally a diagnostic laparoscopy with biopsy of peritoneal nodes together with neck lymph nodes dissection. The patient then underwent cytoreductive surgery: distal pancreatectomy with splenectomy, subtotal colectomy, hysterectomy and peritoneectomy were performed. The final pathological diagnosis was a complex neuroendocrine tumor with NET G2 areas and MANEC amphicrine subtype areas. After 6 months patient developed liver metastases, treated with somatostatin analogs and chemotherapy. Patient is now well and alive after 22 months from surgery.

Conclusions. Aggressive surgical management seems justified for subsets of NET-related PC but requires careful selection of the candidates most likely to benefit. In high-volume centers, a cytoreductive surgery could be attempted in young patients who are fit for surgery, in order to improve survival.

Is pancreaticogastrostomy safer than pancreaticojejunostomy after pancreaticoduodenectomy? A meta-regression analysis of randomized clinical trials
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Context. The superiority of pancreaticogastrostomy (PG) with respect to pancreaticojejunostomy (PJ) after pancreaticoduodenectomy is still under debate.

Objective. To evaluate if PG is superior to PJ in the prevention of clinically relevant postoperative pancreatic fistula (POPF).

Methods. A systematic literature search of all randomized clinical trials (RCTs) comparing PG to PJ with an International Study Group of Pancreatic Fistula (ISGPF) definition of POPF was carried out. Primary endpoint was clinically relevant POPF rates, analyzed using risk difference (RD) and number needed to treat or harm (NNT and NNH). Secondary endpoint was to evaluate the impact of confounding covariates on the meta-analytic results, reported as linear regression between Risk Ratio (RR) of the covariate and the RD of the primary endpoint expressed as a β coefficient±standard error (SE), using meta-regression analysis.

Results. Seven RCTs were identified involving 1184 patients: 603 PG and 581 PJ. The RD in the fixed model of clinically relevant POPFs suggested that PG was superior to PJ (RD -0.07; 95% CI: -0.11 to -0.03) with an NNT of 14. In a random model, PG was no more superior to PJ (RD -0.06; 95% CI: -0.15 to 0.01) with a possibility of harm in some cases (NNH=100). Meta-regression suggested that the increase in the proportion of a “soft pancreas” in the PG arm corresponded to a more positive value of RD (β=-0.47±0.19; P value: 0.045±0.003).

Conclusions. A PG is not superior to PJ in the prevention of clinically relevant POPF. A soft pancreatic remnant represents the main factor limiting the efficacy of PG and PJ anastomoses.

Factors associated with delayed discharge in patients undergoing pancreatic surgery within an enhanced recovery pathway
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Context. The use of standardized discharge criteria is advocated as it may prevent hospital readmission due to premature discharge and decrease medically unnec-
necessary hospital stays. However, patient discharge may also be influenced by patient factors, regional trends and availability of post-discharge support.

Objective. To determine factors associated with delayed patient discharge within a well-established enhanced recovery pathway (ERP).

Methods. Prospectively collected data for 284 consecutive patients after pancreatic resection were reviewed. Time to readiness for discharge (TRD) was defined as the number of postoperative days needed to reach standardized discharge criteria (tolerance of oral intake, recovery of GI function, adequate pain control with oral analgesia, ability to mobilize and self-care, no evidence of complications or untreated medical problems). Delayed discharge was defined as spending 2 or more extra postoperative days in the hospital after reaching TRD.

Results. A major resection (pancreaticoduodenectomy or total pancreatectomy) was performed in 187(66%) patients. Median TRD was 7(IQR 6-11), and length of stay was 9(IQR 7-12) days. 112(39%) patients were discharged 2 or more days after reaching TRD. Delayed discharge patients were older (median age 68 vs. 62, p=0.007), more likely to be females (61 vs. 45%, p=0.009), have a cardiovascular disease (15 vs. 4%, p=0.001), and have undergone a major resection (78 vs. 59%, p=0.001). Delayed discharge patients had lower adherence to ERP elements (mean 73 vs. 77%, p=0.008). Occurrence of clinically relevant pancreatic fistula (CR-PF) was higher in delayed discharge patients (20 vs. 11%, p=0.018), while there was no difference in overall complications (62 vs. 59%, p=ns), and readmissions (9 vs. 11%, p=ns). Multivariate analysis found female gender (RR 1.61, p=0.002), cardiovascular disease (RR 1.52, p=0.020), major pancreatic resection (RR 1.99, p=0.001), and occurrence of postoperative CR-PF (1.78, p=0.001) independently associated with increased chance of delayed discharge, while early postoperative mobilization was a protective factor (RR 0.62, p=0.007).

Conclusions. Despite the use of discharge criteria, delay in hospital discharge is quite common. Patients at risk for delayed discharge should be identified and counselled early during postoperative recovery to limit unnecessary hospital stay.

A subset of CD4+CD8α- Cytotoxic T cells is expanded in patients with IgG4-Related type 1 autoimmune pancreatitis and decreases with glucocorticoid treatment

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Context. Type 1 autoimmune pancreatitis (AIP) represents the most frequent manifestation of IgG4 Related Disease (IgG4-RD), a systemic fibro-inflammatory condition that promptly responds to glucocorticoids. A population of effector memory CD4+ T cells (Tem) expressing SLAMF7 known as ‘CD4+ cytotoxic T cells’ (CTCs) has been recently implicated in the pathogenesis of IgG4-RD-AIP but the effects of glucocorticoids on CD4+CTCs remain unknown.

Objective. To describe the impact of glucocorticoids on CD4+CTCs in patients with IgG4-RD-AIP.

Methods. Eighteen patients with biopsy proven active untreated IgG4-RD were studied at baseline and after 6 months of prednisone. IgG4-RD activity was assessed by means of the IgG4-RD responder index (RI). Flow cytometry on peripheral blood was performed to analyse circulating Tem cells and CD4+CTls subpopulations. CD4+CTls have been further analysed for their CD8α expression. Eighteen healthy age- and sex-matched subjects were used as controls (HC).

Results. Twelve patients of our cohort (66% of cases) had IgG4-RD-AIP. Tem cells were not expanded in patients compared to HC. CD8α- but not CD8α+ SLAMF7+CD4+CTls were expanded in patients with active untreated IgG4-RD compared to HC (p=0.0008 and p=0.05, respectively). After 6 months of therapy with prednisone 15 patients achieved complete remission and 3 patients partial remission. In all patients only the CD8α- population of CD4+CTls decreased together with clinical improvement but no significant changes in TRD. CD8α+CD4+CTls and total Tem cells were not affected by glucocorticoid therapy.

Conclusions. A subset of CD8α-CD4+CTls is specifically expanded in patients with IgG4-RD-AIP and selectively decreases following therapy with corticosteroids. CD8α-CD4+CTls represents a potentially novel T cell population implicated in IgG4-RD-AIP pathogenesis.

Prospective study was to re-evaluate a series of patients with chronic pancreatitis. In the literature there are no studies analysing the exocrine pancreatic function over time. The fecal elastase test is a good test procedure to evaluate the exocrine pancreatic function The objective of the retrospective study was to re-evaluate a series of patients with chronic pancreatitis with the aim to evaluate the pancreatic exocrine function over time, in particular, by comparing the exocrine pancreatic function in subgroups of patients with different types chronic pancreatitis

Methods. Pancreatic exocrine function was evaluated through fecal elastase in 143 patients with at least 2 values each (classified into normal, mild and severe exocrine pancreatic insufficiency), the first one taken at the diagnosis of chronic pancreatitis. Patients undergoing surgical pancreatic resection before the second value of fecal elastase were excluded. Etiology was classified into biliary pancreatitis/sequelae of necrotizing pancreatitis.
Acute pancreatitis in patients with IPMNs: retrospective study of 346 patients observed from 2009 to 2016

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Background. In literature the frequency of acute pancreatitis (AP) in patients with IPMNs varies between 12 and 65%, but most of studies are from surgical series and often pancreatitis occurred after surgery was included. Furthermore, most of the studies includes in the diction of “symptomatic IPMNs” the presence of less severe disorders, such dyspeptic symptoms, making series unclear. The aim of this study was to investigate the correlation between the presence of IPMN and acute pancreatitis to determine the frequency, evaluate the different characteristics from asymptomatic IPMNs patients, evaluate the possible differences between type and localization of IPMNs in occurrence of acute pancreatitis and his disease severity.

Methods. A retrospective analysis was performed on all observed patients with IPMN-MD, IPMN-BD and mixed type at Gastroenterology Unit in the period between January 2009 and March 2016. In the study patients with an instrumental or histological diagnosis of IPMNs were included.

Results. We studied 346 patients (164 males and 182 females, mean age at the first report 61.6±12.2 years). At the time of radiological diagnosis, 45% were asymptomatic, 51% had had symptoms, while 4% of the data to be missing: the frequency of AP (excluding biliary etiology) of all 346 patients with IPMN was 26%. AP was edematous in 85% of patients and necrotic in 15%. We found increased frequency in patients with PA with IPMN of the main pancreatic duct (MD and mixed), and unifocal type. The localization to the body seems to be more correlated with the presence of AP. The number of cysts (for IPMN-BD and mixed type) was significantly lower in patients who have had AP.

Conclusions. Our medical extraction series confirms that the PA is an event that occurs in 26% of patients with IPMNs, with a prevalence of the male sex, it is associated with a IPMN central and mixed type, predominantly localized to the body. The pancreatitis is not associated with malignancy in resected patients.

“Painless” chronic pancreatitis: epidemiological, clinical and radiological characterization

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Background. The “painless” chronic pancreatitis (CP) represents a specific subset of CP characterized by the lack of pancreatic pain. So far, scarcity of data has been reported in the literature about this matter. Aim of the present study is to characterize “painless” CP form the epidemiologic, clinical, radiological, functional, and follow-up standpoint, through a comparison with other forms of chronic pancreatitis presenting with pancreatic pain.

Methods. The Institutional Database of the Gastroenterology Unit of the Verona University was queried, and all chronic pancreatitis cases were retrieved. Patients were clustered based on the presence of “pancreatic-specific pain” into “painless” and “pain-associated” CP. A retrospective case-control analysis was carried out.

Results. Of 678 patients included from March 2006 to March 2016, 436 were considered eligible for the present study. Of these, 368 (84%) were affected by pain-associated CP, while 68 (16%) had “painless” CP. “Painless” patients were older (median age of 58.5±10.8 y/o vs. 42.5±15.3 y/o; P<0.001), less frequently presenting with a history of alcohol consumption (35% vs. 55%; P<0.001), more frequently diabetics (18% vs. 1%; P<0.001), presenting with steatorrhea (16% vs. 2%; P<0.001), and asymptomatic (63% vs. 2%; P<0.001) compared to pain-associated controls. From the radiological standpoint, painless cases were more likely presenting with calcifications at imaging than controls (90% vs. 68%; P<0.001). Moreover, in most of painless cases, the CP cause remained unknown (56%). After a median follow-up of 2.6±2.3 years, the incidence of diabetes was higher in the painless cases than in controls (48% vs. 30%; P<0.006).

Conclusions. The present study represents the first definition of painless CP so far reported in the literature. The painless CP is a distinct entity from the epidemiologic, clinical, and radiological standpoint when compared to other forms of CP characterized by the presence of pancreas-specific pain.

Systematic review and meta-analysis of prognostic role of splenic vessels infiltration in resectable pancreatic cancer

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Context. Identification of factors associated with dismal survival after surgery in resectable pancreatic ductal adenocarcinoma is important to select patients for neoadjuvant treatment.

Objective. To compare the results of pancreatic resection with and without splenic vessels infiltration for resectable pancreatic adenocarcinoma.

Methods. A systematic search was performed of PubMed, Embase and the Cochrane Library in accordance with PRISMA guidelines. The inclusion criteria were studies including patients who underwent distal pancreatectomy for resectable pancreatic cancer with or without splenic vessels infiltration. 5-year Overall Survival (OS) was the primary outcome.

Results. Six articles with 423 patients were analyzed. Overall survival data regarding the preoperative evidence of splenic vessels infiltration in a cohort of patients who underwent neoadjuvant treatment, while the remaining five studies gave only pathological data. Patients with radiological or pathological splenic artery invasion had a worse survival compared with those without infiltration (5-year OS: 7 vs. 30.6%; RR 1.31, 95% CI 1.08 to 1.58; participants=423; P<0.005). A similar result was found when considering only studies with pathological infiltration of the splenic artery (5-year OS: 2.1 vs. 21.3%; RR 1.21, 95% CI 1.12 to 1.30; participants=340; P<0.0001). In the four studies showing data on pathological splenic vessels infiltration, survival was significantly poorer when splenic vein infiltration was present (5-year OS: 6.3 vs. 20%; RR 1.29, 95% CI 1.12 to 1.30; participants=340; P<0.0001).

Conclusions. Survival for patients with splenic vessels infiltration undergoing distal pancreatectomy for resectable pancreatic cancer appears to be worse. Splenic vessels infiltration may be the stigmata of a more aggressive disease and may be the target of neoadjuvant treatment.

Higher number of known pancreatic cancer mutations highlighted by whole-transcriptome and whole-exome sequencing predicts clinical outcome in early stage patients

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Context. TNM classification recently suggested to divide PanNEC-G5 (pancreatic neuroendocrine carcinoma) N+ between N1 (1 to 3 positive lymph nodes (PLN)) and N2 (more than 3 PLN). The role of the number of PLN in predicting recurrence is unclear.

Objective. Aim of the study was to evaluate the effect of the number of PLN on prognosis after pancreaticoduodenectomy (PD) for PanNET G1-G2 (pancreatic neuroendocrine tumors).

Methods. Retrospective analysis of all consecutive radical PDs performed for sporadic nonfunctioning PanNET. Univariate and multivariate analyses of disease free survival (DFS) were performed.

Results. 157 patients were included. The median number of examined lymph nodes (ELN) was 18. Fifty-eight patients (37%) had N0 PanNET whereas 99 patients (63%) had lymph node involvement (N+). Patients with a N+ PanNET had a significantly higher frequency of T3-T4 tumors, perineural and microvascular infiltration. Median Ki67 values and ELN were significantly higher in patients with N+ PanNET. Thirty patients (39%) had a recurrence and 17 (11%) eventually died of disease.
Patients with N0 PanNET had a 3-year DFS rate of 89% compared with 85% and 75% in patients with N1 PanNET and N2 PanNET, respectively. Independent predictors of DFS were the presence of necrosis (HR 4.077, P<0.0001) and nodal status (N1, HR 3.246, P<0.005; N2, HR 9.934, P<0.0001). Factors positively correlated with DFS included a N-stage that distinguishes also between N1 (1 to 3 PLN) and N2 (more than 3 PLN) tumors. Thirteen ELN seems to be the minimum number of LN to be resected/examined in patients who undergo PD for PanNET.

Conclusions. The number of PLN is accurate in predicting recurrence for PanNET. TNM staging systems should include a N-stage that distinguishes also between N1 and N2 PanNET, respectively. Independent predictors of DFS were the presence of necrosis (HR 4.407, P<0.0001) and nodal status (N1, HR 3.246, P<0.005; N2, HR 9.934, P<0.0001). Factors positively correlated with DFS included the Ki67 value, T stage, and number of ELN. Similar percentage of N0 and N+ PanNET was demonstrated for a cut-off of 13 ELN.

Randomized Phase 2 trial of NAB-Paclitaxel plus Gemcitabine, ± Capecitabine, Cisplatin (Paxg Regimen) in unresectable or borderli ne resectable pancreatic adenocarcinoma

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Background. A phase 1b trial defined the recommended phase 2 dose of nab-paclitaxel (150 mg/m²) in combination with cisplatin, capecitabine, and gemcitabine (30, 800, and 1250 mg/m² every 2 weeks, respectively; PAXG regimen). A randomized phase 2 trial of PAXG or nab-paclitaxel-gemcitabine (AG) was performed (NCT01730222).

Methods. Chemo-naive patients with 18-75 years, pathologic diagnosis of unresectable or borderline resectable pancreatic adenocarcinoma (NCCN definition), Karnofsky Performance Status ≥ 70 were eligible for the study. The primary endpoint was resectability rate. According to A’ Hern design (p0=5%; p1=20%; α=0.05; power = 80%), the total number of patients to enrol in each arm was 27. With ≥ 4 of 27 eligible patients resected, each regimen will be considered active.

Results. Between Apr 2014 and Feb 2016, 54 patients (table 1) were randomized at a single Institution to receive PAXG (arm A; N=26) or AG (arm B; N=28). Resection after 4-6 cycles of chemotherapy was performed only in initially borderline resectable patients (8 arm A; 8 R0; 5 N0; 9 arm B; 9 R0; 2 N0). Main grade 3/4 toxicity was (A/B): neutropenia 76/57%; thrombocytopenia 5/9%; fatigue 10/26%; neuropathy 0/22%; diarrhea 5/13%; nausea 5/13%. A partial response was observed in (A/B): 50/36% and stable disease in 50/57% patients. CA19.9 decreased by > 49% in 91/90% (P<0.001) of patients with elevated basal value. Progression was observed in 21 arm A and 24 arm B patients. PFS-6 was 96%/68%, PFS-12 62%/59%, median PFS 9.3 months, in arm A and B respectively. 14 arm A and 19 arm B patients died. Median OS was 19.6+ versus 17.1+ with an 18-months survival rate of 69% and 54%, respectively.

Conclusions. Both AG and PAXG regimens reached the primary endpoint. Results suggest that the addition of cisplatin and capecitabine to AG backbone is feasible and seems to improve the outcome. The PAXG regimen warrant further exploration in this setting of patients.

Randomized Phase 2 trial of NAB-Paclitaxel plus Gemcitabine, ± Capecitabine, Cisplatin (Paxg Regimen) in metastatic pancreatic adenocarcinoma

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Background. The recommended phase 2 dose of nab-paclitaxel (150 mg/m²) in combination with cisplatin, capecitabine, and gemcitabine (30, 800, and 1250 mg/m² every 2 weeks, respectively; PAXG regimen) was 17.1+ with an 18-months survival rate of 69% and 54%, respectively.

Conclusions. Both AG and PAXG regimens reached the primary endpoint. Results suggest that the addition of cisplatin and capecitabine to AG backbone is feasible and seems to improve the outcome. The PAXG regimen warrant further exploration in this setting of patients.

Table 1—Patients’ characteristics.

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>PAXG</th>
<th>AG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Male/female</td>
<td>13/13</td>
<td>7/21</td>
</tr>
<tr>
<td>KPS 90-100</td>
<td>19 (73%)</td>
<td>24 (86%)</td>
</tr>
<tr>
<td>70-80</td>
<td>7 (27%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Age median</td>
<td>60</td>
<td>66</td>
</tr>
<tr>
<td>range</td>
<td>35-75</td>
<td>50-75</td>
</tr>
<tr>
<td>Unresectable</td>
<td>16 (62%)</td>
<td>13 (48%)</td>
</tr>
<tr>
<td>Borderline</td>
<td>10 (38%)</td>
<td>15 (54%)</td>
</tr>
<tr>
<td>Head</td>
<td>18 (69%)</td>
<td>20 (71%)</td>
</tr>
<tr>
<td>Biliary stent</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>CA19.9 &gt;ULN median</td>
<td>22 (85%)</td>
<td>21 (75%)</td>
</tr>
</tbody>
</table>

Randomized Phase 2 trial of NAB-Paclitaxel plus Gemcitabine, ± Capecitabine, Cisplatin (Paxg Regimen) in metastatic pancreatic adenocarcinoma

Between Apr 2014 and June 2016, 83 patients (table 1) were randomized at a single Institution to receive PAXG (arm A; N=26) or AG (arm B; N=28). Resection after 4-6 cycles of chemotherapy was performed only in initially borderline resectable patients (8 arm A; 8 R0; 5 N0; 9 arm B; 9 R0; 2 N0). Main grade 3/4 toxicity was (A/B): neutropenia 76/57%; thrombocytopenia 5/9%; fatigue 10/26%; neuropathy 0/22%; diarrhea 5/13%; nausea 5/13%. A partial response was observed in (A/B): 50/36% and stable disease in 50/57% patients. CA19.9 decreased by > 49% in 91/90% (P<0.001) of patients with elevated basal value. Progression was observed in 21 arm A and 24 arm B patients. PFS-6 was 96%/68%, PFS-12 62%/59%, median PFS 9.3 months, in arm A and B respectively. 14 arm A and 19 arm B patients died. Median OS was 19.6+ versus 17.1+ with an 18-months survival rate of 69% and 54%, respectively.

Conclusions. Both AG and PAXG regimens reached the primary endpoint. Results suggest that the addition of cisplatin and capecitabine to AG backbone is feasible and seems to improve the outcome. The PAXG regimen warrant further exploration in this setting of patients.
tion to receive PAXG (arm A; N=42) or AG (arm B; N=41). PFS6 was 31/42 (74%), and 24/41 (59%), respectively. PFS at 1 year and median PFS was 26% and 8.1 months for arm A and 7% and 6.8 months for arm B. One-year survival was 64% and 42%, 18-months survival was 40% and 22%, median survival was 14.8 and 11.1 months, respectively. PAXG regimen did not increase grade 3-4 extra-hematological toxicity as compared to AG.

Conclusions. The results show that addition of cisplatin and capecitabine to the AG backbone is feasible and linked with improved disease control. The PAXG regimen warrants further exploration in this setting of patients.

Duodenaljejunal or gastroenteric leakage after pancreatic resection: a case control study
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Background. The duodeno-jejunal (DJ) or gastro-jejunal (GJ) anastomosis leakage represents a rare but life-threatening complication after either pancreaticoduodenectomy (PD) or total pancreatectomy.

Objective. To assess the incidence, clinical presentation, risk factors and management of the DJ or GJ leak after either PD or TP.

Methods. Prospectively collected perioperative data were reviewed, and a case-control study was performed. Patients who presented either DJ or GJ leak (cases) were matched in a 1:5 ratio with patients who did not develop it, with the following variables: age, type of disease, type of resection (PD or TP), type of anastomosis (DJ or GJ). Continuous variables were compared by student’s T-test or Mann-Whitney U test, while categorical variables were compared using Fisher’s exact test.

Results. From January 2010, 804 pancreatic resections (674 PD, 130 TP) were performed. A total of 13 cases (1.6%) were observed (11 after PD, 2 after TP), and compared to 61 controls. Median post-operative day of gastroenteric leaks diagnosis was 10 (IQR 9-16). In 12 cases it was managed through relaparotomy. Compared to controls, the cases group had significantly lower preoperative serum haemoglobin (median 11.9 vs. 13.0±1.7 g/dl p=0.018) and increased preoperative radiotherapy (23% vs. 3% p=0.035). Cases also had more complex operations with longer duration (median 360, IQR 315-408 vs. 316, IQR 286-349 min p=0.036), and increased intraoperative blood loss (median 600, IQR 500-700 vs. 400, IQR 250-500 ml p=0.002). The fistula group was more frequently associated with other severe postoperative complications such as clinically relevant pancreatic fistula (45% vs. 8% p=0.006), bile leakage (46% vs. 15% p=0.019), post-operative haemorrhage (54% vs. 15% p=0.005). Length of hospital stay and mortality at 90 days were higher in the cases group (respectably median 40 IQR 29-61 vs. median 10 IQR 7-18, p<0.001 - 25% vs. 3% p=0.035).

Conclusions. DJ or GJ leakage after pancreatic resection is an uncommon and severe complication associated with high mortality. This unusual complication is related to multiple pre and postoperative variables with a high correlation to an impairment perfusion of splanchic circulation, considering the significantly relation to other anastomosis dehiscence. Clinically a high suspicion of DJ or GJ fistula could be the presence of relevant pancreatic fistula and postoperative haemorrhage. Surgery is almost always mandatory.

Prognostic role of the parenchymal frozen transection margin during pancreaticoduodenectomy PD for ductal pancreatic adenocarcinoma
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Context. During pancreatic resection for ductal adenocarcinoma (PDAC) an intra-operative frozen section analysis of the transection margin is usually performed to achieve an R0 resection. An extension of the resection is required for positive margins until a total pancreatectomy (TP). However, it is unclear whether an extended resection up to TP leads to a survival advantage.

Objective. To evaluate disease-specific (DS) and disease-free survival (DFS) in patients who underwent TP for PDAC compared to standard or extended pancreaticoduodenectomy (PD).

Materials and methods. Patients with head PDAC were divided into three groups per type of resection: standard PD (SPD), extended PD (EPD) or TP because of positive transection margin(s). Patients with IPMN associated PDAC were excluded. Survival analysis as well as evaluation of pathological data and postop morbidity/mortality were performed.

Results. Between 2009 and 2016, 313 patients underwent SPD, 22 EPD group and in 36 TP was performed because of repeated positive margins. The three groups were homogenous for age, sex, BMI, ASA score and intra-operative variables. No differences were observed among the three groups regarding N+
rate, number of positive nodes and lymph node-ratio, perineural and microvascular invasion. In the TP group a statistically significant increase in perioperative mortality (O.R. 2.1, IC95% 0.03-0.5, p=0.04) was observed. Moreover, in TP group the rate of R1 resections was significantly higher than in SPD and EPD groups (χ²: 4.52, p=0.033). Compared to SPD and EPD patients, those who underwent TP had a significant decrease of DFS (median: 11 months in TP, 12 in EPD and 20 in SPD, p=0.002) and DSS (median: 16 months in TP, 17 in EPD and 27 in SPD, p=0.001).

Conclusions. In patients with head PDAC, TP performed to achieve a negative pancreatic resection margin is still associated with a significant rate of R1 resection (retroperitoneal margin), with higher postoperative mortality and worse both DFS and DSS, when compared to SPD or EPD. Therefore, in this setting, once after PD the transection margin is positive TP does not seem useful.

Robotic assisted versus open left pancreatectomy for cystic tumors
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1 General Surgery, University of Pisa, Pisa, Italy; 2Surgical Pathology, University of Pisa, Pisa, Italy; 3Gastrointestinal Unit, University of Pisa, Pisa, Italy; 4EndoCAS (Center for Computer Assisted Surgery), University of Pisa, Pisa, Italy

Context. Cystic pancreatic lesions are increasingly found incidentally. Their management may be difficult because often the distinction within this heterogeneous group of pathologies may not be possible despite intensive investigations.

Objective. To compare the robotic assisted surgical (RAS) approach with the open surgery (OS) in the surgical management of cystic lesions of the pancreas, with a view to documenting benefit from the more expensive robotic approach.

Methods. From April 2010 to April 2017 37 robotic-assisted left sided pancreatectomy (LSP) for lesion of the body/tail of the pancreas were performed, of which 27 were patients who had cystic tumours (RAS-group). Baseline features, surgical outcomes and histopathological examination were compared retrospectively with a group of 27 patients treated with open surgery from May 2005 to April 2010, selected from the institutional prospectively collected database (OS-Group).

Results. The spleen-preserving rate was significantly higher in the RAS group (63% vs. 33.3% in the OS-Group, p=0.05). No difference in the post-operative pancreatic fistula and morbidity was found between the two groups. The median postoperative length of hospital stay was significantly shorter in the RAS-group: 8 days (range 3-25) vs. 12 days (range 7-26) in the OS-Group (p=0.01). No conversion to open approach was reported in the RAS-group.

Conclusions. The robot-assisted LSP is a safe and effective procedure. The robotic approach significantly increases the spleen preservation rate and reduces the post-operative hospital stay. By reducing the trauma of access, it results in a smoother post-operative course and faster recovery particularly important in patients harbouring cystic pancreatic tumors, in increasing their acceptance for surgery when recommended. Prospective studies are necessary to validate the clinical benefits of robotic approach for LSP.

Oncological safety of duodenopancreatectomy without vascular resection for Ishikawa type B adenocarcinoma
Simone Guadagni, Desirée Gianardi, Gregorio Di Franco, Matteo Palmeri, Niccola Funel, Matteo Bianchini, Dario Gambaccini, Niccola Funel, Luca Pollina, Santino Marchi, Giulio Di Candio, Franco Mosca, Luca Morelli
University of Pisa, Pisa, Italy

Context. Although venous resection in pancreatic head adenocarcinoma (PHA) is widely used method, several data about its safety and survival benefit showed conflicting results.

Objective. To investigate the impact on local/distant recurrence and on patients survival of Intraoperative Ultrasound (IU) guided conservative approach on a selected group of patients with Ishikawa type B carcinoma in which we separate the neoplasia from the portal- mesenteric axis (PMA) without performing primary vascular resection (VR).

Methods. Retrospective data of patients underwent duodenopancreatectomy (DP) for PHA between 2008 and 2016 were reviewed. After preoperative CT, patients were grouped in 5 types based on relationship of the tumour to PMA, according to Ishikawa classification. We identified an Ishikawa type B (contact tumour/PMA with smooth shift without narrowing) group in which, after checking feasibility with IU, we preserved the vein without macroscopic residual, no vascular resection(nvrDP) group, and compared it with Ishikawa type A standard DP (sDP) group.

Results. 136 DP were performed for PHA, 116 without VR and 20 with VR. NvrDP group consisted in 34 (25%) cases whereas sDP group in82 (60%). Isolated local recurrence rate was not superior in nvrDP group (12.5% vs. 18.9% p=0.56), as well as we didn’t find differences in systemic progression (38.5% in nvrDP group vs. 44.3% in sDP group p=0.38) or local plus synchronous systemic disease rate (4.9% in sDP group vs. 11.5% in nvrDP p=0.26) at Chi-squared test. Into the nvrDP group isolated local recurrence occurred only in 13% vs. 87% of cases in which distant metastatic spread was found. There were no differences in overall survival rate (1-year: 61% in sDP vs. 53% in nvrDP; 3-year: 22% vs. 18%; 5-years: 14% vs. 17% p=0.9).

Conclusions. PD without VR could be considered a safe and oncologically acceptable approach in pre-operative Ishikawa type B PHA, without significant influence on oncologic outcomes respect to sDP. Poor prognosis of PHA is more related to the aggressive biology and systemic spread of the tumor, rather than the local control.
**Context.** The treatment of pancreatic stump is a critical step of pancreaticoduodenectomy (PD) because leaks from this anastomosis incur major morbidity and mortality. There is still no universally accepted technique for pancreaticojejunalostomy (Pj).

**Objective.** To describe technical details of our modified - double layer - invagination Pj (mPj) technique and report on its safety.

**Methods.** From October 2008 to June 2017, 424 pancreatic resections were performed, of which 203 were PD. A modified personal invagination pancreaticojejunalostomy (mPj) was introduced in November 2010 and used in 100 consecutive patients. Data were retrieved from a prospectively collected Institutional database, and used for present retrospective evaluation of the mPj. Postoperative pancreatic fistulas (POPF) were stratified with the Fistula Risk Score (FRS). This was based on 2005-International Study Group of Pancreatic Fistula classification (ISGPFc) and on 2016-revised International Study Group in Pancreatic Surgery classification (ISGPSc).

**Results.** ISGPFc POPF occurred in 17/100 (17%); grade A in 10/100 (10%), grade B in 6/100 (6%) and grade C in 1/100 (1%). On the ISGPFc, POPF rate averaged 7%: grade B in 6/100 (6%) and grade C in 1/100 (1%). POPF rate associated with high FRS was 18.9%/6.2% (ISGPFc/ISGPSc). With low and intermediate FRS, POPF rates were 5.3%/0% (ISGPFc/ISGPSc) and 21.3%/9.8% (ISGPFc/ISGPSc) respectively. Reoperation rate was 3% (3/100). In-hospital mortality rate was 2% (2/100) and specific mortality rate for POPF was 1% (1/100).

**Conclusions.** The mPj technique is associated with a POPF rate which was less than expected, especially for “difficult” pancreas with high FRS (soft gland texture and small duct). A larger prospective series is needed in addition to comparative studies with other techniques for robust assessment.

**Is there a role for palliative primary resection for pancreatic neuroendocrine neoplasms with liver metastases? A systematic review**

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**Context.** Pancreatic Neuroendocrine Neoplasms (PanNEN) are often associated with unresectable liver metastases (LM). The role of palliative PanNEN resection (pPanNEN-R2) is still controversial.

**Objective.** This study was designed as a meta-analysis of studies which allow a comparison of pPanNEN-R2 and non-surgical management (PanNEN-nR).

**Methods.** All published studies until 2017 allowing for the comparison of pPanNEN-R2 and PanNEN-nR were reviewed. Studies were required to make an objective evaluation of 5-year overall survival (OS). Secondary outcomes measures included postoperative morbidity, reoperation, readmission, length of hospital stay (LOS), and quality of life (QoL). OS outcomes were compared using weighted mean differences and risk ratios (RR).

**Results.** Six studies were included. There were 5 retrospective studies and only one prospective. A total of 849 patients were included in the analysis, of whom 234 (27%) underwent pPanNEN-R2 and 615 (73%) underwent PanNEN-nR. Overall quality of included studies was fair. OS was significantly longer in patients underwnt palliative resection compared to those patients who underwent non-surgical treatment (RR 0.63, 95% CI [0.50 to 0.74]; participants = 851; studies = 7; T2 = 10%). Data on postoperative morbidity, reoperation, readmission, LOS, and QoL were not properly reported and meta-analysis was not allowed.

**Conclusions.** Despite the limitations of this meta-analysis, pPanNEN-R2 in patients with unresectable LM is associated with a better survival compared to non-surgical management.

**Surgical and oncological outcomes of neoadjuvant peptide receptor radionuclide therapy for resectable or potentially resectable pancreatic neuroendocrine neoplasms**

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**Context.** PRRT is a valid therapeutic option for pancreatic neuroendocrine neoplasms PanNENs.

**Objective.** To evaluate the impact of neoadjuvant peptide receptor radionuclide therapy (PRRT) on perioperative and long-term outcomes of resectable or potentially resectable pancreatic neuroendocrine neoplasms (PanNENs).

**Methods.** The postoperative outcomes of 23 patients with resectable or potentially resectable PanNENs at high risk of recurrence who underwent neoadjuvant PRRT (neoadjuvant group) were compared with 23 patients who underwent upfront surgery (upfront surgery group). Patients were matched for tumor size, tumor grading, tumor staging, and resection margins.

**Results.** Median primary PanNENs size significantly decreased after neoadjuvant PRRT (59 mm versus 50 mm, P=0.047). There were no differences in terms of all intraoperative and postoperative outcomes, but the risk of developing pancreatic fistula (PF) that was higher in the upfront surgery group (n=5;17%) compared to the neoadjuvant group (n=2; 9.1%). Overall postoperative mortality rate was nil. Incidence of nodal metastases was
significantly higher in the upfront surgery group (n=17, 74%) compared with the neoadjuvant group (n=9, 39%, P=0.017). In the entire population median progression-free survival (PFS) from diagnosis was similar in two groups (P=0.242). Among 31 patients (67%) who underwent curative R0 resection, PFS was significantly longer in the neoadjuvant group compared to upfront surgery group (P=0.042).

Conclusions. Neoadjuvant PRRT for resectable of potentially resectable PanNENs in patients with high-risk features of recurrence is safe and associated with a lower risk of postoperative PF and nodal metastases leading to a longer PFS when radical resection is achieved.

Pancreatic resections for nothing: is it possible to avoid them?
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Context. Despite the progresses of imaging unexpected benign diseases occur in 5-10% of PD for presumed malignancy, especially in the peripancreatic area and almost 2% of DP for presumed NET are performed for accessory spleen.

Objective. The aim is to analyze the rate of benign pathology in resections for presumed malignancy or pNETs and discuss pitfalls in the diagnostic workup.

Methods. All patients resected for presumed malignancy from January 2009 to February 2017 are included. Clinical presentation, imaging, pathology and outcome are reported. All the unexpected benign diseases have been reconsidered in a multidisciplinary setting.

Results. In the study period we collected 865 pancreatic resections, 14 (1.6%) of which for unforeseen benign disease: 8 PD, 5 DP, 1 middle pancreatocystic (MP). Post-operative complications occurred 13 (9.5%). A clinical relevant POPF rate was 28% (n=4). Mortality rate was 14% (n=2). Clinical presentation includes jaundice (n=5), abdominal pain (n=6), weight loss (n=2) and acute pancreatitis (n=1). Symptoms started at least 4 months before surgery in 4 patients. Five were asymptomatic. Ca 19.9 was abnormal in 4 (28%). Preoperative pathological biopsy was performed in 10 (71.4%): 1 positive for malignancy, 9 with inflammatory/benign findings. At the imaging 7 (87%) head lesions showed suspicious stenoses on biliary tract, 5 of which with associated a dilatation of main pancreatic duct (> 4 mm). Gallium 68 PET/CT scan was positive in 2 of 4 patients with suspected pNET of the tail of pancreas. Six (43%) didn’t presented with a discrete mass. On final pathology, the most common report was chronic inflammatory ampullary fibrosis in cases suspected for periampullary/bile duct cancer.

Conclusions. Diseases of peripancreatic area are the most challenging to manage. Accurate imaging is mandatory in case of long duration of symptoms or absence of clear solid mass. Benign strictures of distal bile duct are common and should be considered as an alternative diagnosis. Pathology could obfuscate the diagnosis but must be considered in case of uncommon clinic presentation. Short follow-up could represent an alternative to up-front resections in unclear findings.

Adjuvant chemotherapy after surgery for intraductal papillary mucinous neoplasms of the pancreas: promising observational data call for controlled studies
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Context and Objective. Little is known about the role of adjuvant treatment after surgery for malignant Intraductal Papillary Mucinous Neoplasms (IPMNs). The aim of this study is to assess the potential role of adjuvant chemotherapy in terms of improvement of survival.

Methods. Retrospective evaluation of all patients with resected IPMNs with high grade dysplasia (HGD) or invasive carcinoma (iCa) at the Department of General and Pancreatic Surgery – The Pancras Institute, University of Verona, with univariate and multivariate analysis for determinants of disease specific survival (DSS) were performed. Kaplan-Maier curves were used to compare patients treated with surgery and adjuvant therapy to those treated with surgery alone.

Results. From 467 resected IPMNs, we identified 195 patients: 110 (56%) with iCa and 85 (44%) with HGD. The median follow-up for the entire cohort was 80 months (range 5-327). As expected, none of the patients with HGD received adjuvant therapy, while 22.7% of patients with IPMN-iCa did. The most used chemotherapy regimen was Gemcitabine (72%). Overall, the median DSS for IPMN-iCa was 208 months. The median DSS of IPMN treated with adjuvant therapy was not reached, while it was 94 months for surgery alone (p<0.01). Predictors of DSS were adjuvant therapy (HR=0.42; CI=0.26-0.67; p<0.01), tubular invasive component (HR=5.79; CI=2.69-12.45; p<0.01) and pancreatobiliary epithelial type (HR=2.85; CI=1.3-7.87; p=0.03). At multivariate analysis, adjuvant therapy resulted an independent predictor of DSS (HR=0.45; CI=0.20-0.98; p=0.04). Stratifying for pathological features, at univariate analysis adjuvant therapy significantly increased the DSS in case of IPMN with iCa with negative lymph nodes and resection margins, colloid invasive component and intestinal epithelial subtype. Adjuvant therapy was independently associated with DSS only in case of tubular invasive component.

Conclusions. Adjuvant therapy following resection for IPMN with iCa is associated with improved DSS compared with surgery alone, especially in case of tubular invasive component. Future controlled trials are needed to improve the level of evidence regarding the use of adjuvant chemotherapy for resected IPMN with iCa.

Efficacy of oral chemotherapy with capecitabine and temozolomide (CapTem) in metastatic neuroendocrine tumors (NETs). A single-institution experience
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Context. CapTem chemotherapy regimen is a standard treatment for NETs but scientific data on its efficacy and tolerability are limited.

Objective. Retrospective evaluation of the results achieved at our institution in 4 yrs period with the CapTem regimen in patients (pts) with metastatic NETs.

Methods. This retrospective analysis included all pts with metastatic NETs treated with CapTem regimen in our hospital from April 2013 to April 2017. This oral chemotherapy included capecitabine 600 mg/m2/BID (capped at 1,000 mg BID total dose) on days 1-14 and temozolomide 75 mg/m2/BID on days 10-14 every 28 days according to the schedule published by Fine RL et al. (Cancer Chemother Pharmacol, 2013). Overall survival (OS), progression free survival (PFS), overall response rate (ORR) and toxicities were retrospectively evaluated.

Results. Twenty-seven pts (15 males) were included. Median age was 61 yrs (range 46-85). Primary tumor included pancreas in 8 pts (29.6%), midgut 8 pts (29.6%), lung 8 pts (28%), other NETs 3 pts (11.1%). Most of pts had well-differentiated tumors (88.8%) and ki67 was less than <20% in 59% of pts. Median number of cycles was 6 (range 2-25). Ten pts (37.0%) received CapTem as 1st line treatment, 7 pts (25.9%) as 2nd line and 10 (37.0%) as >3rd line. ORR was 33.3%; 31.2% for ki67<20% and 40.0% in ki67>20%. DCR (partial response + stable disease) for the entire cohort was 59.2%. Median PFS was 4 mos, without any differences between pancreatic, midgut and lung groups, but mPFS was 8.0 mos for pts who received CapTem as 1st line treatment. At present mOS was not reached. In term of toxicity CapTem regimen was very well tolerated and only 1 pt reported a G3 reversible toxicity (neutropenia). No G3/4 toxicity were observed.

Conclusions. Our experience confirms that CapTem regimen is effective and well tolerated. Efficacy does not seem to be related to the primary tumor or Ki67.

Role of cyst features and patients' factors in predicting the risk of progression in BD-IPMN undergoing follow-up

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Patterns of recurrence after resection for pancreatic neuroendocrine tumors: who, when and how?

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Context. Pancreatic Neuroendocrine Tumors (pNETs) represent an increasing indication for pancreatic resection. Because of their heterogeneous behavior, rarity, and usually favorable prognosis, still little is known about their postoperative recurrence.

Objective. The aim of this study is to describe the patterns and timing of recurrence after curative resection for pNETs and to provide indications for the follow-up accordingly.

Methods. From the institutional Pan-NEN database, 587 cases resected between 1990 and 2015 were extracted. Exclusion criteria were R2 resection, concomitant malignant cancer (PDAC, kidney, adrenal, MANEC) and associated genetic syndromes. Predictors of recurrence were assessed by univariate and multivariate analysis and survival analysis was conducted using Kaplan-Maier function. Time interval between surgery and recurrence was stratified for pattern of recurrence.

Results. A total of 487 cases were included, with a median follow-up of 69 months. Sixty patients (12.3%) developed disease recurrence: liver was the most frequent site of recurrence (10%), local recurrence was present in 2.2% cases, nodal in 2.1% and other organs were affected in 1.2% cases. Nodal status (HR 2.42),
Can bioimpedance vector analysis (BIVA) predict the surgical risk in cancer patients undergoing pancreatic surgery?

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Context. Bioimpedance vector analysis is a validated tool for the assessment of body composition and hydration index. Sarcopenia, sarcopenic obesity and hydremia have been associated with adverse postoperative outcomes in pancreatic surgery.

Objective. Aim of our study was to evaluate the usefulness of bioimpedance vector analysis (BIVA) in the assessment of perioperative cancer patients undergoing pancreatic resection.

Methods. We performed a multicentric prospective observational study, including consecutive adult patients undergoing pancreatic surgery. Exclusion criteria were with chronic kidney failure, ASA score > 3 and diagnosis of compartmentalized fluid collection. BIVA was measured prior to surgery and on postoperative day 1.

Results. Among 104 patients, 64 (61.5%) had any-grade postoperative complications and 10 (9.7%) experienced major morbidity. The preoperative value of the standardized phase angle (SPA) was significantly lower in patients with postoperative major complications if compared with those without (-0.60±1.13 vs. -0.50±1.64, p=0.043). The predictive ability of SPA was investigated by ROC-curves (AUC=0.728) and the optimal cut-point value was assessed at -0.55.

Quantitative measurement of 18F-FDG PET/CT uptake reflects the expansion of circulating plasmablasts in IgG4-related type 1 autoimmune pancreatitis and other organs

Alvise Berti, Emanuel Della Torre, Francesca Gallivannone, Carla Canevari, Raffaella Milano, Marco Lanzillotta, Emanuele Bozzalla, Enrica Bozzolo, Paolo Giorgio Ardiconato, Gianpaolo Balzano, Massimo Falconi, Luigi Gianolli, Lorenzo Dagna

PROCEEDINGS OF THE XLI NATIONAL AISP MEETING
Quality of life and functional outcomes after pancreatic resection for intraductal papillary mucinous neoplasms

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Context. The treatment of intraductal papillary mucinous neoplasms of the pancreas (IPMNs) is influenced by both IPMNs and patients’ characteristics. Moreover, there is a considerable risk of preoperative misdiagnosis and overtreatment in IPMNs. In this setting, surgery may be associated with impairment of pancreatic function and quality of life (QoL).

Objective. Aim of this study is to determine functional outcomes and QoL in patients who underwent pancreatic resection for IPMNs.

Methods. The SF-12 Health Survey and the General Health questionnaire were used to evaluate QoL. Clinical signs of exocrine insufficiency (EI) were recorded as for pancreolipase daily intake. Presence of diabetes, related therapy and hypoglycemic episodes were investigated.

Results. 157 patients who underwent resection for histologically confirmed IPMN, between January 2009 and January 2016, were interviewed. Of these 122 (77.7%) returned questionnaires. Median follow-up (FU) was 30 months. Iatrogenic diabetes occurred in 52 patients (42.6%) and 50 (41%) developed at least one sign of EI. QoL scores were equal compared to normative population (42.6%) and 50 (41%) developed at least one sign of EI. QoL resulted inversely correlated with age and duration of FU (P<0.001). QoL was impaired in all domains in patients with EI and higher intake of pancreolipase (P<0.001). Among partial resections, pancreaticoduodenectomy was mostly associated with EI (P<0.024). Iatrogenic diabetes determined lower scores of QoL only in physical domain, as for insulin therapy and hypoglycemic episodes (P<0.001). On univariare analysis, iatrogenic diabetes, age and FU duration were negatively associated with QoL.

Conclusions. Pancreatic surgery is associated with development of exocrine and endocrine insufficiency and this negatively impact on QoL. This outlook should lead to careful and proper surgical indications, especially in elderly patients with possible benign disease.

Methotrexate as induction of remission therapy for IgG4-Related type 1 Autoimmune Pancreatitis

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Context. Medium to high dose glucocorticoids represent the treatment of choice for inducing remission in IgG4-related type 1 autoimmune pancreatitis (IgG4RD-AIP). However, in clinical settings where long-term corticosteroids treatment is contraindicated (e.g. diabetes and osteoporosis), the use of alternative equally effective drugs would be recommendable.

Objective. To assess the efficacy of methotrexate (MTX) as induction of remission therapy in selected cases of mild IgG4RD-AIP complicated by clinical scenarios that might advise against the use of corticosteroids.

Methods. Three patients with active untreated IgG4RD-AIP were started on oral or subcutaneous MTX. Efficacy of MTX in inducing remission was assessed at 6 months by 18F-FDG PET/CT scan, IgG4 RD Responder Index (RI), serum IgG4 levels and circulating plasmablasts (PBs).

Results. All included patients presented with exocrine pancreatic insufficiency; none had obstructive jaundice; all had overt diabetes. Baseline and post-treatment characteristics are presented in Table 1. After 6 months of MTX all patients were on complete remission with decreased circulating PBs and markedly improved PET findings.

Conclusions. In some cases of IgG4RD-AIP with mild manifestations but with contraindications to glucocorticoids, MTX might represent a promising alternative strategy for inducing disease remission.

IPMN of the pancreas in younger individuals share the same risk of malignant progression than in the elderly: the role of age in the decision making

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Context. Intraductal Papillary Mucinous Neoplasms (IPMNs) of the pancreas are usually diagnosed in the sixth decade of life. Once they are detected in younger individuals, the treatment of choice is surgical. Since IPMN of the pancreas is influenced by both IPMNs and patients’ characteristics, there is a considerable risk of preoperative misdiagnosis and overtreatment in IPMNs.

Objective. To assess the efficacy of methotrexate (MTX) as induction of remission therapy in selected cases of mild IgG4RD-AIP complicated by clinical scenarios that might advise against the use of corticosteroids.

Methods. Three patients with active untreated IgG4RD-AIP were started on oral or subcutaneous MTX. Efficacy of MTX in inducing remission was assessed at 6 months by 18F-FDG PET/CT scan, IgG4 RD Responder Index (RI), serum IgG4 levels and circulating plasmablasts (PBs).

Results. All included patients presented with exocrine pancreatic insufficiency; none had obstructive jaundice; all had overt diabetes. Baseline and post-treatment characteristics are presented in Table 1. After 6 months of MTX all patients were on complete remission with decreased circulating PBs and markedly improved PET findings.

Conclusions. In some cases of IgG4RD-AIP with mild manifestations but with contraindications to glucocorticoids, MTX might represent a promising alternative strategy for inducing disease remission.

Table 1.—Methotrexate as induction of remission therapy for IgG4-Related type 1 Autoimmune Pancreatitis.

<table>
<thead>
<tr>
<th>Patient #1 (M, 78)</th>
<th>Patient #2 (M, 67)</th>
<th>Patient #3 (M, 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 AIP, aortic, submandibular gland, lymph node involvement</td>
<td>Type 1 AIP</td>
<td>Type 1 AIP, lymph node involvement</td>
</tr>
<tr>
<td>Pre-Treatment</td>
<td>6 months (MTX 20 mg/week)</td>
<td>Pre-Treatment</td>
</tr>
<tr>
<td>IgG4-RD RI</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>IgG4 (mg/dL)</td>
<td>498</td>
<td>513</td>
</tr>
<tr>
<td>PBs/mL</td>
<td>2520</td>
<td>250</td>
</tr>
<tr>
<td>18F-FDG-PET/CT</td>
<td>Increased activity in all affected organs except pancreas</td>
<td>Increased activity in submandibular glands; negative in all the other organs</td>
</tr>
</tbody>
</table>
individuals, their actual natural history has been scarcely defined.

Objective. To evaluate whether clinical features and malignant degeneration of IPMNs can be affected by patient’s age of diagnosis.

Methods. A population of 2113 progressively observed IPMNs was included in the study and categorized according to a 50-years cut-off (<50 y/o vs. >50 y/o). We compared pathological features for those patients who underwent surgery. For followed up patients we evaluated the progression to malignancy intended as the development of a new worrisome feature (WF), high risk stigmata (WF) or death due to pancreatic cancer.

Results. The overall median age at diagnosis was 66 years. Patients <50 y/o had a higher rate of abdominal pain (33.2% vs. 20.3%; p<0.01) and acute pancreatitis (21.4% vs. 9%; p<0.01) at presentation. Patients >50 y/o had more frequently multifocal IPMNs (50.2% vs. 38.6%; p<0.01) and IPMNs involving the entire duct (8.4% vs. 4%; p 0.02). HR were more common among patients >50 y/o (11.7% vs. 9.1%; p 0.04), while patients <50 y/o presented more frequently with WF (31.4% vs. 22%; p<0.01). There were no differences in terms of patients treated with surgery (14.5% vs. 14.3%, p=0.1) or follow-up (74.5% vs. 78.3%, p=0.1) comparing patients >50 and <50 y/o, respectively. At pathology, invasive IPMNs were more common in patients >50 y/o (24.1% vs. 12.5%; p 0.03). Kaplan Maier curves showed no differences in followed-up patients in terms of disease progression between the two groups, even when considering only those with more than 60 months of follow-up (15.3% developed a new HR or WF after a median time of 89 months, 1% died due to pancreatic cancer after a median time of 48 months).

Conclusions. The natural history of IPMNs does not seem to be affected by patients’ age at diagnosis. As younger individuals have more time to develop disease progression, patient’s age should be considered as key for the clinical decision making.

The prognostic value of Mural Nodules and their size in IPMN of the Pancreas: high-volumetric center experience, systematic review and meta-analysis

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Context. One of the controversial issues in the diagnosis of pNETs is the accurate prediction of their clinical behaviour.

Objective. To evaluate the role of EUS biopsy in the diagnosis and grading of pNETs.

Methods. A prospectively maintained database of EUS biopsy procedures was retrospectively reviewed to identify all consecutive patients referred to a certified ENETS center with a suspicion of pNET between June 2014 and April 2017. The cytological and/or histological specimens were stained and the Ki-67 labeling index was evaluated. In patients undergoing surgery, the grade obtained with EUS-guided biopsy was compared with the final histological grade. The grade was evaluated according to the WHO 2017 classification.

Results. The study population included 60 patients. EUS biopsy material reached an adequacy of 96.6% and was adequate for Ki-67 evaluation in 71.7% of cases. Twenty-eight patients (46.7%) underwent surgery. Of these, 20 patients had Ki-67 evaluated on EUS-biopsy: the agreement between EUS biopsy grading and surgical specimen grading was 90%.

Pancreatic neuroendocrine tumors: role of endoscopic ultrasound biopsy in a certified enets center

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1Endoscopy Unit, Division of Gastroenterology, Division of Gastroenterology; 2Humanitas University, Department of Biomedical Sciences; 3Department of Pathology; 4Pancreatic Surgery Unit; 5Division of Gastroenterology; 6Division of Oncology; 7Division of Endocrinology, Humanitas Clinical and Research Center, Rozzano, Milan, Italy

Context. Mural nodules (MNs) are predictors of malignancy in intraductal papillary mucinous neoplasms of the pancreas (IPMN). Little is known about their prognostic value and the role of size in risk assessment.

Objective. Aim of this study is assessing the accuracy of MN as a predictor of invasive cancer (iCa) or high grade dysplasia (HGD) in IPMNs and to investigate the role of MN size in risk prediction.
Table I — Concordance between endoscopic and surgical Ki-67.

<table>
<thead>
<tr>
<th>N</th>
<th>Ki-67 EU biopsy</th>
<th>Ki-67 surgery</th>
<th>Grade EU biopsy</th>
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</table>

Conclusions. EUS biopsy is an accurate method for the diagnosis and grading of pNETs based on the WHO 2017 Ki-67 labeling scheme.

Effects of glucocorticoids on B cell subpopulations in patients with IgG4-related type I autoimmune pancreatitis

Marco Lanziotitta, Emanuel Della Torre, Raffaella Milani, Enrica Bozzolo, Paolo Giorgio Arcidiacono, Gianpaolo Balzano, Stefano Crippa, Stefano Partelli, Massimo Falconi, Lorenzo Dugna
IRCCS-San Raffaele Scientific Institute, Milan, Italy

Context. Type 1 autoimmune pancreatitis (AIP) represents the most frequent manifestation of IgG4 Related Disease (IgG4RD), a systemic fibro-inflammatory condition responsive to glucocorticoids (GC). Different B cell subpopulations have been implicated in IgG4RD-AIP pathogenesis but the effects of GC on these immune cells remain unknown.

Objective. To describe the impact of GC on B cell subpopulations in patients with IgG4RD-AIP.

Methods. 50 patients with active IgG4RD were studied. Flow cytometry was performed on peripheral blood in order to identify total B cells (CD19+CD20+ and CD19+CD20+ cells), circulating plasmablasts (CD19+CD20+CD27+CD38+ cells), naïve B cells (CD19+CD20+CD27-CD38+ cells), memory B cells (CD19+CD20-CD27+CD38- cells), and circulating plasma cells (CD38+CD138+ cells). Disease activity was assessed by means of the IgG4RD responder index (IgG4RD RI). Flow cytometry was performed at baseline and after six months of immunosuppressive therapy with GC (0.6-1mg/kg/day). 20 sex and age matched healthy subjects were used as controls (HC).

Results. 28 patients (56% of our cohort) had IgG4RD-AIP. At baseline, circulating plasmablasts and plasma cells were expanded in IgG4RD patients (median 2815 and 200 cell/mL, respectively) compared to HC (p<0.05). Circulating plasma cells were not detected in HC. Total B cells and naïve B cells were reduced in IgG4RD patients compared to HC (p<0.05). No differences in memory B cells were observed (p>0.05). After six months of GC the median IgG4RD RI decreased from 9 to 2. Circulating plasmablasts, circulating plasma cells, and naïve B cells counts decreased in all patients together with disease improvement (p<0.05 compared to baseline). Total B cells and memory B cells were unaffected by GC.

Conclusions. Clinical improvement induced by GC in patients with IgG4RD and IgG4RD-AIP correlates with depletion of circulating plasmablasts and plasma cells, and with reduction of naïve B cells counts. Our study provides evidence that circulating plasmablasts and plasma cells are linked to the pathogenesis of IgG4RD-AIP and can be used to monitor disease activity.

EUS-elastography (strain ratio) in the diagnosis of solid pancreatic lesions: a prospective cohort study

Francesco Auricemma 1, Milena Di Leo 2, Rahal Daoud 3, Francesca Gavazzi 4, Paolaletto Pretoni 1, Silvia Bozzarelli 5, Loredana Correale 6, Andrea Anderloni 1, Alessandro Repici 1 2, Silvia Carrara 1
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Context. EUS elastography is a non-invasive ultrasound technique that measures the stiffness of tissues. Both a qualitative score and a quantitative method (strain ratio; SR) can be used to study the hardness of solid pancreatic lesions (SPL).

Objective. This single center prospective cohort study aimed to evaluate the efficacy of the combination of EUS elastography and SR for the diagnosis of SPL.

Methods. Two different areas were selected: area A included the tumor; area B was placed in a soft peripancreatic normal (parenchymal SR, pSR) and in the GI

Table I — Diagnostic performance of EUS elastography for discriminating ADC from benign lesions. Data in parentheses are 95% CI.

<table>
<thead>
<tr>
<th>Lesion-to-parenchyma SR</th>
<th>Lesion-to-wall SR</th>
<th>Both SR PA and SR WALL</th>
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<td>accuracy</td>
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*The probability for malignancy corresponding to a value >9.10 and 16.2 for lesion-to-parenchyma and lesion-to-wall SR, respectively.
BRCA2 germline mutations and gastroenteropancreatic neuroendocrine tumors (GEP-NETs): report of three cases

Carlo Carnaghi, Valeria Smiroldo, Monica Zurredelli, Andrea G. Lania, Lorenza Rimassa, Nicola Personeni, Paola Spaggiari
Institutions Humanitas Clinical and Research Hospital, Rozzano, Milan, Italy

Context. BRCA2 mutations (muts) are mainly associated to an increased risk of breast/ovarian cancers and less frequently to other tumors. These muts seem to have a key role in one of the pathogenetic pathways of a specific PNETs subtype. With the aim to identify the possible association of BRCA2 mut and NETs we made a retrospective analysis of medical records of patients (pts) with a diagnosis of NET or BRCA2 mut, followed at our Institution and 3 cases were found.

Case report. Patient 1: 36 yo female, with no family history of cancer. At 34 yo she developed breast cancer, stage pT1c pN1a M0, ER and PgR 70%, Ki67 6%, HER2+ and underwent surgery, radiotherapy and adjuvant chemo-immuno-endocrine therapy. BRCA testing, requested due to the young age, resulted positive for BRCA2 mut. A distal splenopancreactectomy was performed when she was 36 with diagnosis of PNET G1 Ki67 1%, stage pT3 N0 M0. So far no recurrence of pancreatic and breast cancer has been detected.

Patient 2: 60 yo male, with family history positive for breast cancer in his sister and for breast and gastric cancer in the father’s side of the family. He had an ileum (midgut) NET, Ki67 1%, G1, with liver metastases. He received primary and metastases resection and he is still alive after 7 yrs from diagnosis. The BRCA2 mut detected was equivalent to the one tested in his sister.

Patient 3: 60 yo male with family history of breast cancer in his sister and father. He had a diagnosis of gastric neuroendocrine carcinoma G3, Ki67 >90% and liver metastases. He underwent chemotherapy with CDDP and VP16. After 6 cycles a partial response was achieved and treatment temporarily stopped. BRCA2 mut was detected at age 57 after the identification of the same mut in his relatives.

The type of surgical drain does not significantly impact on postoperative outcome after a pancreatic resection. A prospective observational study

Giampaolo Perri, Giovanni Marchegiani, Stefano Andrianello, Erica Secchettin, Laura Maggino, Giuseppe Malleo, Claudio Bassi, Roberto Salvia
Department of General and Pancreatic Surgery – The Pancreas Institute, University of Verona Hospital Trust, Verona, Italy

Context. Drain policies in pancreatic surgery still represent a matter of debate. Open passive drains (OPD) and closed-suction drains (CSD) are both currently used.
in the clinical practice worldwide, however a potential superiority of one system above the other has not been assessed yet.

**Objective.** To compare OPD and CSD in determining post-operative drainage fluid contamination and consequent effect on post-operative morbidity and mortality.

**Methods.** Prospective observational analysis of 273 consecutive standard partial resections (pancreateco-duodenectomy – PD vs. distal pancreatectomy – DP) at a single Institution from April 2016 to April 2017. Either OPD (n=165) or CSD (n=108) were randomly placed according to operator’s choice. Postoperative outcomes were registered including samples of drainage fluid collected on postoperative day (POD) 5 and sent for microbiological analysis.

**Results.** The OPD and CSD cohorts did not differ in terms of clinical features, neoadjuvant chemotherapy, preoperative biliary drainage, fistula risk zone, and surgical procedures (PD vs. DP). The overall rate of POD 5 drainage fluid contamination was similar between the groups (58.9% vs. 55.8%, p=0.7), as well as the POPF rate (33.3% vs. 29.6%, p=0.5). The same result was confirmed also after dichotomizing between PD and DP. The postoperative outcomes such as overall 30 days morbidity, intra-abdominal fluid collections, percutaneous drainage, wound infections, reintervention, mean length of hospital stay and mortality did not differ between the two groups. After qualitative microbiological analysis, the 61.4% of bacteria contaminating drainage fluid of PD were attributable to human gut flora, while in DP the 82.7% of bacteria belonged to human skin and mucous flora (p<0.01). The spectrum of bacterial contamination did not significantly differ between the OPD and CSD groups.

**Conclusions.** The use of OPD and CSD for major pancreatic resection does not significantly impact on postoperative outcome. PD and DP are associated with different microbiological spectra of fluid drain contamination, independently from the type of drain used.

**Prognostic value of dual tracer PET/CT in localized pancreatic neuroendocrine tumors**

Paola Mapelli¹, Stefano Partelli¹, Matteo Salgarello¹, Paola Rancoita¹, Stefano Pasetto¹, Francesca Muffatti², Valentina Andreasi², Maria Picchio¹, Luigi Gianoli¹, Massimo Falconi²

¹Nuclear Medicine Department, San Raffaele Scientific Institute, Milan, Italy; ²Pancratic Surgery Unit, Pancreas Translational & Clinical Research Centre, San Raffaele Scientific Institute, Milan, Italy; ³Department of Nuclear Medicine, Sacro-Cuore Don Calabria Hospital; Negrar, Verona, Italy; ⁴University Centre of Statistics in the Biomedical Sciences, Vita-Salute San Raffaele University, Milan, Italy

**Context.** In metastatic pancreatic neuroendocrine tu-mours (PanNETs), dual tracer PET/CT with 18F-FDG and 68Ga-DOTA-DTPA-peptides is used for a better characterization of tumour heterogeneity. In localised PanNETs, the role of these examinations is uncertain.

**Objective.** To investigate the prognostic role of 18F-FDG and 68Ga-DOTA-TOC for risk stratification in localized PanNETs.

**Methods.** Overall 45 pts with localized PanNETs underwent 18F-FDG and 68Ga-DOTATOC PET/CT. PET-derived parameters (PETpar) were: mean and maximum standardized uptake value (SUVmean and SUVmax), metabolic tumour volume (MTV) and tumour lesion glycolysis (TLG). Clinical and pathological variables were correlated to PETpar, using nonparametric Spearman’s correlation coefficient and ROC curve analysis were appropriate.

**Results.** At histological analysis, 12 pts had nodal metastases (N1), a cut-off of 17.5 for SUVmean 68Ga-DOTA-TOC was able to predict N1 (p=0.02, sens=67%, spec=74%), a cut-off of 647.7cc for 68Ga-DOTATOC TLG was able to predict N1 (p=0.03, sens=75%, spec=62%). Sixteen pts had microvascular invasion, PETpar (except for 68Ga-DOTATOC SUVmax, SUVmean and MTV) predicted the pathological finding. Seven pts had metastatic disease and SUVmax and MTV derived from 18F-FDG and 68Ga-DOTATOC MTV and TLG were able to discriminate the presence of metastatic disease. TLG from 18F-FDG (cut-off 32.4, p<0.02, sens=60%, spec=70%) and 68Ga-DOTATOC (cut-off 861.8, p<0.01, sens=60%, spec=78%) and MTV from 18F-FDG (cut-off 8.9, p<0.01, sens=60%, spec=80%) discriminated pts with a Ki67>5%.

**Conclusions.** Combined use of 18F-FDG PET/CT and 68Ga-DOTATOC in localized PanNETs has a prognostic role in risk stratification. PETpar may represent a reliable support for a tailored treatment by identifying pts with localized PanNETs that might benefit from neoadjuvant treatment strategies and tighter follow-up.

**Ex-vivo radiofrequency ablation of porcine liver: a preliminary study of efficacy of a new system**

Gemma Rossi, Maria Chiara Petrone, Emanuele Dabizzi, Alberto Mariani, Sabrina Gloria Giulia Testoni, Mariaemilia Traini, Pietro Magnoni, Livia Archibugi, Paolo Giorgio Arcidiacono

Pancreato-Biliary Endoscopy and Endosonography Division, Pancreas Translational & Clinical Research Center, San Raffaele Scientific Institute IRCCS, Vita Salute San Raffaele University, Milan, Italy

**Context.** There are few published studies (animal ex-vivo or in-vivo and human case-series) about a novel radiofrequency ablation (RFA) system (EUSRA RF needle; VIVA RF generator; STARmed Co, Ltd; Koyang, Korea) resulting in poor procedure standardization and results heterogeneity.

**Objective.** To standardize RFA procedure with this new system with ex-vivo tests on porcine liver in order to find the best ablation power and time in terms of maximum histological coagulative necrosis and surrounded zone diameters (millimeters).

**Methods.** The system consists in: a radiofrequency generator, a 19 Gauge needle (length 150 cm, 10 mm monopolar electrode) and a peristaltic pump (to perfuse the needle with chilled saline solution, maximizing the ablation volume avoiding tissue charring). Liver samples were treated at 40-30-20-10 Watts (W); each power was applied for a duration of 1-3-5-7-15 minutes (min), according to Fibonacci escalation dose scheme, used in phase I studies. Macroscopic global treated areas diameters were registered and histological results (coagulative necrosis and surrounded zone di-ameters) was assessed by an expert pathologist blinded about ablation powers and times of RFA.
Results. At first liver samples were ablated at different powers (10-20-30-40 W) in order to find the best ablation power, obtaining the maximum macroscopic ablated area at the lower power of 10 W (R=0.74, P-value=4.7 E-4). Samples were finally treated at the best power (10 W) for 1–3–5–7–15 minutes in order to find the best ablation time: ablation time was linearly and significantly related (R=0.92, P-value=8.9 E-08) to the macroscopic global treated areas diameters. Then the pathologist microscopically evidenced two different injured zones: a small central coagulative necrosis area (“A zone”) and a surrounded larger “diaphanization” area (“B zone”) showing mild cellular alterations without effective necrosis. “A zone” diameter didn’t change among ablation powers (R=0.24, P-value 0.35) and among ablation times at 10 W (mean size: 3.25 mm) but “B zone” increased linearly, positively and significantly (R=0.8, P-value=3.6 E-4) with RFA times at low power (10 W).

Conclusions. RFA with this new system is feasible and effective to produce small coagulative necrosis (few milimeters) but it can produce larger zones of mild cellular alterations at low power: future in-vivo animal studies are needed in order to assess the evolution of this area (necrosis fibrosis recovering?).

The additive value of endoscopic ultrasound (EUS) guided fine needle aspiration (FNA) in differential diagnosis of pancreatic cystic lesions in a tertiary-care center

Gemma Rossi, Pietro Magnoni, Mariemilia Traini, Maria Chiara Petrone, Sabrina Gloria Giulia Testoni, Emanuele Dabizzi, Alberto Mariani, Livia Archibugi, Claudio Doglioni, Paolo Giorgio Arcidiacono

Pancreatic-Biliary Endoscopy and Endosonography Division, Pancreas Translational & Clinical Research Center, Pancreato-Biliary Endoscopy and Endosonography Division, San Raffaele Scientific Institute IRCCS, Vita Salute San Raffaele University, Milan, Italy

Context. Endoscopic ultrasound (EUS) with fine needle aspiration (FNA) is the diagnostic procedure of choice for pancreatic lesions differentiation. Nonetheless, literature data show a low sensitivity (30-50%) for EUS-FNA in differential diagnosis of pancreatic cystic lesions (PCL), thus hampering the use of this procedure in clinical routine.

Objective. The aim of the study is to assess the value of EUS-FNA in defining the final diagnosis of PCL in a tertiary care center and its impact on patient outcome.

Methods. EUS-FNA of PCL performed in our Institute during the last 3 years was retrospectively analyzed. All the biopsies of PCL were performed with a 22-gauge needle through a linear echoendoscope (EG3870UTK, Pentax Medical, Tokyo, Japan).

The cytological samples were reviewed by an highly experienced cytopathology pancreatic team. Data recorded were: age, sex, EUS morphological variables of the cyst with diagnostic suspicion (IPMN, serous cystic adenoma, cystic neuroendocrine tumor, pseudocysts or unclassified cysts) and cytological results.

The finding of mucus was considered suggestive for IPMN and the absence of malignant neoplastic cells was considered to be consistent with a diagnosis of serous cyst adenoma or pseudocyst.

Results. 231 cytological samples of 201 (102 males/99 females, mean age 66.3±11.4 years) total patients were analyzed. 21 patients underwent to two or more EUS-FNA. Sampled cysts were located at: pancreatic head (n. 63, 31.3 %), uncinated process (n. 22, 10.9 %), neck (n. 42, 20.9 %), body (n. 47, 23.4 %) and tail (n. 27, 13.4 %). 113 patients (56.2 %) showed multiple cysts. Mean size of the major sampled cyst was 30.3±16.1 mm. The presumptive diagnoses of EUS were: 191 IPMNs (82.7%), 15 serous cystic adenomas (6.5%), 12 pseudo-cysts (5.2%), 11 unclassified cystic lesions (4.8%) and 4 cystic neuroendocrine tumors (1.7%).

Final cytological results were achieved in 66.7 % of patients (154/231 samples).

When considering diagnostic subgroups, final cytological results were achieved in 65.4% for IPMNs (125/191), 93.3% for serous cystic adenomas (14/15), 91.7% for pseudocysts (11/12) and 100% for cystic neuroendocrine tumors (4/4).

Conclusions. In a tertiary care center with an highly experienced cytopathology team, EUS-FNA cytology impact on differential diagnosis of PCL can be obtained in nearly 70 % of cases. In this setting we suggest to perform EUS-FNA in patients with PCL.
only patients with adenocarcinoma. By evaluating OR for all diameters between 6-10 mm, 9 mm was identified as the best cutoff diameter to predict HGD/malignancy. At multivariate analysis, jaundice, presence of vascularized nodules, positive cytology and MPD ≥9 mm were independent predictors of malignancy (p 0.000 for MPD ≥9 mm).

Conclusions. Our study confirms that, while for diameters ≥1 cm the risk of degeneration is high and surgical treatment is recommended, smaller MPD diameters ≤9 mm were independent predictors of malignancy (p 0.012) for MDR, 5.04 (95% CI 2.35-10.80, P<0.001) for non-infectious complications was 2.67 (95% CI 1.24-5.77, P=0.012) for MDR, 5.04 (95% CI 2.35-10.80, P<0.001) for the MDR, and 58.8% in the XDR (p<0.001). The median time of infection occurrence was postoperative days 4 (2-7 IQR) and 7 (3-12 IQR) non-infectious complications. At multivariate analysis, the risk of having major non-infectious complications was 2.67 (95% CI 1.24-5.77, P=0.012) for MDR, 5.04 (95% CI 2.35-10.80, P<0.001) for MDR, and 9.64 (95% CI 2.71-34.28, P<0.001) for XDR.

Conclusions. Antimicrobial resistance is significantly associated with the risk of major non-infectious morbidity.

Consequences of increases in antibiotic resistance pattern on outcome of pancreatic resection for cancer

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Context. Although the role of drug-resistance infections on surgical outcomes is controversial, one major concern is the rapidly growing number of infectious complications involving resistant bacteria after pancreatic surgery.

Objective. The aim of the study was to determine whether increase antibiotic resistance was an independent risk factor for development of major non-infectious postoperative complications.

Methods. This work included a multicenter cohort study of patients who underwent pancreatic resections for cancer over a 3-year interval. The primary outcome was major non-infectious complication rate developing after the occurrence of multi-drug sensitive (MDS) infection, multi-drug-resistant infection (MDR), and extensive drug-resistant (XDR) infection. Multivariate logistic regression models were used to adjust for patient and operative effects.

Results. Eligible patients (517) were selected for the analysis. One hundred and thirteen (21.8%) patients had major non-infectious complications with a rate of 12.9% in the no infection group, 29.3% in the MDS, 41.5% in the MDR, and 58.8% in the XDR (p<0.001). The median time of infection occurrence was postoperative days 4 (2-7 IQR) and 7 (3-12 IQR) non-infectious complications. At multivariate analysis, the risk of having major non-infectious complications was 2.67 (95% CI 1.24-5.77, P=0.012) for MDR, 5.04 (95% CI 2.35-10.80, P<0.001) for MDR, and 9.64 (95% CI 2.71-34.28, P<0.001) for XDR.

Conclusions. Antimicrobial resistance is significantly associated with the risk of major non-infectious morbidity.

Post-pancreatectomy hemorrhage. Experience in 519 pancreatic resections

Fabio Giannone, Giovanni Guarneri, Nicolo Pecorelli, Massimo Venturini, Roberto Nicoletti, Francesco De Cobelli, Massimo Falconi, Gianpaolo Balzano

Division of pancreatic Surgery, Pancreas Translational & Clinical Research Center, San Raffaele Hospital, Milan

Context. Post-pancreatectomy hemorrhage (PPH) is a life-threatening complication of pancreatic surgery, frequently associated with pancreatic fistula (PF). In recent years, non operative approach of PPH has gained widespread acceptance.

Objective. Aim of the study was to report an updated experience about its incidence, management and treatment success or failure in a high-volume pancreatic surgery centre.

Methods. Between January 2015 and December 2016, 519 patients underwent a pancreatic resection in our Institution. A retrospective analysis on prospectively collected data was performed, focusing on PPH. PPH was categorised according to ISGPS classification.

Results. PPH occurs in 31 out of 519 resections (6%), range 0-27 POD, 2 PPH after discharge). Twenty-five PPH were severe while 6 were mild. In 17 pts (54.8%) PPH was associated to PF. Early PPH (within 24h from resection) occurred in 12 pts and was mainly treated conservatively (6 patients) or by re-laparotomy (5 pts); in one case angiography was performed. No death was observed after early PPH. As regards bleeding occurring after 24h post-resection (late PPH), it was observed in 19 pts (61.3%), with 3 deaths (15.8%). CT scan, performed in 16 pts, identified an active blushing in 9 cases (56.2%). Management was conservative in 6 pts (31.6%) whereas 13 cases needed an invasive treatment. Nine pts underwent primary angiography and 4 underwent primary reoperation. One patient was reoperated immediately after the endovascular procedure because of failure to stop the bleeding while in two cases a re-bleeding after the first angiography occurred. In both cases a second angiography with embolization was successfully performed. Primary re-laparotomy was performed in 4 pts (21%) with late PPH. In 2 pts surgery was successful to prevent further bleeding while it failed in the other 2, with a new bleeding in one case and a death after a packing in the other.

Conclusions. When feasible, angiography is the best approach to manage late PPH; it allowed to prevent re-laparotomy in 62% of patients needing invasive treatment, with an 86% success when an active bleeding is detected during angiography.

Statin use and the risk of acute pancreatitis: a meta-analysis of observational studies

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Context. Reports on the association between statin use and the risk of acute pancreatitis (AP) are contradictory. 
Statins are widely perceived as potential etiological factors for AP, but more recent evidence suggests the opposite. The mechanisms of their possible benefit is still unclear, with experimental studies showing potential anti-inflammatory aspects. A specific anti-inflammatory aspect suggests the absence of an increased risk in statin users. The mechanisms of their possible benefit is still unclear, with experimental studies showing potential anti-inflammatory aspects.

Objective. To conduct a systematic review and meta-analysis to evaluate the association between the use of statins and the risk of developing AP.

Methods. Medline, Scopus, and Web of Science were searched for cohort (C) and case-control (CC) studies with statins included as an intervention and AP as an outcome. Eligible studies were selected according to the PRISMA statement. Pooled adjusted ORs with corresponding 95% CIs were calculated using random effects models. Publication bias was assessed through Begg and Mazumdar test. Heterogeneity was assessed by means of the I2 value.

Results. 13 studies (7 CC, 6 C) contributed to the analysis. A total of 34899 AP patients and 537794 control were included. Pooled prevalence of statin use was 9.8% (3411/34899) among AP patients and 25% (135715/537794) among controls. Pooled adjusted OR for the 13 studies was 1.00 (95% CI 0.63-1.59; p=0.99) with considerable heterogeneity (I2=98%). In a sensitivity analysis for study design, CC studies were associated to an increased risk (OR 1.35; 95% CI 1.20-1.47; p<0.0001), but cohort studies were not (OR 0.69; 95% CI 0.37-1.31; p=0.26). Similarly, in a sensitivity analysis for country of origin no association with the risk was seen for Western countries (OR 0.90; 95% CI 0.52-1.56; p=0.7) while there was an increased risk in studies conducted in Asia (OR 1.39; 95% CI 1.10-1.75; p=0.006). There was evidence of publication bias (Begg and Mazumdar Kendall’s tau =-0.549; p<0.006).

Conclusions. This first meta-analysis of observational studies for the association between statins use and AP suggests the absence of an increased risk in statin users. Evidence for an increased risk is limited to CC studies, while C studies showed no global effect, similarly to previous data from controlled trials. Further research on the topic is needed to clarify whether statin type, dosage, length of use or etiology of AP might account for this difference.

Needle tract seeding of pancreatic cancer after EUS-FNA: systematic review of the literature, discussion of its management and report of a case

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Context. EUS-FNA is commonly used for tissue acquisition of pancreatic cancer (PC). Needle-tract cancer seeding (NTCS) has been reported with few sporadic case reports as a rare EUS-FNA long-term complication, but is a poorly investigated entity. However, with the increased incidence of PC and the spreading use of EUS-FNA, its recognition and standardized management seems necessary. Management of NTCS localization varies in reported cases from treatment with chemotherapy and palliation, considering the case as metastatic with expected survival<12 months, to surgical excision of the NTCS nodule, considering it a de novo T2N0M0 patient with a potential median survival of 34 months when resected.

Objective. To conduct a systematic review of cases of EUS-FNA NTCS of PC and analyze their management and outcome, including a report from our center.

Methods. Adhering to PRISMA guidelines, a systematic search was performed with different domains of MeSH terms and keywords combined with ‘AND’ and ‘OR’. The first domain included words related to PC, the second domain related to NTCS.

Results. Up to July 2017, the search retrieved 227 reviews with 9 reports of cases between 2005 and 2017 and one recently developed at our center, for a total of 10 cases. 4 (40%) being males, mean age 69.3 years. All PC arose from the body/tail. The caliber of the needles used to acquire tissue for the primary cancer diagnosis was either 22 G or 25G, with 2-5 passes. 9 out of 10 patients underwent initial N0R0 surgical resection, with only 3/9 (33%) undergoing adjuvant chemotherapy. Mean NTCS nodule size was 31.8±12 mm, all in the posterior gastric wall, developing 4-36 months after resection (mean RFS 17.8±10 months). 2 patients were treated with palliation, 6 underwent surgical resection of the seeding. Follow-up after NTCS diagnosis and treatment is reported only in 3 patients.

Conclusions. NTCS after EUS-FNA of PC is rare, occurs late and should be recognized from “typical” disease recurrence as it might be treated aggressively with repeated surgery with good results. Interestingly, only 39% of the patients who developed NTCS underwent adjuvant chemotherapy suggesting a possible link to the lack of adjuvant treatment.

Statin use decreases the risk of pancreatic cancer occurrence: a meta-analysis

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Context. Statins are widely prescribed for primary and secondary prevention of cardiovascular diseases. Several studies evaluated the association between statin use and the onset of pancreatic cancer (PC) in order to evaluate a possible chemopreventive effect, with heterogeneous results. Previous meta-analyses evaluating researches published up to 2012 did not find any association, but in the latest years new studies with interesting results have been published.

Objective. To conduct a new systematic review and meta-analysis to clarify the association between statin use and PC risk.

Methods. Literature search up to November 2016 of PUBMED for articles and abstracts presented at DDW and ASCO conventions was carried out. Eligible studies were case-control studies(CC), cohort studies(C) and randomized controlled trials(RCTs) assessing the effect...
of statin use on the risk of PC, compared with placebo or no treatment. Studies had to report Odds Ratio (OR), Relative Risk (RR), or Hazard Ratio (HR). Estimates with corresponding 95% confidence intervals (CI) or sufficient data for their calculation. Pooled adjusted ORs with corresponding 95% CIs were calculated using random effects models. Publication bias was assessed through Begg and Mazumdar test, heterogeneity by means of the I² value.

Results. A total of 21 studies (12 CC, 6 C, 3 RCTs) contributed to the analysis. 11383 PDAC patients and 2991004 controls were included. The pooled incidence of PC was 0.27% (916/1167130) among statin users and 0.44% (8144/1835153) among the non-users. The overall pooled result for all studies demonstrated a reduced risk of PC among statin users (OR 0.82; 95% CI 0.69-0.96; p=0.019), compared to non–statin users. In a subgroup analysis, the protective effect was limited to case-control studies (OR 0.72; 95% CI 0.56-0.93) and not to cohort ORs (OR 0.93; 95% CI 0.73-1.19) nor RCTs (OR 1.04; 95% CI 0.56-1.94). No publication bias was found.

Conclusions. This is the first meta-analysis showing that statins exert a protective effect on the incidence of PC. Further studies taking into account statin dose, duration and subgroups of patients are needed in order to clarify the association.

EUS and CT scan accuracy in establishing the T stage in surgically resected pancreatic cancer based on the upcoming TNM 8th edition

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Context. Pancreatic cancer (PC) has a dismal prognosis with 5-year survival of surgically resected patients<25%. It has been recently suggested that patients with a tumor >2 cm might harbor micrometastases at diagnosis. In this view, given the availability of new highly effective chemotherapy regimens to be neoadjuvantly employed, the correct T stage evaluation plays a key role. The new proposed AJCC Staging System TNM 8th edition, in fact, differs from the 7th mostly for the evaluation of the T, giving high importance to the diameter of PC and predicting survival more efficiently. In this context, a correct preoperative evaluation of the T is of high importance as it might shift the therapeutic decision from upfront surgery to neoadjuvant chemotherapy, that could be preferred in tumors>2 cm (T2). For this reason, the accuracy of CT scan vs. EUS in evaluating the dimension of the tumor with heterogeneous results and dated machines, and no study adopted the new TNM system for the preoperative staging.

Objective. To evaluate the accuracy of CT vs. EUS in establishing the T stage of surgically resected PC, as defined by the new upcoming TNM 8th edition and to establish sensitivity and specificity of the two techniques in discriminating T1 from more advanced stages.

Methods. Retrospective/prospective unicenter cohort of surgically resected PC patients. Inclusion criteria: a) having preoperative EUS and CT scan evaluation performed at our centre, at the latest 30 days apart from each other and from surgical resection; b) no neoadjuvant chemo/radiotherapy performed. The evaluation of the T by both imaging modalities was compared to the final pathology T re-established based on the new TNM 8th edition, calculating accuracy, specificity and sensitivity. T-test was used for comparison of continuous variables, Fisher's test was used for comparison of categorical variables.

Results. Among 209 PDAC patients surgically resected in 2015-2017, 40 met inclusion criteria, 23(57.6%) being males, mean age at resection 68.7 years. The tumor was located in the head in 29(72.5%) patients. Mean diameter of the tumor at pathology was 25±9.6 mm, at EUS 23.8±8.7 mm (p=0.55), at CT 25.6±10 mm (p=0.79). In 5(12.5%) cases CT was not able to detect the lesion; mean diameter of undetected lesions was 22.4±3.7 mm. Accuracy in T assessment was 57.5% for CT and 62.5% for EUS; when considering detection of ≥T2 lesion in any of the two imaging modalities the accuracy increased to 75%. Sensitivity and specificity in discriminating T1 lesions from ≥T2 lesions was respectively 64.0% and 80.0% for EUS and 66.7% and 60.0% for CT.

Conclusions. This is the first study evaluating the accuracy of CT vs. EUS imaging modalities in establishing the T in the setting of the new TNM 8th edition. In our study, CT and EUS have both a low accuracy in determining the right T stage when used alone, while it raises significantly when used in combination. CT was not able to detect up to 12.5% of lesions. EUS resulted having a lower sensitivity but higher specificity in discriminating T1 lesions from ≥ T2 lesions compared to CT. These preliminary results suggest how EUS, often adopted only as a means to obtain a cytological specimen, has a key role in determining the T stage, and that the two imaging modalities should be used in combination to better assess the proper therapeutic management as for neoadjuvant chemotherapy or upfront surgical resection.

Inhibition of the glucose transporter 1 (Glut1) overcomes resistance to the cytotoxic and pro-apoptotic effects of Akt inhibitors in primary pancreatic cancer (PDAC) cells

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Context. The PI3K/Akt pathway plays a key role in cell proliferation, survival and motility. However, perifosine, as well as other Akt inhibitors, showed disappointing response rates as a single agent in most solid tumors, including pancreatic ductal adenocarcinoma (PDAC).

Objective. To investigate the expression of (phospho-
Akt in PDAC cells, and to evaluate the effects of Akt inhibitors combined with gemcitabine and new glycolytic inhibitors.

**Methods.** PDAC primary cultures LPC006 and LPC028 (with low- and high-Akt expression) were used to unravel key factors, affecting cell-cycle, apoptosis, as well as inhibition of cell migration/invasion and glucose transport after exposure to Akt inhibitors and their combination with gemcitabine.

**Results.** Akt inhibitors reduced growth and migration, and synergistically enhanced the antiproliferative activity of gemcitabine in LPC028, while this combination was antagonistic in LPC006 cells. This combination significantly increased apoptosis, associated with induction of caspase-3/6/8/9, PARP and BAD, and inhibition of Bcl-2 and NF-kB in LPC028, but not in LPC006 cells. However, targeting the key glucose transporter Glut1 in similar apoptosis induction in LPC006 cells.

**Conclusions.** Our data support the rational development of new therapies targeting Akt in PDAC, and further studies on the inhibition of Glut1 to overcome resistance to these therapies.

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**Using RNA-seq to detect novel splice variants related to drug resistance in pancreatic cancer models**

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**Context.** Drug resistance is a major problem in the treatment of pancreatic ductal adenocarcinoma (PDAC). Recent data showed that other than by well-known genetic and epigenetic modifications, drug resistance mechanisms might be regulated by splicing aberrations. This is a rapidly growing field of investigation that deserves future attention in order to plan more effective therapeutic approaches.

**Objective.** This study aims to investigate the impact of aberrant splicing on drug resistance through transcriptomic profiling by RNA-seq and qRT-PCR based methods to validate candidate genes.

**Methods.** We selected the Panc-1 cell line and its gemcitabine-resistant subclone Panc-IR obtained by continuous incubation with 1 μM of the drug and validated a RNA-seq/qRT-PCR-based pipeline to identify novel splice variants related to drug sensitivity/resistance.

**Results.** The computational tools MATS and Integrative Genomics Viewer showed different splice variants in the parental vs. resistant cells. In particular we observed a lower PKM2/PKM1 ratio, in the Panc-IR compared to Panc-1 cells, underlying the potential role of metabolic reprogramming and glycolysis in drug-resistance.

**Conclusions.** Our innovative protocol constitutes a suitable approach for the discovery of splice variants involved in drug resistance, suggesting novel therapeutic approaches, including spliceosome and glycolytic inhibitors to overcome PDAC chemoresistance.

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**Antitumor activity of a new O-glucosconjugate lactate dehydrogenase (LDH-A) inhibitor in hypoxic preclinical models of pancreatic cancer**

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**Context.** The muscle isoform of lactate dehydrogenase (LDH-A) is a viable target in pancreatic ductal adenocarcinoma (PDAC), and novel LDH-A inhibitors displayed synergistic cytotoxic activity with gemcitabine, offering an innovative tool in hypoxic tumors (Grasso et al, Crit Rev Oncol Hematol 2017).

**Objective.** In order to carry on the biopharmaceutical evaluation of LDH inhibitors, we evaluated a new O-glucosconjugate, which can be tested in previously established orthotopic bioluminescent (BLI) models.

**Methods.** The cytotoxic activity in PDAC cell lines and primary cultures was evaluated with SRB assays, whereas modulation of LDH-A activity was investigated by enzymatic assays, and apoptosis induction with flow cytometry. All these experiments were performed in both normoxic and hypoxic conditions (1% O2). In vitro studies were performed in the most representative hypoxic model.

**Results.** LDH-A expression significantly increased under hypoxic conditions. The novel LDH-A inhibitor demonstrated a good antiproliferative activity, and proved to be particularly effective under hypoxic conditions, with up to 10-fold increased activity. Furthermore, this compound induced a significant reduction of tumor growth compared to untreated control, as monitored longitudinally with BLI, CT-PET, MRI and high-frequency ultrasound.

**Conclusions.** These data provide further evidence that targeting lactate metabolism is a promising approach for PDAC therapeutics.

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**Bioluminescent chick chorioallantoic membrane (CAM) models from primary pancreatic cancer (PDAC) cells unravel the modulation of key microRNAs in crizotinib/gemcitabine synergistic interaction**

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**Context.** Our previous studies demonstrated that crizotinib inhibits metabolic inactivation of gemcitabine in c-Met-driven PDAC (Avan et al., Cancer Res 2013), but further studies on molecular mechanisms underlying this synergistic interaction are warranted.

**Objective.** To investigate the modulation of key microRNAs involved in the interaction of crizotinib and gemcitabine in new CAM models.
Methods. Primary PDAC cells transduced with lentivirus expressing Firefly-luciferase (Fluc) were established and inoculated onto CAM membrane, with >80% engraftment. Fluc signal reliably correlated with tumor growth. Tumor features were evaluated by immunohistochemistry and genetic analyses, including mRNA expression of pivotal genes, as well as microRNA profiling.

Results. Array and PCR studies showed that microRNA profiles of the CAM reflected the originator tumors. The combination of gemcitabine and crizotinib treatment resulted in 63% inhibition of tumor growth on CAM tumors, as compared to control (p < 0.01). These results were associated with reduced expression of miR-21 and increased expression of miR-155.

Conclusions. Our study provides the first evidence that modulation of key microRNAs might play a role in the antitumor activity of new drugs/combinations, as observed using transduced primary PDAC cells that form tumors on the CAM, which retain both the histopathological and (epi)genetic characteristics of original tumors.

Superior mesenteric/portal vein resection and reconstruction during pancreatic resections: propensity score matched analysis of open versus robotic procedure
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Context. Resection and reconstruction of the superior mesenteric/portal vein during pancreatectomy (VP-R) has become an accepted procedure in patients with pancreatic tumors and it seems to be feasible by robotic approach (Langenbecks Arch Surg, 2016).

Objective. Provide an unadjusted and propensity score matched comparison between open and robotic VP-R. Primary endpoint is the rate of severe post-operative complications (POC) (Clavien-Dindo≥3b), 90-day mortality and R1 resection.

Methods. Only patients undergoing upfront surgery were analyzed, since the need for a neoadjuvant treatment was considered an exclusion criterion for robotic VP-R. Relationship between primary endpoints and surgical approach was evaluated by linear logistic regression. Overall survival was analyzed in patients with pancreatic cancer using Kaplan-Meier curves and Log-rank test. Propensity score (PS) was used to balance possible confounders between the two groups and to perform a nearest-neighbor 1-to-1 match.

Results. Between 2011 and 2016, 100 patients underwent VP-R (85 open and 15 robotic procedures). Severe POC occurred in 4 (26.7%) and 12 (14.1%) patients (p=0.25) after robotic and open VP-R, respectively, with an odd ratio (OR) of 2.21 (0.60-8.09). Equivalent figures for 90-day mortality were 2 (13.3%) and 7 (8.2%) (p=0.48) with an OR of 1.71 (0.32-9.18). R1 resection occurred in 4 (26.7%) and 22 (25.9%) patients (p=1.00), respectively for robotic and open VP-R with an OR of 1.04 (0.30-3.61). Median survival (IQR) was 31 months (31-NA) after robotic VP-R and 31 months (15-47.3) after open VP-R. Age, gender, BMI and ASA score were used to perform PS. Ten open VP-R were matched to 10 robotic VP-R by PS. In either groups the rate of severe POC, 90-day mortality and R1 resection was 30%, 10% and 30%, respectively. After matching, we observed a reduction of the OR to a value of 1 (0.15-6.77), 1 (0.05-18.57) and 1 (0.15-6.77) for severe POC, 90-day mortality and R1 resection rate.

Conclusions. In selected patients, robotic VP-R are feasible and achieve results comparable with open VP-R in terms of post-operative morbidity, mortality, R1 resection rate and long-term survival. These results need to be confirmed in large series.

Robot-assisted versus open pancreaticoduodenectomy for ductal adenocarcinoma: a propensity score analysis of R1 rate, overall survival and recurrence
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Context. The pancreatic ductal adenocarcinoma (PDAC) still remains associated to a poor survival and an R0 resection seems to be the only chance of cure.

Objective. Provide a propensity score matched comparison between robotic pancreaticoduodenectomy (RPD) and open pancreaticoduodenectomy (OPD). Primary endpoint is the rate of R1 resection. Secondary endpoints are overall survival (OS), disease free survival (DFS) and sample size calculation for randomized controlled trial (RCT).

Methods. We have considered only PD performed for PDAC without vascular resection and analyzed with a standardized histopathologic method performed from February 2014 to February 2017. Propensity score (PS) full match analysis was used for comparison. Relationship between R1 rate and surgical approach was evaluated by linear logistic regression. OS and DFS were calculated using Kaplan-Meier curves and Log-rank test. Sample size for RCT was calculated performing Farrington & Manning score test (non-inferiority margin of 10%, alpha=0.025, power=90%).

Results. Twenty-six OPD and 24 RPD were considered. PS analysis was performed using as covariate CT scan tumor dimension, pathological tumor dimension, lymph node ratio and duodenal infiltration. PS analysis matched 24 OPD and 20 RPD. No statistical differences were noted for R1 rate (41.7% for OPD vs. 55% for RPD, p=0.37) and recurrence rate (54.6% for OPD vs. 60% for RPD, p=0.73). The mean OS was 28.2±3 and 30.8±2.6 months, respectively for OPD and RPD (p=0.87). The mean DFS was 22±3.52 and 16.7±3.55 months, respectively for OPD and RPD (p=0.21). A non-inferiority RCT comparing OPD and RPD would require 1235 pairs of patients.

Conclusions. In this retrospective analysis, performed using PS full match method, R1 resection rate and mean OS resulted comparable in RPD and OP. DFS is lower in RPD than in OPD, but without statistical evidence. The result of the sample size calculation for a non-inferiority RCT demonstrated the need to enroll a large number of patients. Multicenter studies are needed to reach a conclusion.
Efficacy and safety of EUS-guided drainage of pancreatic fluid collections via Hot Axios™ lumen-apposing metal stents: a single-center experience

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Context. EUS-guided drainage of pancreatic fluid collections via fully covered self-expandable metal stents (FCSEMS) has overcome other radiological and surgical approaches. In 2014, a new lumen-apposing metal stent (LAMS) with an electrocautery-enhanced delivery system (Hot Axios™, Boston Scientific) was approved for pancreatic pseudocyst drainage.

Objective. To evaluate the safety and efficacy (i.e. technical and clinical success) of the Hot Axios™ system in a series of patients undergoing EUS-guided drainage of post-pancreatitis or post-surgical pancreatic fluid collections.

Methods. A retrospective review of all patients undergoing placement of a Hot Axios™ stent in our Institute between October 2014 and July 2017 was performed. Rates of technical success (TS) and clinical success (CS), defined as successful stent placement and >50% resolution of the fluid collection respectively, and occurrence of any adverse events were reported.

Results. 27 patients were identified, two of them undergoing placement of two separate Hot Axios™ stents for a total of 29 procedures. Our case series included drainage of post-pancreatitis pseudocysts (n=10, 34.5%), post-pancreatitis walled-off necroses - WON (n=12, 41.4%) and post-surgical necrotic fluid collections (n=7, 24.1%). The overall TS and CS rates were 100% and 93.1%. Two cases of clinical failure were recorded in the WON group, but the difference in TS between necrotic and non-necrotic collections (89.5% vs. 100%) did not reach statistical significance (p=0.532). Adverse events occurred in 8 out of 29 cases (27.6%) and consisted of hemorrhage caused by gastroduodenal or splenic artery pseudoaneurysm (n=6, 20.7%), stent dislodgement and stent occlusion (n=1, 3.4% each), and a peculiar case of “buried stent syndrome” recorded in a long-term follow-up EUS examination (n=1, 3.4%). One death caused by hemorrhagic shock was also reported one month after drainage of a WON. For patients with post-pancreatitis fluid collections, undergoing at least one session of necrectomy resulted to be a risk factor for hemorrhage (OR 15.0, p=0.046).

Conclusions. In our experience, the Hot Axios™ system proved successful for EUS-guided drainage of necrotic and non-necrotic pancreatic fluid collections. Nonetheless, the relatively high rate of hemorrhage and the occurrence of one death following drainage of a WON warrant further evaluation and extreme caution.

The immunohistochemical (IHC) analysis of CDX2, CK7 and CK20 identify pathological subtypes and their progression in ampullary adenocarcinomas (AACs) patients

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Context. Ampullary Adenocarcinomas (AACs) are heterogeneous tumors, and subtyping based on caudal-type homeodomain transcription factor-2 (CDX2) and Cytokeratins (CK7/CK20) stainings has been used to identify Intestinal (INT), Pancreato-Biliary (PB) and Mixed-Type (MT) tumors. However, MT are difficult to detect and correlation with outcome is unclear.

Objective. To validate a novel subtyping immunohistochemical (IHC) scoring of AACs and to correlate the subtypes with clinical outcome.

Methods. Tissue-microarrays of 20 resected AACs were used to evaluate a global IHC score (GS) of CDX2, CK7 and CK20, considering both the number of positive cells (0:no stained cells; 1<25%; 2<50%; 3>50%) and their intensity (1=weak; 2=middle; 3=strong). MT were assigned to INT or PB groups on the basis of the predominant phenotype. Correlation with survival was evaluated using Kaplan-Meyer curves.

Results. Our AAC samples included 15% INT, 45% PB and 40% MT, and using the GS (average=9.5, range=4-16) 75% and 25% of MT were assigned to INT and PB, respectively. Notably, INT were characterized by high expression of CDX2 and CK20, while PB showed high expression of CK7 but no expression of CK20. Survival of INT was significantly longer than PB (85.7 vs. 20.3 months, HR=8.39; 95%CI=1.38-18.90; p=0.0152).

Conclusions. Our novel histopathologic criteria define clinically relevant histomolecular phenotypes of AACs with potential implications for therapeutic strategies.

Total pancreatectomy for mucinous cystic neoplasm with associated invasive carcinoma: a case report

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Context. Pancreatic cystadenocarcinoma is a rare neoplasm and clinical symptoms and signs may be not initially sufficient to make an accurate and early diagnosis. The prognosis for MCN (mucinous cystic neoplasm) treated with radical surgical pancreatic resection is excellent, instead of that associated with carcinoma which has a poorer survival. We report a case misdiagnosed as acute pancreatitis with pseudocysts, then revealed as a cystadenocarcinoma with already lymph node metastasis.

Case report. A fifty-six year old female was admitted...
to our department of surgery with a mild jaundice and epigastric irradiated pain like an acute pancreatitis. Her past medical history revealed an uncompensated diabetes onset one year before and multiple episodes of abdominal pain. She had been treated as an acute pancreatitis in an alcohol consuming patient. MRI (magnetic resonance imaging) and pancreatic endoscopic ultrason sound revealed a disomogeneous pancreas as an acute pancreatitis with a large complex cystic and a solid component in the body causing both bile duct and Wirsung dilatation. A total splenopancrectomy was performed and the histopathologic examination revealed a mucinous cystoadenocarcinoma extended to almost all the pancreatic parenchima, associated with pancreatitis and lymph node metastasis (PT3N1).

**Conclusions.** MCN in association with carcinoma could be initially misdiagnosed. It should be suspected in young female patients with recent uncompensated diabetes with a pancreatitis—like clinical history and radiological features with pancreatic cysts. A correct diagnosis and management with an early surgery may change the prognosis of patients with MCN.

### A pancreatic arteriovenous malformation causing recurrent abdominal pain: a case report

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**Context.** Arteriovenous malformation of the pancreas is a rare entity, first reported in 1968 by Halpern et al. in a patient with Rendu-Osler-Weber disease. It consists of a vascular anomaly that can be either congenital or acquired (as a result of inflammation, tumor, or trauma) and it is constituted by an aberrant anastomosis between the arterial and venous systems in the pancreas. It is usually asymptomatic but it may occasionally cause epigastric pain, gastrointestinal bleeding or portal hypertension. Pancreatic arteriovenous malformations must be differentiated from other hypervascular pancreatic lesions as neuroendocrine tumors, hypervascular metastases and angiosarcoma.

**Case report.** A 76-year-old man in good general condition was referred to our Center for recurrent epigastic pain, radiating to the back, lasting for almost a year. The physical examination was substantially negative as well as the laboratory data. An abdominal ultrasonography revealed a 3 cm lesion in the pancreatic body. A CT scan demonstrated a hypervascular mass in the pancreatic body of 3 x 2.5 cm without dilatation of the main pancreatic duct. An abdominal MRI was then performed and it showed a hypervascular area in the pancreatic body, constituted of ectatic vessels, consistent with an arteriovenous malformation. The patient underwent a diagnostic angiography which confirmed the presence of a large pancreatic arteriovenous malformation, with multiple arterial feeders originating mainly from the splenic artery and, to a lesser extent, from the pancreaticoduodenal arcades. Furthermore, an early venous return to the portal vein was detected. A surgical resection was proposed and the patient underwent a laparotomic distal splenopancreatectomy. The postoperative course was complicated with a grade B pancreatic fistula, managed by radiological percutaneous drainages. Histological examination of this surgical specimen confirmed the presence of a arteriovenous pancreatic malformation. The patient is well and asymptomatic 5 months after surgical resection.

**Conclusions.** Pancreatic arteriovenous malformations are a rare cause of abdominal pain and they should be considered in the differential diagnosis of a hypervascular pancreatic lesion. They can be diagnosed by contrast-enhanced dynamic CT scan or MRI, even if angiotherapy represents the gold standard for the diagnosis. In symptomatic patients fit for surgery, surgical resection represents a definitive treatment.

### A complete pathologic response of pancreatic adenocarcinoma to neoadjuvant chemotherapy (FOLFIRINOX): a case report

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**Context.** Pancreatic ductal adenocarcinoma presents as locally advanced disease in 30-40% of patients at diagnosis. Recently, the randomized phase III PRODIGE trial evaluated FOLFIRINOX versus gemcitabine alone in patients with metastatic pancreatic cancer and good performance status with a dramatic improvement in both median progression-free survival and median overall survival in favour of the group receiving FOLFIRINOX. However, a complete pathological response after neoadjuvant chemotherapy in advanced pancreatic adenocarcinoma is a very rare event. We report a case of complete tumor response after FOLFIRINOX treatment of a locally advanced pancreatic cancer that was successfully resected.

**Case report.** A 68-year-old woman was referred to our Center in July 2014 for a 2-month history of right abdominal pain and weight loss. Abdominal US and CT scan showed a 3 cm pancreatic lesion involving the uncinate process and the retroperitoneal tissue with a pathologically enlarged left para-aortic nodes until iliac artery bifurcation. CEA levels were 159.2 U/ml (normal value <37 U/mL). US-guided percutaneous biopsy of the mass showed poorly differentiated pancreatic adenocarcinoma. The patient underwent neoadjuvant chemotherapy with FOLFIRINOX (6 cycles). A CT scan showed reduction of the tumor after chemotherapy together with para-aortic lymph nodes. 18-FDG-PET/CT did not show any pathological uptake of the radiotracer, and CA 19-9 levels normalized. The patient underwent pylorus-preserving pancreaticoduodenectomy. Pathological examination did not show residual cancer cells, and no adjuvant therapy was administered. Sixteen months after surgery, brain metastasis occurred in absence of other sites of recurrence. Pathological examination of resected specimen confirmed brain metastasis from pancreatic adenocarcinoma. One month later, CT-scan showed multiple brain metastases, treated with palliative stereotactic radiotherapy.
The patient died of progression of disease 25 months after pancreatic resection. **Conclusions.** In conclusion, FOLFIRINOX neoadjuvant therapy for locally advanced pancreatic cancer may allow resection in a significant percentage of patients. Complete pathologic response is a rare event, which does not mean cure because tumor’s recurrence may happen.

**Body composition assessed by CT scan on pancreatic cancer patients**

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**Context.** Cancer cachexia is a syndrome characterized by muscle loss, depletion of lipid stores, anorexia and weakness. Almost one third of cancer’s related deaths are attributable to cachexia. It has also been suggested that body composition is related to overall survival and post-operative complications in surgical patients. The aim of the present study was to assess the body composition of pancreatic cancer patients candidate to upfront surgery at the time of diagnosis and investigate the possible different body composition among cachetic and non-cachetic patients.

**Objective.** Cancer cachexia, sarcopenia, pancreatic cancer, CT scan, body composition.

**Methods.** We retrospectively identified all patient with a clinical suspect or pathological diagnosis of ductal adenocarcinoma for whom we had complete anamnestic information and the pre-operative abdominal CT scan from January 2015 to December 2016. Body composition has been assessed using Synapse3D software (Fujifilm) to determine: visceral adipose tissue area (-150; -50 HU), subcutaneous adipose tissue area (-190; -30 HU), skeletal muscle area (-29; 150 HU) and intramuscular adipose tissue area (-190; -30 HU) at the L3 level.

**Results.** A total of 22 patients has been identified. Among them there were 14 females and 8 male and the median age was 68.5 years (50.84). Eleven patients underwent pancreaticoduodenectomy, two patients total pancreatectomy and splenectomy, one patient distal pancreatectomy and splenectomy and eight patients were found to be metastatic or primary non-resectable at the time of surgery. Morbidity rate was 50%. Mean BMI was 23.9 (18.9; 35.9); mean weight loss (WL) in 6 months was 6.8Kg (0;20) and mean WL% was 9.4% (0%;24.4%). According to Fearon et al. there were 15 cachetic patients and their mean WL in 6 months was 9.7 Kg (2; 20) and WL% in 6 months was 13.48% (5.5%; 25%). The mean time from the collection of the CT scans and the diagnosis is 27 days (6;97). Surprisingly, cachetic patients are not sarcopenic if compared to non cachetic patients, in fact they didn’t shown a significant difference in skeletal muscle area. Considering adipose tissue area, cachetic patients has a significant loss of intramuscular adipose tissue and visceral adipose tissue compared to non-cachetic ones. No difference has been found on subcutaneous tissue area among the two groups.

**Conclusions.** CT assessment of body composition is a promising tool to investigate how cancer cachexia modify both adipose tissue and skeletal muscle. A future prospective is to correlate the body composition to surgical morbidity, mortality and overall survival of pancreatic cancer patients, in order to better quantify the surgical risk.


**Tumor volume ratio (TVR) correlates with lymph node ratio (LNR) in pancreatic ductal adenocarcinoma**

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**Context.** Tumor diameter and lymph-node ratio (LNR) are important prognostic factors after pancreatic ductal adenocarcinoma (PDAC) resection. There are no pre-operative factors that can reliably identify patients with high LNR.

**Objective.** We aimed to correlate tumor volume ratio (TVR) with LNR and describe its’ association with survival-outcomes.

**Methods.** Tumor staging was performed in 173 PDACs. TVR was defined as the ratio between tumor volume and specimen volume (both in cm3). LNR was defined as the ratio between examined lymph-nodes and metastatic lymph-nodes.

**Results.** Patients included stage IIA (n=29; no metastases), stage IIB (n=125; metastases in regional lymph-nodes) and stage IV (n=19; metastasis in extra-regional lymph-nodes). The mean number of examined lymph-nodes was 35.8 (range 7-108); with no difference between stages. In stage IIB patients, mean LNR was 17.3% (range 1.7%-77.7%), and mean TVR was 19.3% (range 0.8%-72.9%). There was good linear regression observed between TVR and LNR (r2=0.994; P<0.0001). Mean TVRs in stage IIA and IIB patients were 8.6% and 19.3%; respectively (P=0.021). Furthermore, mean TVR showed a correlation with both nodal (N) and metastatic (M) status (P=0.013).

**Conclusions.** LNR is a prognostic factor for PDAC. Patients with high LNR do poorly even after radical resection. We are currently unable to reliably identify patients with high LNR until histological analysis. Our data shows a strong correlation between TVR and LNR in resected PDACs. If radiologic determination of TVR leads to the same results, we would be able to pre-operatively identify patients with anticipated high LNR among those with resectable PDACs.
IGF-II and NSC-631570 compounds affect PMP22 gene expression in pancreatic ductal adenocarcinoma. Could it be the new target for both chemo-resistance and neuronal invasion?

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Context. Peripheral myelin protein 22 gene (PMP22) encodes a membrane protein of myelin in the peripheral nervous system. PMP22 is also capable of delaying the transition from G0/G1 to S phase (Growth Arrest Specific Gene 3, GAS3). However, growth factors involved in PMP22 regulation, such as Insulin-like growth factor-II (IGF-II), are up-regulated after radiation in fibroblast cells, and might influence chemo-radio resistance. Since the compound NSC-631570 had a protective effect on human fibroblasts but not human tumour cells against ionizing radiation, and showed beneficial effects in phase II studies in metastatic and locally advanced PDAC patients.

Objective. The aim of this study was to evaluate the interaction between PMP22, IGF-II and NSC-631570 in PDAC Primary Cell Cultures (PCCs).

Methods. DNA duplication of PMP22 gene was evaluated by PCR and specific digestion by the endonucleases EcoRI and NsiI in 13 PDAC tissues, 2 PCCs and PBMCs from 3 healthy subjects (used as negative controls in genetic tests for the CMT1A syndrome). PMP22 protein expression was evaluated in tissues and cells by IHC, using a quantitative scoring. The PCCs were also exposed to IGF-II, NSC-631570, and their combination.

Results. The PMP22 duplication was observed in 44% (7/16) of PDAC patients and in both PCCs. DNA duplicated samples showed significantly higher score of PMP22 protein expression (p=0.0262). PMP22 protein was correlated with decreased cell growth, whereas 400 nM IGF-II reduced PMP22 expression and increased cell proliferation. Conversely, the addition of 1μM NSC-631570 increased PMP22 expression, and overcame IGF-II induced proliferation.

Conclusions. This is the first study reporting PMP22 duplication in PDAC specimens and cells. This duplication was correlated with PMP22 expression. PMP22 protein was inversely related to cell proliferation and its inhibition by IGF-II might explain chemo-radioresistance caused by PDAC associated fibroblasts.

TGF-β/EGFR autocrine cross-talk affects EMT process and migration in 3D tissue-engineered model of pancreatic ductal adenocarcinoma

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Context. Preclinical models close to PDAC are needed. Growth factors play a pivotal role on the aggressiveness and migration. TGF-β expression represents the master factor involved in epithelial mesenchymal transition (EMT) phenomenon.

Objective. Aim of this study was to investigate cell migration in 3D tissue-engineered model of PDAC through TGF-β protein expression.

Methods. Primary PDAC cells were seeded into sterile polyvinyl alcohol/gelatin (PVA/G) scaffolds at a density of 1x105 cells/mm3 and cultured for 4 different times (2, 5, 8 and 15 days). Six scaffolds for each time were performed. The medium was replaced as needed in group A, while in group B, the medium was not replaced. Twenty-four formalin-fixed paraffin embedded (FFPE) 3D model were obtained. Analyses included: viability, morphology, histology marker expressions by immunohistochemistry (PanCk, EGFR, TGF-β, MMP9) and cell migration by computerized analyzes of images. ELISA test (EGF concentration in the medium). Data were analyzed using ANOVA and Student’s tests. A p value <0.05 was considered significant.

Results. Significant differences comparing Group A vs. Group B models were observed at 15 days, respectively: Metabolic activity (46.6% vs. 57.2%, p=0.001), cell migration (r²=0.9726; p=0.0138), distribution of cells in the border of scaffolds (mean difference 74.6%; p=0.0020). Number of mesenchymal-shape cells (80% vs. 10%, p<0.01). Group A showed high expression of PanCk, EGFR, TGF-β and MMP9. Constitutive expression of TGF-β was confirmed and difference in EGF secretion in 3D models was observed (group A vs. group B: 11:17 vs. 6.97 pg/ml; p<0.05).

Conclusions. Recently is reported that cross-talk between TGF-βRs and EGFR in pancreatic cancer and the autocrine secretion of their growth factors induce a series of processes including cell proliferation, tumor growth and EMT. Autocrine secretion of EGF could control the balance between proliferation and EMT process. These experiments may be use to suggest treatment anti TGF-β and EGFR in patients with PDAC.

The titanium surface modulates the expression of beta-catenin and DLX5 genes in pancreatic ductal carcinoma in vitro. Can the metallic stent increase PDAC aggressiveness?

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Context. Adenoductal pancreas (PDAC) is a fatal cancer. Its aggressiveness is associated in part with the EMT process of metastasis. Two genes specifically involved in these phenomena are β-catenin and DLX5. While the first gene has been widely studied also in pancreatic cancer, few data are associated with DLX5. However, its over-expression has been recently associated with the formation of metastases in breast cancer in vitro. An exogenous factor involved in the modulation of the expression of these genes seems to be titanium. This
compound is usually employed for the pallia action of patients with PDAC, to reduce stenosis choledochal due to compression.

**Objective.** The purpose of this study was to assess whether titanium is able to modulate the expression of these two genes in vitro. Clinical studies are needed to find out which type of stent can be used in the surgical operation with palliative intent.

**Methods.** We used a primary cell culture of PDAC (PP78). The cells were seeded and cultivated in contact with two different titanium surfaces for 10 days. After this period the total mRNA was extracted and the quantification of β-catenin and DLX5 genes was performed by RT-PCR according to the ΔΔCt analysis. Then cells were stained using the immunofluorescence technique (IF) to quantify the β-catenin protein expression using a computerized high-resolution acquisition system (D-Sight, Menarini Florence - Italy). The cells were scored evaluating the cytoplasmic positivity as follows (0 absent, 1 Low, 2 middle, 3 strong). The experiment was carried out in triplicate and untreated cells (without titanium contact) were used as control.

**Results.** Quantitative analyses showed that both titanium surfaces positively affected beta-catenin (mean 2.8 fold) and DLX5 (2.0 fold) mRNA expressions with respect to the controls (p<0.0007). Both titanium surfaces also increased the protein score 3 values of β-catenin in treated cells with respect to their controls (p=0.0158).

**Conclusions.** Our data showed that several titanium surfaces positively modulated the expression of two genes associated with the increase of the aggressiveness of PDAC in vitro. Clinical studies are needed to find out which type of stent can be used in the surgical operation with palliative intent.

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**Secondary tumors of the pancreas: a tertiary center experience**

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**Context.** Metastatic tumors to the pancreas may occur with an incidence ranging from 3% to 12%. The most common primary cancers are renal cell, lung, breast, colorectal carcinoma, and melanoma.

**Objective.** The aim of the study was to describe demographic, clinical, endosonographic, pathological, therapeutic, and follow-up data of patients with a diagnosis of pancreatic metastasis.

**Methods.** A retrospective review of a prospectively maintained database of EUS procedures was carried out between May 2014 and January 2017(NCT02855151).

**Results.** Thirty-three patients were included in the present study. Mean age was 64.1 years, with a prevalence of male gender (63.3%). In 26 patients (78.8%), pancreatic metastasis was asymptomatic. The primary site was kidney in 25 patients (75.7%), melanoma in 3 patients (9.1%), breast in 2 patients (6.1%), colon in 1 patient (3.0%) and lung in 2 patients (6.1%). The mean time of recurrence was 6 years. At EUS evaluation all lesions were solid and 85.7% were hypovascular. In most cases the masses had homogeneous pattern (57.1%). Sixteen lesions (76.2%) showed hypervascular echotexture at High Resolution Flow mode. The majority of cases (71.4%) had regular and well-defined borders. Twenty-five patients (75.8%) underwent surgical resection of the pancreatic metastasis. A mean follow-up of 28.7 months was recorded. None of the patients died during follow-up.

**Conclusions.** The clinical scenarios of metastases to the pancreas may be very variable: they may occur synchronous to the primary tumor, or many years after the diagnosis and the treatment of the primary tumor. A multidisciplinary team approach is mandatory to suggest the patients the right diagnostic path and best treatment modality tailored for each patient.

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**Gemcitabine resistant pancreatic cancer cells are sensitive to taxane treatment**

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**Context.** Pancreatic cancer remains a highly lethal disease. Adjuvant treatment with gemcitabine improves the disease-free survival of surgical patients from 6.9 to 13.9 months. However, resistance to gemcitabine hampers the efficacy, warranting the development of new adjuvant regimens to improve survival of patients suffering from this disease.

**Objective.** We aim to identify the mechanisms underlying gemcitabine resistance and to identify new drug regimens to target resistant pancreatic cancer cells.

**Methods.** A gemcitabine resistant pancreatic cancer cell line was created by selection of cells capable of proliferating at treatment dose of 1uM gemcitabine. Proteins from this cell line and its sensitive counterpart were isolated. Additionally, phosphorylated proteins were enriched and identified via mass spectrometry. The inhibitory effect of chemotherapeutics was evaluated using 72-hour drug exposure.

**Results.** The resistant cell line showed a ten-fold resistance against gemcitabine over the normal sensitivity. Differential protein analysis showed microtubule-associated protein 2 to be significantly overexpressed, and highly phosphorylated in resistant cells. Microtubules are structural proteins important for migration and proliferation, and can be inhibited by paclitaxel. Indeed, in vitro treatment showed that gemcitabine resistant cells are sensitive to paclitaxel. Moreover, in vitro the resistant cells responded to nab-paclitaxel treatment.

**Conclusions.** Gemcitabine resistant pancreatic cancer cells were found to be sensitive to taxane treatment. This result underlines the importance of combination treatment to target subclones with divergent sensitivities in pancreatic cancer. Moreover, these findings might explain the encouraging efficacy of nab-paclitaxel/gemcitabine combination treatment as metastatic regimen. Future clinical trials are needed to evaluate combination treatment in the adjuvant setting.
Comparative genomic analysis of small size (<3 cm) well-differentiated pannets reveals genetic alterations associated with distant metastases

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Background. Non-functioning PNETs are characterized by heterogeneous clinical course, from indolent to highly malignant because of the development of distant metastases. We first characterized ATRX and DAXX protein expression and telomere status and them we performed a genomic analysis comparing metastatic and non-metastatic tumors <3 cm.

Methods. 32 small well-differentiated metastatic PNETs and other 55 non metastatic PNETs after a 5-year follow-up were collected from multiple institutions. ATRX and DAXX expression was studied with ICH and a telomere-specific FISH aimed to detect ALT positive tumors. 24 PNETs from the metastatic group and other matched 24 PNETs from the control group were therefore included in the genetic analysis. Targeted next generation sequencing (NGS) on genes commonly mutated on PNETs was performed to check out the mutations and whole genome high density SNP-array to evaluate the copy number variations (CNV).

Results. Variables associated with the development of liver metastases by univariate analysis were tumor size, Ki67, WHO grade ALT positivity and DAXX loss of expression. On multivariate analysis, only Ki67, N stage and ALT positivity were independent risk factors for liver metastases. A cluster analysis identified different subtypes of PNETs on the basis of types and frequencies of CNVs. Targeted DNA sequencing identified somatic mutations in MEN1 (16/48), DAXX (9/48), TSC2 (9/48), PSEN1 (1/48), ATRX (1/48), CDKN2A (1/48) and TP53 (1/48).

Conclusions. Integrating copy number, mutational and expression data for ALT revealed 3 different subtypes characterized by distinct molecular and clinical patterns. Group 1: Tumors were characterized by recurrent chromosomal gains, by DAXX or ATRX loss of function and exhibited a positive “ALT” phenotype. 73% of these tumors were metastatic. Tumors in Group 2 did not exhibit significant copy number variations or somatic mutations and 42% were metastatic. In Group 3, Tumors with recurrent chr 11 loss, harbored a MEN1 mutation in 8/14 cases and 35% were metastatic.

Clinical implications of intraoperative fluid therapy in pancreatic surgery: it is not “just water”

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Context. Recent studies on fluid administration in patients undergoing major abdominal surgery have suggested that increased fluid loads are associated with worse outcomes. However, systematic data regarding the influence on complications after pancreatic resections are lacking.

Objective. To examine the influence of intraoperative fluid administration on morbidity following pancreatic resections.

Methods. Analysis of 350 patients who underwent pancreaticoduodenectomy (PD n=209), distal (DP n=96), and total pancreatectomy (TP n=45) in 2016. Intraoperative fluid administration was analyzed and related with postoperative morbidity.

Conclusions. According to intraoperative fluid volume administration, patients were divided into two groups: a near-zero fluid balance (infusion 3ml/kg/h, n=55) and a liberal fluid balance group (>3ml/kg/h, n=295). Patients treated with a near-zero balance had higher weight (p=0.02), longer operations (p<0.01) and lower administration of neoadjuvant treatment (p<0.01); while ASA score was similar. The intraoperative fluid volume was higher for patients who underwent PD (p<0.01), vascular resection (p<0.01), especially for those with high fistula risk score (p=0.02) and soft pancreas texture (p=0.03). Postoperative severe overall morbidity was significantly increased in the liberal fluid group (50.5% vs. 34.5%; p=0.02), as DGE (8.8% vs. 1.8%; p=0.05), while post-operative hemorrhage, POPF and in-hospital mortality were not impacted. A near zero fluid balance increased the rate of post-operative acute pancreatitis (75% vs. 49.2%; p=0.02) after PD; particularly in presence of soft pancreas texture (93.3% vs. 73.6%; p=0.05). However, it reduced the incidence of biliary fistula (0% vs. 7.9%; p=0.05) and DGE (5% vs. 11.6%; p=0.04).

Conclusions. The intraoperative management of fluid had relevant implications in the postoperative outcome.
A liberal fluid management is associated with an increased rate of Clavien-Dindo ≥3 complications. A near-zero fluid balance is related to an increased risk of acute pancreatitis in specific clusters of patients. Intraoperative fluid management should be balanced according to patient's and pancreatic surgery-specific risk factors.

**Genetic variability of the ABCC2 gene and overall survival in pancreatic cancer**

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**Context.** The ABCC2 gene is overexpressed in pancreatic cancer and the protein encoded by this gene mediates the transport of a large variety of anticancer drugs and it is involved in drug resistance in mammalian cells. Single nucleotide polymorphisms (SNPs) in ABCC2 have been associated with differential outcomes and prognosis in several tumours.

**Objective.** The aim of this study was to test whether SNPs within ABCC2 are associated with pancreatic cancer survival.

**Methods.** A total of 12 polymorphisms, including tagging-SNPs covering all the genetic variability of the ABCC2 gene chromosomal region and SNPs that are eQTLs, have been selected and genotyped in PDAC patient collected through the PANDoRA consortium.

**Results.** The association between ABCC2 SNPs and PDAC overall survival have been tested using Cox proportional hazard models but none of the SNPs showed a statistical significance association. The most interesting result have been found for the SNP rs717620 showing an HR of 1.52 (95% CI 0.98-2.36, p-value=0.063). According to GTEx portal, this SNP is not able to alter expression levels in pancreatic tissues. However, previously published studies indicated that it could be a functional polymorphism in vitro.

**Conclusions.** In conclusion, according to this study ABCC2 polymorphisms are not associated with PDAC overall survival. However, further studies in a larger sample size are warranted to clarify the role of rs717620 in the disease outcome.

**Gene and Genetic variability of the ABCC2 gene and overall survival in pancreatic cancer**

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**Context.** Telomere length in normal tissues such as in leucocytes (LTL) has been shown to be a risk marker for several cancer types.

**Objective.** To determine if LTL is associated with PDAC risk, we used genetic determinants of telomere length as proxies of LTL as it has been successfully done for several cancer types.

**Methods.** We analyzed 10 SNPs alone and combined in a LTL genetic score in relation to PDAC risk in 2,374 cases and 4,326 controls from the PANDoRA consortium.

**Results.** We identified several new associations, among which the strongest were with the TERT-rs2736100 SNP (OR=1.54 [95% CI 1.35-1.76] p=1.54x10^-10) and with the NAF1-rs7675998 SNP (OR=0.80 [95% CI 0.73-0.88] p=1.82 x 10^-10 as a continuous variable).

**Conclusions.** In conclusion we here a completely new signal (NAF1-rs7675998) for PDAC risk that approaches the genome-wide threshold and we propose short telomeres as strong risk factor for pancreatic cancer.

**Inability to comply with an enhanced recovery protocol after a pancreaticoduodenectomy**

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**Background.** despite all the papers assessing safety and feasibility of enhanced recovery protocols (ERP) in pancreaticoduodenectomy (PD) few is know of the real compliance with the main goals of these ERPs.
Objective. Evaluate the compliance to an ERp after PD and assess if there are some prognostic factors that can predict the failure to follow an ERp.

Methods. For 1/1/2014 to 31/1/2016 253 consecutive patients underwent a PD in our center and were managed accordingly to an ERp. Perioperative data were prospectively collected in a database including all the specific ERp goals. Failure to comply with postoperative items were defined as: less than 4 hours out of bed postoperative day (POD) 2 (mobilization); no active deambulation POD3; removal of NGT and bladder catheter after POD1 and 3 respectively; reintroduction or suspension (at least 1 day) of oral feeding after POD4; prosecution of intravenous infusions after POD4. Univariate and multivariate analysis were conducted using chi², non-parametric test and regression models when indicated. Data are presented as percentage, median [IQR].

Results. Registered failure rate were: 44.7% for mobilization; 15.2% for deambulation; 2.3% for removal of NGT and 44.7% for bladder catheter, 33.7% for solid diet; 49.7% for infusions. 59.2% of our patients failed at least two of the evaluated goals. Despite that, the median in which patients were fit for discharge was 10[9]. However there is a strong linear correlation between the number of goals failed and the length of stay (from 7 to 18 days; B = 2.32, P<0.001). At a multivariate analysis BMI and the consistency of the pancreatic stump resulted as independent predictors of failure of at least two goals (OR 1.177 p=0.036; OR 3.572 p=0.029). This finding can be related to the correlation between failure and the postoperative developing of a pancreatic fistula, a postoperative overall or major complication (OR 5.989 p<0.001; OR 6.482 p<0.001; OR 4.068, p=0.034). A validated risk score for postoperative complications (Braga et al.) resulted able to predict the failure of EPs OR 1,247 p=0.003 with a good fitting ability.

Conclusions. Despite the crude rate of patients that didn’t underwent adjuvant CT, the percentage of patients who are excluded for surgery-related reasons is small. In most of cases, comorbidity and age are the main drivers that restrain the administration of adjuvant CT.

The spectrum of germs and their antibiotic resistances in patients that pancreatico-duodenectomy: is the cefazoline-based antibiotic prophylaxis useful? Ucelli F.1, Nappo G.1, Morelli P.2, Casari E.3, Gavazzi F.1, Ridolfi C.1, Capretti G.1, Omolegi P.1, 2Medical Oncology Unit; Humanitas University; 3Humanitas Research Hospital, Rozzano (MI), Italy; 1Pancreatic Surgery Unit, Humanitas Research Hospital, Rozzano, Italy; Infectious Diseases Unit, Hospital Health Direction, Humanitas Research Hospital, Rozzano, Italy; Microbiology Unit, Analysis Laboratory, Humanitas Research Hospital, Rozzano, Italy; Gastroenterology Unit, Humanitas Research Hospital, Rozzano, Italy

Context. Infectious complications remain a major clinical problem after pancreatic surgery. Guidelines for antibiotic prophylaxis recommend the use of cefazoline for patients undergoing Pancreatico-Duodenectomy (PD).

Objective. The aim of the study was to evaluate the spectrum of germs and their antibiotic resistances in

| Table 1: Spectrum of antibiotic resistances of isolated germs. |
|-----------------|-----------------|-----------------|-----------------|
| Cefazoline resistance (%) | Amoxicilline/ clavulanic acid resistance (%) | Gentamicine resistance (%) |
| Enterococci | 93.6 | 34.9 | 25.4 | 17.5 |
| Klebsiella | 29.3 | 80.1 | 29.3 | 4.3 |
| E. Coli | 54.4 | 61.8 | 40.9 | 7.27 |
| Enterobacter | 86.3 | 95.4 | 88.6 | 11.3 |
post-operative cultures of patients undergoing PD, in order to evaluate the efficacy of the antibiotic prophylaxis.

**Methods.** We retrospectively evaluated by a prospective collected database all consecutive PD performed from June 2015 to June 2017 in our center. Intraoperative bile, culture and culture of drain fluid in post-operative day 5 were performed in all patients. Data regarding isolated germs and their antibiotic resistances were collected and evaluated.

**Results.** During the study period, 177 patients underwent PD in our center. Enterococci were the most common germs isolated (in 71.2% of cases), followed by Klebsiella, Escherichia Coli and Enterobacter (in 65.5%, 62.1% and 24.8% of cases, respectively). In the majority of cases, same isolated germs in intraoperative bile and drain fluid cultures were found. Concerning antibiotic resistance (table 1), Enterococci, Enterobacter, Escherichia Coli and Klebsiella were resistant to cefazoline in 93.3%, 86.3%, 54.4% and 29.3% of cases, respectively. An analysis of sensitivity of different antibiotics revealed that gentamicin had the lowest percentage of resistances for these germs.

**Conclusions.** Germs frequently isolated after PD are resistant to cefazoline. Gentamycin seems to be a better choice for these germs.

Ten years of post-operative pancreatic fistula (POPF) definition (2005-2016). Does the new classification really change something?


**PANCREATIC SURGERY UNIT, HUMANITAS UNIVERSITY, HUMANITAS RESEARCH HOSPITAL, ROZZANO (MI), ITALY**

**Context.** In 2005 International Study Group of Pancreatic Surgery (ISGPS) classified Post-Operative Pancreatic Fistula (POPF) into three different grades of severity (A, B, C). This classification has been worldwide adopted. In 2016, ISGPS revised and updated this classification.

**Objective.** The aim of this study was to compare the incidence and severity of POPF in our series of Pancreatico-Duodenectomies (PDs) using the two ISGPS classifications.

**Methods.** All consecutive PDs performed from 2010 to 2016 were retrospectively evaluated from a prospective collected database. In addition and grade of POPF according to the two classifications were recorded and compared.

**Results.** A total of 502 patients were included in the study. The overall incidence of POPF was 35.2% and 30.7% adopting the old and new classification, respectively (p=0.01). POPF was classified as grade A, B and C in 26.1% and 4.6%, 26.1% and 4.6%, respectively, according to the old classification, while was classified as grade B and C in 26.1% and 4.6%, respectively, according to the new one (biochemical leak was observed in 4.6% of cases). Reasons of grade B POPF were extremely heterogeneous: antibiotic administration (10.7%), drain > 3 weeks (67.9%) and radiological procedures (drainage/embolization) (21.4%).

**Conclusions.** The updated classification deletes grade A POPF, introducing the concept of biochemical leak. Consequently, it reduces significantly the overall rate of POPF. However, this classification doesn’t change the criteria of grade B POPF, that continue to be too much dependent to the post-operative management policy (antibiotics administration, timing of drain removal) and to group cases with different clinical severity.

**Biliary stenting before pancreaticoduodenectomy: an unsolved problem**


**Pancreatic Surgery Unit, Humanitas University, Humanitas Research Hospital, Rozzano (MI), Italy.**

**Context.** Pancreatico-Duodenectomy (PD) is affected by high rate of morbidity and mortality, even in high-volume pancreatic centers. In literature, it’s well known that Preoperative Biliary Stenting (PBS) significantly increases morbidity after PD. For this reason, it’s recommended to avoid the use of PBS in absence of clear clinical indication.

**Objective.** The aim of the current study was to review our series of PD, evaluating the rate of PBS and its impact on post-operative outcomes.

**Methods.** We retrospectively reviewed by a prospective collected database all patients underwent PD in our center. The overall rate of PBS and the rate of PBS performed in tertiary hospitals before our preoperative consultation were calculated. The impact of PBS on post-operative outcomes was also evaluated.

**Results.** From January 2010 to June 2017, 531 patients underwent PD. At least one complication occurred in 61.2% of cases, while severe complications (grade III-IV according to Clavien-Dindo classification) was recorded only in 18.6% of cases. Mortality rate was 2.2%.

Two-hundred-seventy-five patients (51.8% of all cases) underwent PBS; interestingly, 168 PBS (61.1%) was performed in tertiary centers before our preoperative consultation. Stratifying PD per year, the rate of PBS performed in tertiary centers remains constantly high (table 1). Patients with PBS had significantly higher rate of severe complications (grade III-IV) (22.9%) if compared with non-stented patients (18.7%) (p<0.05).

**Conclusions.** PBS increased severe morbidity after PD. The rate of stented patients that underwent PD in high-volume pancreatic center still remains high, due to the attitude of tertiary centers to perform PBS. A better awareness of tertiary centers is mandatory in order to reduce the rate of avoidable PBS and to improve outcomes after PD.

**Table I.**—Rate of PBS and PBS performed in tertiary centers per year

<table>
<thead>
<tr>
<th>Year</th>
<th>PD (%)</th>
<th>PBS (%)</th>
<th>PBS in tertiary centers (%)</th>
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<tr>
<td>2010</td>
<td>34</td>
<td>55.9</td>
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<tr>
<td>2017</td>
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<td>42.5%</td>
<td>64.7%</td>
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New molecular diagnostic approaches based on fluorescence microscopy in pancreatic ductal adenocarcinoma (PDAC): validation of the prognostic value of CYB5A and of FAD lifetime imaging for margin discrimination

Nicola Funel 1, 2, Ranieri Bizzarri 2, Barbara Storti 2, Elisa Giovannetti 1, 2, Ugo Boggi 1, on behalf of the investigators (from Istituto di Tecnologie Biomediche ed Istituto Nanoscienze del Cnr; Fondazione Istituto Italiano di Tecnologia - Center for nanotechnology innovation IIT@NEST; Scuola Normale Superiore) of the project DIAMANTE (Regione Toscana - Fas Salute grant)

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Context. Several clinicopathologic factors, such as stage, are prognostic variables in PDAC. Nevertheless, initial staging currently relies on relatively non-discriminatory imaging and stage definition, which is not known until resection, appears of limited use for the choice of the best therapeutic approach. Analysis of biomarkers in biopsies collected before surgery could improve stratification of patients to different clinical management. However, intracellular localization of biomarkers at submicron-scale is a key factor in the comprehension of effective prognostic factors, and this issue can be addressed only by cutting-edge imaging based on fluorescence microscopy.

Objective. Through a multidisciplinary scientific enterprise including physicians, biophysicists, computational/experimental chemists and one industrial partner (Biomedica-Mangoni) we will achieve high-sensitivity and high spatial-resolution detection, by the use of microscopy techniques based on the spatial modulation of light excitation.

Methods. We will use computationally-designed recognition motifs with super-bright fluorescent qDots to afford novel probes for high-sensitivity detection of selected biomarkers, such as CYB5A (Giovannetti et al, JNCI 2014), in biopsies and tissue-microrrays of (N>200) PDACs. Further, recent data emphasized how some optical properties of the endogenous fluorophores NADH and FAD, such as fluorescence lifetime, can unravel the metabolic difference between tumor and normal tissues. Therefore, we tested an established method of confocal fluorescence microscopy, namely the phasor approach to lifetime imaging, in order to distinguish tumor from normal tissue taking advantage of FAD endogenous fluorescence. With a confocal microscope apparatus interfaced with a pulsed laser source (470 nm) and a spectral acquisition system range by time-correlated single photon detection.

Results. We previously correlated CYB5A expression with survival. Here we further explored the relevance of this discovery by correlating the expression of this gene by both IHC and immunofluorescence, demonstrating that PDACs are more aggressive if they have low expression of this microsomal protein. Moreover, phasor lifetime maps clearly highlighted different responses of FAD emission in mPDAC vs. L in which normal regions were characterized by a shorter lifetime (1-2 ns) as compared to tumor regions (2-3 ns). Some images showed also a clear neoplastic margin infiltration.

Conclusions. Our novel imaging methodologies improve the definition of clinically relevant biomarkers, with potential implications for new therapeutic strategies. Furthermore the analysis of the FAD optical response could represent a supporting approach helping surgeons to assess safe resection margin during PDAC surgery.

Association of miR-100 and miR-125b expression with epithelial-to-mesenchymal transition (EMT), metastasis and poor prognosis in pancreatic ductal adenocarcinoma

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Context. TGF-ß/activin induces epithelial-to-mesenchymal transition (EMT) and stemness in pancreatic ductal adenocarcinoma (PDAC), yet the role of microRNAs (miRNAs) in this response is unknown. We demonstrated that TGF-ß transcriptionally induces miR-100 and miR-125b.

Objective. To investigate miR-100 and miR125 as prognostic biomarkers, as well as their role in EMT, stemness and invasion/metastasis.

Methods. EMT and metastasis were evaluated in PDAC cells and xenografts using miRNA mimics, miRZip technology, spheroids, wound-healing scratch assays followed by video-tracking, and analysis of liver metastatic colonization. Tissue microarrays including 100 PDAC cases were evaluated by validated chromogenic in-situ hybridization protocols. Experimental findings were tested for their correlation with clinical and follow-up data.

Results. MiR-100 and miR-125b each triggered EMT and stemness and consequently reduction of their activity stunted in vivo tumorigenesis. Additionally, inhibition of miR-125b blocked in vivo experimental metastasis and overcame gemcitabine-resistance. High miR-100 and miR-125b levels in tumor cells were an independent predictor of survival, while no significant differences were associated with stromal miRNA expression.

Conclusions. Our results support a key role for miR-100 and miR125 as prognostic factors, and either single or concurrent inhibition of these miRNAs should be considered as a future PDAC therapy.

Serum amylase level in the first postoperative day and after pancreaticoduodenectomy: what are they related to and what can they predict?

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Context. Values of serum amylases in the first postoperative day after pancreaticoduodenectomy (PD) are part of the diagnosis of acute postoperative (PAP). Still there are some evidence that it can be related also with other postoperative complications as pancreatic fistula (PF).

Objective. The aim of the study was to evaluate the role of serum amylase level in the first postoperative day, its correlation with the developing of a PAP and PF with a multivariate approach.

Methods. We collected the data from 173 consecutive pancreaticoduodenectomy performed in our center between January 2015 and January 2017. We collected data about postoperative morbidity and serum amylase level in the first and third postoperative day. Acute postoperative pancreatitis was defined by serum amylase level and typical pain. Morphological features of pancreatic stump were recorded intraoperatively. PF was defined according to the ISGPS.

Results. Of our patient 17.3% have a serum postoperative amylase day 1 up to 500 UI/L. Several factors correlate with an increased level of postoperative amylase POD 1 such as small pancreatic duct (P=0.05) or the total area of the pancreatic stump (P=0.047). Of this patients only 26.7% (8/30) develop PAP. Its overall rate was 4.6% (8/173). Other factors were related with the occurrence of a PAP such as duct decentralization on stump anteroposterior axis (P=0.012 OR 0.477) and the total area of the pancreatic stump (P=0.052 OR 1.108). Interestingly patients with an higher postoperative level of serum amylase show an higher POPF rate 78.6% vs. 21.4% (P=0.001). In multivariate analysis this correlation is so strong that the consistency of the pancreatic parenchyma loose its significance.

Conclusions. POD 1 serum amylase levels is elevated in a conspicuous percentage of patients after PD, only in one third of cases this was associated with a PAP. Developing of a PAP seems correlated with the geometric features of the pancreatic stump. Interestingly POD serum amylase seem strongly correlated with the developing of a PF.

Biliary metal stents in patients with malignant jaundice and CBD stricture: a retrospective cohort study

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Context. Endoscopic transpapillary biliary drainage is the treatment of choice for obstructive jaundice caused by malignant strictures. Different types of self-expanding metal prostheses (SEMS) are available: fully covered (FC) SEMS, partially covered (PC) SEMS and uncovered (UC) SEMS. The advantage of metal compared to plastic prostheses is the reduced risk of rehospitalization and complications especially in patients expected to survive for more than 3 months. However what is the most effective type of metal prosthesis is still debated.

Objective. To evaluate the reintervention rate after the positioning of metal stents, comparing FC versus PC versus UC SEMS.

Methods. retrospective single center cohort study including patients undergoing ERCP with positioning for the first time of SEMS for CBD malignant stenosis, independently of stage of disease. A repeated ERCP was indicated in case of jaundice and/or cholangitis. T-test was used for comparison of continuous variables, Fisher’s test was used for comparison of categorical variables. Reintervention probability was calculated with the Kaplan-Meier curve, and Cox analysis was employed to calculate hazard ratios (HR). Tests of statistical significance and confidence intervals were two-sided; p≤0.05 was considered to be statistically significant.

Results. 193 patients (34 FC, 34 PC, 125 UC) were included in this preliminary analysis, (mean age 69.3±11.9 years, 50.8% being males); 90.2% had pancreatic cancer, 4.7% cholangiocarcinoma, the rest had ampullary tumor or pancreatic neuroendocrine tumors. 40.4% patients were metastatic, 37.5% were locally advanced, 22.3% were surgically resectable. Overall reintervention rate for FC vs. PC vs. UC SEMS was respectively of 23.5% vs. 5.8% vs. 32%. Patients with fully covered vs. uncovered SEMS had a HR of 1.05 (95% CI 0.48-2.27 P=0.89); patients with partially covered SEMS vs. uncovered SEMS had a HR of 0.27 (95% CI 0.12-0.61; P=0.04); patients with fully covered vs. partially covered SEMS had a HR of 4.58 (95% CI 1.52-15.86; P=0.03) for repetition of ERCP.

Conclusions. To our knowledge, this is the first study evaluating all three different types of SEMS to each other in terms of reintervention rate in patients with malignant CBD stricture and jaundice. The lower reintervention rate after PC SEMS positioning should encourage controlled studies to verify their higher benefit compared to FC and UC SEMS in the treatment of malignant jaundice.

“Delayed” needle-knife fistulotomy versus standard biliary sphincterotomy for choledocholithiasis: rate of post-ERCP pancreatitis and recurrence of common bile duct stones

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Context. Common Bile Duct (CBD) stones account for 8-20% of gallstone disease and are usually treated with ERCP with biliary sphincterotomy and stone extraction. The access to the CBD can be achieved through the papilla orifice followed by endoscopic sphincterotomy (ES), or through a precut fistulotomy (PF) in case of difficult cannulation; the two methods alter papilla anatomy differently, therefore intuitively leading to a different rate of post-ERCP acute pancreatitis (PEP) and recurrence of CBD stones. Although some studies suggested that the use of PF might be related to a higher risk of...
PEP, when performed early it isn’t. No data on either the risk of PEP or stones recurrence in patients with of CBS stones after PF has ever been published.

**Objective.** To evaluate the rate of PEP and the recurrence of CBD stones and of re-intervention of PF versus ES.

**Methods.** Retrospective single center cohort study including patients undergoing for the first time ERCP for CBD stones with PF in case of failed repeated cannulation attempts (>15 minutes or ≥5 passages of the guidewire into the MPD) (“delayed” PF). PF patients were matched for same sex and age (±1 year) to ES patients extracted from our database after randomization. T-test was performed for comparison of continuous variables. Fisher’s test was used for comparison of categorical variables. Recurrence probability was calculated with the Kaplan–Meier curve, and Cox analysis was employed to calculate hazard ratios (HR). Tests of statistical significance and confidence intervals were two-sided; p<0.05 was considered to be statistically significant.

**Results.** Between November 2008 and May 2015, 2219 patients underwent ERCP for CBD stones for the first time with PF and 85 matched controls were randomly selected (mean age 68.8 years, 45.9% being males). Compared to ES, patients undergoing PF had a higher rate of PEP (17.2% vs. 8.6%), although not statistically significant. PF patients had the same re-intervention rate of ES (14.1% vs. 12.9%) with a HR of 1.11 (95% CI 0.49–2.50, p=0.81), but the mean time to re-intervention was significantly lower (74.9±74.6 vs. 765.6±961.3 days; p=0.001).

**Conclusions.** The high risk of PEP after “delayed” PF in patients with CBD stones suggests that this technique should be avoided, possibly in favor of an “earlier” PF. The risk of re-intervention is not increased after “delayed” PF, but the mean time to re-intervention is significantly shorter.

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Utility of cystic fluid cytological analysis in the evaluation of malignant potential of pancreatic cystic lesions
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**Background.** Pancreatic cystic lesions (PCL) may be incidentally detected in approximately 13.5% of patients. Among the cystic lesions four histological types can be recognized: serous cysts (serous cystadenoma), largely benign; mucinous cysts (intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN)), that have a malignant potential, and pseudo-papillary solid tumor. The difficulty in distinguishing between the various PCL and their malignant potential, makes their management complicated. The diagnostic evaluation involves, among other investigations, the use of endoscopic ultrasoundography (EUS) and fine needle aspiration (EUS-FNA) for the analysis of cystic fluid, with evaluation of tumor markers, cytopology, mucins, amylase and DNA analysis. CEA is considered the most accurate tumor marker for the distinction of mucinous cysts versus non mucinous cysts.

**Methods.** Data regarding EUS examinations and FNA performed at our center between January 2015 and December 2016, were retrospectively analyzed.

**Results.** Out of 535 EUS, 90 were performed for pancreatic cysts, of which, according to EUS features, 53 appeared to be IPMN, 8 serous cystadenoma, 1 pseudo-papillary tumor, 1 pseudocyst, 27 unclassified. FNA was performed in 56 cases, of which in 45 it was possible to perform cytology examination, one of which was diagnostic for neuroendocrine tumors; between the cases in which were not highlighted worrisome features (35), 4 showed the absence of atypical cells, 31 were not diagnostic for the presence of: acellular material (6),...
Drug-induced acute pancreatitis: loperamide and adverse event
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Introduction. Drug-induced acute pancreatitis is responsible for only 0.1-2% of cases, but it seems to be underdiagnosed and classified as of “idiopathic etiology”. Loperamide is an opiate with peripheral action, used in the treatment of diarrhea. In 2012 the FDA puts loperamide on watch list to monitor after having identified potential signs of serious risk for acute pancreatitis. In this article we present three case of acute pancreatitis probably caused by loperamide.

Case report. CASE 1. A 77 years old woman with a remote cholecystectomy and a strong history of ischemic cardiomyopathy presented herself to our emergency room for abdominal pain, diarrhea and fever. She referred the appearance of diarrhea the day before for which she had taken loperamide. After she developed fever, stomach ache and nausea. She denied any alcohol consumption, smoking or family history for pancreatic disease. Lab tests revealed elevated serum amylase 184 U/L and liver function tests altered: aspartate transaminase 36 U/L with normal levels of serum bilirubin. White cell count, C-reactive protein were high: 13.3 x 10^9 and 28 mg/L. An abdominal ultrasound confirmed status post-cholecystectomy with choledochus 1 cm wide, no intra-hepatic bile duct dilation and no other relevant lesion. Since loperamide was discontinued, patient condition improved and she was released 5 days after admission. A pancreatic magnetic resonance imaging (MRI) including MR-cholangiopancreatography was performed during the hospitalization, showing a well-defined pancreatic gland without any sign of acute inflammation. The principal pancreatic duct was essentially regular. The MRI confidently excluded common bile duct lithiasis.

CASE 2. A 46 years old woman with a history of laparoscopic cholecystectomy in 2005 and hereditary thrombophilia, presented herself to emergency room for abdominal pain (overall in right-hypochondrium and mesogastrum) and nausea. No associated fever. She referred diarrhea the week before and she taken loperamide for this the day before the hospitalization. She denied any alcohol consumption or smoking. Lab tests revealed elevated liver function tests: aspartate transaminase 406 U/L, alanine transaminase 381 U/L with median-high levels of serum bilirubin: 21.8 mmol/L. White cell count, C-reactive protein and amylase were normal. She performed an abdominal ultrasound confirmed status post-cholecystectomy in a steatosic liver and no other relevant lesion. A pancreatic magnetic resonance imaging (MRI) including MR-cholangiopancreatography was performed after the hospitalization, showing no acute inflammation of pancreas. The main pancreatic duct seems to continue preferentially in the duct of Santorini, cause of an angled origin of Wirsung. The MRI confidently excluded common bile duct lithiasis or bile duct dilatation.

CASE 3. A 23 years old woman with previous parathyroid adenomas presented herself to emergency room for epigastric pain and nausea. The days before she referred a gastroenteritis with fever, vomiting and diarrhea for which she had taken loperamide and acetaminophen. She referred occasional alcohol consumption and denied smoking. Lab test revealed elevated CRP 79 mg/L and amylase 262 u/L, mild elevated serum bilirubin 39.1 umol/L and aspartate transaminase 36 U/L. She performed an abdominal ultrasound in which found only gallbladder sludge. A pancreatic magnetic resonance imaging (MRI) including MR-cholangiopancreatography was performed after the hospitalization, showing no common bile duct lithiasis or bile duct dilatation.

Conclusions. Reviewing the histories, the intake of loperamide was the most relevant element that coincided with the onset of both episode. In literature there are only other five cases of acute pancreatitis induced by loperamide, but this relationship doesn’t seem so uncommon like we demonstrated with these cases. Besides a recent study demonstrated that opiate intake is a frequent cause of suspicion of sphincter of Oddi dysfunction after cholecystectomy, especially in young women with a narrow common bile duct.

Challenging postoperative diagnosis of celiac disease in a young woman undergoing radical pancreaticoduodenectomy for duodenal adenocarcinoma
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Background. Celiac disease (CD) is an autoimmune disorder associated with diarrhoea, abdominal distension, malabsorption and an increased risk of some types of neoplasms like lymphoma and adenocarcinoma of the small intestine. Some studies indicate a growing incidence of CD among adults and that undiagnosed cases or patients not promptly undergone to a gluten-free diet are exposed to the risk of long term complications.

Case report. A 45 years old woman presented to our attention complaining of weight loss, nausea, diarrhoea, asthenia, and anorexia. Familial and pathological medical history were unremarkable. Routine blood exams were irrelevant. The gastroscopy showed a hypertrophic cobblestone duodenal mucosa and a 20 mm concentric stenosis of the second duodenal portion, findings consistent with an inflammatory disease. Conversely, the histological exam demonstrated an undifferentiated ad-
enocarcinoma with ring cells. Thus, the patient underwent an intervention of radical pancreaticoduodenectomy (pTNM: pT3, N0, LV0). Postoperative course was complicated by persistent diarrhoea, vomiting, asthenia, with resulting life-threatening weight loss leading to recurrent admissions in our unit. Firstly, we deemed the issue as a consequence of the surgery, but instrumental, radiological and microbiological exams did not show complications or other pathological conditions. Therefore, going back to the findings of the first gastroscopy, we valorised the hypothesis of an inflammatory disease and found elevated levels of the antibodies associated with celiac disease. A review of the histological samples confirmed the diagnosis (Marsh and Oberhuber grade 3b/c). The patient finally started a gluten-free diet, with progressive full recovery.

Conclusions. Our report confirms that a celiac disease onset in adult age may represent a diagnostic challenge. Following surgery, the initiation of the gluten-free diet represented the key element of the treatment for our patient. Since the inflammatory environment enhances neoplasm formation, the late starting of the correct alimentary regimen could have fostered the neoplasm in this woman.

Myotonic dystrophy and chronic pancreatitis: a casual association or an underestimated correlation?
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Context. Steinert's disease, myotonic dystrophy type 1, MD, is an autosomal dominant multisismetic disorder with genetic heterogeneity. Although involvement of the gastrointestinal tract is frequent and may occur at any level, involvement of the pancreas is rarely reported.

Case report. We report on a 50 years old male patient, C R, who presented to our ambulatory for signs and symptoms suspected for chronic pancreatitis (weight loss, diarrhea, typical pain). He had a diagnosis of MD (followed in an other specialist center), reported no alcohol consumption, but smoking (20 cigarettes a day). His past surgical history included only a laparoscopic cholecystectomy in 1995. From 2006 to 2013 he has been hospitalized several times (in an other hospital) for recurrent acute pancreatitis; he underwent Computed Tomography, Magnetic Retrgrade Cholangiopancreatography and Endoscopic Ultrasonography (negative for cholestolithiasis or pancreatic parenchima abnormalities). Endoscopic Retrograde Cholangiopancreatography with sphincterotomy, in the suspect of Sphincter of Oddys Dysfunction. Screening for primary pancreatic cancer (genetic testing), autoimmune pancreatitis (IgG4 and autoantibodies) and metabolic disorder were negative.

To our visit, clinical examination found a slim man (BMI 17) with diffuse muscular weakness and bloated abdomen. Laboratory test showed a reduction in fecal elastase and plasma level of Vitamin D; lactulose breath test was negative for intestinal bacterial overgrowth.

Ultrasound of upper abdomen showed a pancreas with irregular contour, atrophic parenchima, a dilated irregular main duct with intraductal calcification.

Pancreatic enzyme replacement therapy was started and patient followed according to our protocol.

Conclusions. Our case-report outlines the need of evaluating pancreatic function in patients with MD presenting with gastrointestinal symptoms, because demonstrated an association of MD and CP; the pathophysiological mechanism of this association remains unclear. We could hypothesize that acute recurrent inflammation evolving in chronic pancreatitis represents a cell membrane defect affecting also the contractility of pancreatic ducts.

Vitamin D insufficiency in patients with newly diagnosed chronic pancreatitis: experience of a little center
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Background. Patients with Chronic Pancreatitis (CP) are at risk of vitamin D insufficiency or deficiency (according to recent data 88% and 65% respectively, compared with 36%-47% of healthy adult population) that can be associated with osteoporosis and increased risk of fractures.

Methods. We examined all patients with newly diagnosed CP (according to recent guidelines: typical history and risk factors + typical imaging finding and/or abnormal pancreatic test, such as serum nutritional markers and fecal elastase), scheduled for an outpatient visit at our institution and followed from 2014 to 2017.

Serum concentration of vitamin D was determined immediately (in our laboratory) and Bone Mass Density was assessed by means of bone densitometry; fecal elastase and serum nutritional markers were determined too.

Results. Thirty six patients were included, five missed after the first admission, thirty one followed; 13% female; mean age of 58; the causes of CP were: alcohol abuse (19 patients), hypertrigliceridemia (1 patient), Hyperparathyroidism (1 patient), idiopathic (8 patient, one of them with Steinert dystrophy), Inflammatory Bowel Disease (two patients), genetic (one patient) and obstructive (one patient).

According to our laboratory standard, vitamin D insufficiency (10-30 nd/ml) was present in 100% of patients; Vit D deficiency (<10 ng/dl) was present in 13 patients (42%); fecal elastase resulted abnormal in 10 patients (32%). Bone densitometry was determined in 22 patients and resulted abnormal in 63% of them. All the patients were treated with Vit D supplement.

Conclusions. We observed a prevalence of Vitamin D insufficiency higher than those reported from the published meta-analyses, (100% of our patients, most of them without sign of pancreatic insufficiency); our experience outlines the importance of Vitamin D assessment in patient with CP, also in absence of pancreatic function impairment.

Vol. 63 - Suppl. 1 to No. 4 MINERVA GASTROENTEROLOGICA E DIETOLOGICA 53
Authors’ Index

A

Acquaviva G, 1.
Adamberg K, 4.
Adamberg S, 4.
Aita A, 9.
Alaggio R, 7.
Aleotti F, 20, 29, 34.
Allavena P, 10.
Allegrini V, 26, 32.
Alvarez-Pérez CA, 8.
Ambrosini V, 17, 18.
Amodio A, 19, 20.
Andreasi V, 16, 21, 25, 33.
Andrianello S, 3, 26, 27, 29, 30, 32, 45.
Andriulli A, 4, 46.
Angrisani M, 28.
Archibugi L, 10, 13, 27, 33, 34, 35, 36, 37, 40, 50.
Arcidiacono P, 19, 29.
Arcidiacono PG, 2, 22, 28, 31, 33, 34, 36, 37, 40, 50.
Ariotti R, 25.
Arricò S, 2.
Arrigoni G, 9.
Astolfi A, 21.
Auriemma A, 8.
Auriemma F, 31, 44.
Avan A, 37, 38.
Beretta L, 18.
Bernardoni L, 19, 20.
Bernasconi DP, 35.
Berti A, 25.
Bertani E, 25.
Berti A, 28.
Biancelli M, 24, 25, 40.
Biondi C, 26.
Birin A, 26, 30.
Borso P, 2.
Bottaro L, 2.
Bozzalla Cassione E, 19, 29.
Bozzalla E, 28.
Bozzarelli S, 5, 14, 26, 31, 44, 47.
Bozzato D, 9.
Bozzolo E, 28, 29, 31.
Braga M, 8.
Brambilla T, 15.
Brandolese A, 20.
Brefor T, 9.
Breni I, 20.
Brighi N, 17, 18.
Brozzi L, 20.
Braggini E, 24, 25, 40.
Büchler M, 46.
Butturini G, 11, 12, 26, 51.

B

Balbinot P, 2.
Balzano G, 16, 18, 19, 22, 23, 28, 29, 31, 34, 35, 36.
Bannone E, 45.
Barbarello L, 42.
Barbuscio I, 51, 52.
Baretta L, 18.
Bertolomei M, 25.
Bass L, 3, 8, 26, 27, 28, 29, 30, 32, 45.
Basso D, 9.
Basso S, 40.
Benati G, 52.
Bencini L, 9.
Benini I, 11.

C

Baccalanza R, 28.
Calculli L, 16, 17.
Camp a D, 46.
Campionano P, 19, 20.
Capanna D, 17, 18.
Canevari C, 28, 29.
Caniglia F, 43.
Canzian F, 46.
Capalbo C, 13.
Caparelli C, 2.
Capelli P, 11, 12, 27.
Caprini G, 10, 28, 35, 46, 47, 48, 49.
Caprini GL, 30.
Capuano F, 19.
Capurso G, 10, 13, 27, 35, 36, 37, 46.
Caputo F, 2.
Cavallin E, 24, 25, 40.
Cavestro GM, 6, 46.
Ceneda E, 9.
Cerulo D, 22.
Cereda M, 28, 35, 46, 47, 48, 49.
Chiaravalle M, 22.
Ciafardini C, 3.
Ciccocioppo R, 19, 20.
Cimarosti P, 2.
Cinaglia E, 11, 12, 27.
Cicconardi R, 20, 25.
Clerici E, 14, 15.
Costello E, 46.
Cova C, 29.
Crinò SF, 19.
Cristel G, 8.
Curti R, 52.

D

D’Agostino GR, 14, 15.
D’Errico A, 21.
D’Onofrio M, 8, 11, 12, 27, 30.
Dabizzi E, 33, 34, 37, 40, 50.
Dacapito F, 52.
D’Albò E, 22, 28, 30.
Damascoli A, 8.
De Biase D, 1.
De Carlì G, 35.
De Cobelli F, 35.
De Giorgio R, 16.
De Madara E, 35.
De Marchi G, 1, 19.
De Pastena M, 1.
De Quarti A, 20.
De Robertis R, 11, 12.
De Vasto M, 19.
Del Chiaro M, 40.
Della Torre E, 19, 28, 29, 31.
Delle Favé G, 10, 15, 27, 36.
Denaro M, 43.
Di Brì L, 14, 15.
Di Candio G, 24, 25, 40.
Di Franco G, 24, 25, 40.
di Giacomo S, 1.
Di Leo M, 30, 31, 44.
Di Marco M, 16, 21.
Di Sandro S, 35.
Di Stefano S, 20.
Di Tommaso L, 30.
Dijk F, 46.
Dolgoni C, 6, 16, 22, 23, 25, 34, 36, 37.
Durante S, 21.

E

Eikermann M, 8.
El Hassouni B, 38, 44.
Ercolani G, 52.
Erreni M, 10.
Esposito A, 1.
AUTHORS' INDEX

Pollini T, 1, 30.
Polzoni A, 42.
Poropat G, 35.
Pozza G, 14, 41, 42.
Preatori P, 30, 31, 44.
Pressiani T, 5, 14.
Prini N, 3.
Puchalt García P, 46.
Pulvirenti A, 32.
Pusceddu S, 3.
Qadan M, 8.
Rahal D, 10, 31, 44.
Rancoita P, 16, 33.
Regi P, 11, 20, 51.
Renì M, 6, 22.
Ricci C, 16, 17, 18, 21, 43.
Ridolfi C, 10, 30, 46, 47, 48, 49.
Rimassa L, 5, 15, 26, 32, 47.
Rinzivillo M, 13.
Riva L, 8.
Roccamatissi L, 28.
Rogger T, 19.
Roggiolani R, 13.
Romanchuck V, 43.
Romanò G, 30.
Romì S, 22.
Roncalli M, 10.
Rosati R, 6.
Rossi G, 35, 34, 40, 50.
Rossi RE, 3.
Rossin R, 2.
Rovati L, 19, 29.
Roviti M, 38.
Rubini C, 16, 23, 34.
Ruffo G, 29.
Ruscin KJ, 8.
Russo Raucci A, 6.
Sacco Manano E, 40.
Sahani D, 8.
Sahani DV, 5.
Sahora K, 5.
Sala S, 5.
Salandini MC, 8.
Salgarello M, 33.
Salvia R, 1, 5, 26, 27, 29, 30, 32, 45.
Sandini M, 3, 8, 16, 17, 18, 21, 28, 35.
Santoro A, 5, 14, 15.
Santoro L, 7.
Sarti R, 42.
Scabini A, 2.
Scarpa A, 11, 12, 30, 45, 46.
Schiavo Lena M, 25.
Schmid T, 6.
Sciarrullo R, 38.
Sciarati C, 19.
Scopelliti F, 26, 51.
Scorsetti M, 14, 15.
Secchettin E, 1, 32.
Sereni E, 32.
Serra AM, 53.
Serra C, 16, 17, 21.
Sessa F, 21.
Siddiqui I, 10.
Signoretti M, 10, 13, 27.
Smiroldo V, 26, 32.
Soucek P, 46.
Spada A, 15.
Spaggiari P, 10, 32.
Sperti C, 14, 41, 42, 51.
Stebbings J, 49.
Stigliano S, 10, 13, 27.
Stornello C, 13.
Storti B, 49.
Sturmiolo GC, 51.
Surace A, 53.
Taffurelli G, 16, 17, 18.
Talar-Wojnarowska R, 46.
Tamagno G, 3.
Tamburino D, 16, 23, 25, 37.
Tamini N, 35.
Tarantino G, 21.
Tarocchi M, 9.
Tavano F, 4, 46.
Gaddes G, 8.
Tempesti S, 9.
Terracciano F, 4.
Testino G, 2.
Testoni PA, 6, 50.
Testoni SGG, 33, 34, 40, 50.
Tinazzi Martini P, 11, 12, 26.
Tortora G, 11, 12.
Tozzi A, 14, 15.
Traini M, 33, 34, 40, 50.
Tronconi MC, 5.
Ubiali P, 40.
Uccelli F, 46, 47, 48.
Valbona Liço, 7.
Valente R, 27.
Valentini G, 53.
Vanella G, 13, 27.
Vashist YK, 46.
Vasile E, 4, 40.
Veni K, 4.
Venturini M, 35.
Vernetto A, 53.
Viecelli F, 20.
Viliu R, 4.
Vitali E, 15.
Vicentini P, 46.
Warshaw AL, 5, 8.
Weiss M, 21, 45.
Wojtuszkiewicz A, 38.
Wolfgang C, 45.
Wolfgang CL, 21.
Wood L, 45.
Yu J, 45.
Zambetti M, 6.
Zamboni MF, 9.
Zanesini F, 2.
Zanoni S, 6, 22.
Zerbi A, 10, 15, 28, 30, 35, 44, 47, 48, 49.
Zerboni G, 10, 13, 27.
Zilli A, 3.
Zuppardo RA, 6.
Zuradelli M, 32.