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Orals

O-01

Single-cell profiling of GP2-enriched pancreatic progenitors to simultaneously create acinar, ductal and endocrine organoids

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Abstract

Background: Early human pancreas development is poorly understood, mainly due to a lack of data and tissue availability for ethical reasons. Most knowledge comes from rodent data, despite relevant differences between species. In human pancreas development, a tripotent pancreatic progenitor (PP) population serves as a common ancestor in the developing bud, further diverging into exocrine and endocrine lineages. Current stem cell-based in vitro differentiation protocols is often associated with an endocrine lineage bias, focusing rather on the generation of beta cells or islets. The evaluation of these in vitro-generated PPs is based solely on the co-expression of PDX1 and NKX6-1, neglecting other markers to properly assess the progenitors and impurities.

Methods: Since true tripotent PPs are of utmost interest to studying exocrine and endocrine diseases, we used an advanced design of experiment for detailed stage-specific compound screening. Importantly, we developed a genuine protocol that generates PPs substantially expressing Glycoprotein-2 in addition to the common markers NKX6-1 and PDX1, with minimal lineage contamination. These progenitors were successfully challenged for their endocrine, ductal, and acinar differentiation capacities in vivo.

Results: The progenitors showed the ability to undergo directed lineage bifurcation in vitro by differentiation into functional beta cells, mature ductal cells, and furthermore, acinar-like organoids expressing the expected marker profiles. Single-cell transcriptomics confirmed the presence of multipotent progenitor cells and addressed the heterogeneity and early lineage determination at the PP stage. Clustering with human foetal pancreas cells proved the reliability of our system for modelling the earliest events in human foetal pancreas development. Cell-cell interaction analysis revealed ligand receptor-based crosstalks between the different clusters within the PP population, providing an important resource for further identification and purification of specific progenitor subtypes.

Conclusion: Thereby we provide a unique resource to model various pancreatic disorders affecting distinct three pancreatic lineages including cell type of origin in pancreatic cancer.

O-02

GATA6 functions at distal enhancer regions to control classical pancreatic ductal carcinoma identity by promoting promoter-proximal pause release

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal forms of cancer, with a five-

year survival rate of 8% and a median survival of just 5.5 months. PDAC can be subdivided into two major molecular subtypes referred to as classical and basal, with the classical subtype representing the most frequent form. However, the understanding of the role of subtype-specific master transcription factors (MTF) in driving cellular identity in classical PDAC is largely unknown.

Methods: We used RNA- and ChIP-seq to identify putative candidate MTFs driving the classical identity. Moreover, we have utilised RNA interference and CRISPR-Cas9 mediated genome editing to determine the role of these MTFs in controlling the activity of distal enhancer regions controlling subtype-specific gene expression. By combining data from RNA- and ChIP-seq analyses, together with chromatin topology (HiChIP), we can unequivocally relate MTF function at distal regulatory regions to target gene expression.

Results: Our results uncover three major MTFs, including GATA6, that co-occupy distal regulatory regions specifically marked in classical PDAC. Notably, our results suggest that GATA6 functions to activate these genes by controlling promoter-proximal pausing of RNA Polymerase II at classical-specific GATA6-target genes.

Conclusion: By integrating various next generation sequencing (NGS) applications, coupled with CRISPR-Cas9 genome editing, we provide evidence that GATA6 regulates the classical PDAC phenotype and targeting the transition from promoter-proximal pausing to productive elongation may be a viable therapeutic option for classical PDAC.

O-03

HNF1A plays a context-dependent role in pancreatic cancer initiation and progression

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Abstract

Background: Increasing evidence using genetic mouse models (GEMMs) supports the notion that, in the pancreas, acinar cell differentiation suppresses mutant Kras-induced cancer initiation. HNF1A is a critical component of the transcriptional networks governing embryonic pancreas development and differentiation of both acinar and beta cells. HNF1A mutations are the cause of MODY3 and the HNF1A locus harbours susceptibility variants for pancreatic ductal adenocarcinoma (PDAC) and type 2 diabetes mellitus. In addition, HNF1A is a critical hub of the PDAC lineage identity (Laise et al., BioRxiv 2023). We have previously reported, using Pdx1Cre(+/T);KrasG12D(+/KI) mice, thatHnf1a deficiency promoted Kras induced oncogenesis (Kalisz et al., 2020).

Methods: We use GEMMs and organoids to assess how HNF1A contributes to PDAC initiation and progression.

Results: In a Ptf1aCre(+/KI); KrasG12V(+/KI) (KC) background, homozygous Hnf1a deletion resulted in delayed tumour development and a 2.6-fold increased mouse survival (p=0.039), regardless of the Trp53 genetic status (+/+, lox/+, or lox/lox). When using Ptf1aCre-ERT2(+/KI); KrasG12V(+/KI) mice, tamoxifen administration at 8 weeks revealed that homozygous Hnf1a deletion resulted in accelerated pre-neoplastic lesion development. To address the molecular basis of these contrasting findings, we have established organoids from KC mice and show that Hnf1a deficiency provides growth factor independency (Rspondin1, EGF, FGF10) through mechanisms that need to be fully elucidated. To acquire mechanistic insight, we have established organoids from Tg.Ela1-tTA(+/T);Tg.tetO-FlpO(+/T);Kras_FSFG12V(+/KI);Trp53_frt(frt/frt);Tg.hUBC-CreERT2(+/T); Hnf1a_lox(lox/lox) mice and have efficiently deleted Hnf1a using TMX in vitro. Preliminary data from these experiments show decreased organoid number and size upon Hnf1a ablation, suggesting a protumourigenic effect of HNF1A.

Conclusion: Our findings provide strong evidence that HNF1A plays a critical, context-dependent, role in pancreatic tumourigenesis. The use of organoids, genetic mouse models, and omics analysis should provide clues as the "contextual" mechanisms involved.

O-04

Chronic pancreatitis in children - report of 484 cases

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Abstract

Background: Chronic pancreatitis (CP) is of a rare occurrence in childhood. The aetiology of CP in children is varied and includes anatomic anomalies, gene mutations, metabolic disorders and others. The aim of this study was to investigate the etiological aspects of CP in children from well-defined homogenous cohort.

Methods: 484 children with CP (aged: 0.2-18 years; hospitalized between 1998 and 2021 were enrolled into the study. The diagnosis of CP was established according to INSPPIRE recommendations. Clinical and epidemiological data were recorded and analysed. All patients were screened for mutations in the high-risk genes associated with CP (*CFTR*, *CTRC*, *PRSS1*, *SPINK1*, *CPA1*, *CEL-HYB*, *TRPV6*). All children had preceding imaging studies, including US, CT, MRCP and/or ERCP.

Results: Gene mutations were found in 315 children (65%) (*SPINK1* mutation in 133 children, *CTRC* in 110 patients, *CFTR* in 72 patients, *PRSS1* in 59 children, *TRPV6* in 16, *CEL-HYB* in 9 and *CPA1* in 5; 83 pts (17.1%) have 2 or more mutations).

Anatomic anomalies of pancreatic duct were diagnosed in 83 patients (17.2%) (51- pancreas divisum, 15- ansa pancreatica, 7- ABPU, 3- two main pancreatic ducts, 8-other).

Toxic-metabolic risk factors were found in 63 children (14.9%) with chronic pancreatitis, with dominance of lipid disturbances. Hyperlipidaemia was present in 46 patients (9.5%), including isolated in 18 patients (3.7%) and coexisting with obesity/metabolic syndrome in 28 (5.8%). CP associated with medication was present in 17 (3.5%) children (mostly with antiepilepsy drugs). Alcohol abuse history was present in 9 (1.7%) patients. Smoking (>5 cigarettes/day) history was present in 8 (1.7%) children. Chronic renal failure was present in 4 (1%), mitochondrial cytopathies in 3 (0.6%) and hypercalcaemia (hyperparathyroidism) in 2 (0.5%) patients with CP. CP was associated with biliary tract diseases in 52 patients (10.7%). Autoimmune pancreatitis was diagnosed in 18 children (3.7%). Idiopathic CP was diagnosed in 37 children (7.6%).

Conclusion: 1. The most common etiologic factors of chronic pancreatitis in children are gene mutations and anatomic anomalies of pancreatic duct. 2. CP is a multifactorial disease. 3. Our data demonstrate the need for genetic testing in children with chronic pancreatitis.

O-05

Carboxyl ester lipase (CEL) in pancreatic disease: pathogenicity of CEL-MODY, but not CEL-HYB1, depends on cysteine residues in the hypervariable tail region

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Abstract

Background: Carboxyl ester lipase (CEL) is a digestive enzyme produced by pancreatic acinar cells. The last exon of the human *CEL* gene contains a variable number of tandem repeats (VNTR) region, consisting of 3 to 23 repeats that each encodes an 11-amino acid polypeptide. All verified pathogenic mutations of *CEL* are located within the VNTR and involve the generation of cysteine residues in the polypeptide repeats. These mutations either cause the endocrine/exocrine pancreatic disorder MODY8 (Ræder et al., Nat. Genet. 2006) or confer 5-fold increased risk for chronic pancreatitis (*CEL-HYB1*; Fjeld et al., Nat. Genet. 2015). Our project aims to understand the role of the *CEL* VNTR in pancreatic health and disease.

Methods: We collected CEL protein sequences from 265 different vertebrate species and analysed the variation of the C-terminal region with bioinformatic methods. Cysteine residues of the pathologic variants CEL-MODY and CEL-HYB1 were changed to alanine by in vitro mutagenesis of plasmid constructs. The plasmids were expressed in HEK293 cells, and effects on the CEL protein were studied by immunoblotting and immunofluorescence.

Results: The globular CEL protein is present in all vertebrate groups. However, the *CEL* VNTR encodes an intrinsically disordered protein region that is unique for mammalian taxa except monotremes. The pathogenic CEL-MODY variant showed elevated intracellular accumulation, reduced secretory levels and co-localisation with ER stress markers such as BiP and calnexin when compared to normal CEL. After the 10 cysteines of CEL-MODY were mutated to alanine, properties of this variant became normalized and, in some cases, identical to those of wild-type CEL. For CEL-HYB1, which has only 3 repeats and 2 cysteines, properties did not change significantly when mutating the cysteine residues to alanine.

Conclusion: The hypervariable protein tail of CEL was added during evolution of mammals. Cysteines residues are central in the pathogenesis of CEL-MODY, whereas cysteine-mediated effects on CEL-HYB1 were not revealed. In the CEL-MODY tail, the high number of cysteines enables intra- and intermolecular disulphide bonds that induce protein aggregation and ER stress. For CEL-HYB1, we propose that it is primarily its short tail length that plays a role in pathogenicity.

O-06

Creation of a GATA transcription factor binding site as underlying pathogenic mechanism of the common SPINK1 p.N34S pancreatitis risk haplotype

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Abstract

Background: The variant p.N34S in *SPINK1*, which has been described worldwide, is the most relevant genetic risk factor for idiopathic chronic pancreatitis (CP). Although the association of p.N34S and CP is well established, the underlying pathological mechanism remains enigmatic.

Methods: We extracted variants in LD with p.N34S from 1000 Genomes data, and prioritized regulatory variants using an integrative approach combining bioinformatics phylogenetic module complexity analysis, public domain pancreas epigenomic marks of regulatory regions and population specific genomic data. We additionally tested allele-specific effects on protein-DNA interaction in different cell lines by electrophoretic mobility shift assays (EMSA) and on transcriptional activity by reporter gene assays. Based on these analyses and current literature, we selected three variants, *rs148276928*, *rs148911734*, and *rs142703147*, for affinity-chromatography/pull-down assays coupled to liquid chromatography tandem-mass spectrometry (LC-MS/MS). We confirmed allele-specific differential protein-DNA binding of transcription factors identified in LC-MS/MS by supershift EMSA. In addition, we performed DNA sequencing in Indian CP patients and controls.

Results: In LC-MS/MS analysis we identified GATA4 and GATA6 as binding partners for *rs148911734C>T* (c.1-7321G>A) that preferentially bound to the risk allele. We confirmed binding in supershift EMSA. In reporter gene assays we observed clear differences between the *rs148911734* alleles. Genetic analyses of the Indian cohort revealed a stronger P-value for *rs148911734* compared to *rs142703147* or even p.N34S.

Conclusion: A regulatory variant located about 7 kb from the start codon, *rs148911734*, is the causal variant in the *SPINK1* p.N34S haplotype. The variant creates a GATA4/GATA6 binding site leading to reduced gene expression.

O-07

Characterisation of a new form of pancreatitis

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Abstract

Background: The causes of chronic pancreatitis in children remain incompletely understood. Predisposing genetic mutations is the most frequent cause of chronic pancreatitis in children. In this context, among paediatric patients with signs of pancreatitis (suggestive symptoms, increased lipase >3x upper limit of normal, and/or pancreatic imaging anomalies, and/or endocrine/exocrine pancreatic dysfunction), we identified a category of patients with signs typically associated with ciliopathies, namely cholestatic liver disease, renal cysts or cognitive deficit. Therefore, we aim to identify mutations in ciliary genes in these patients, and to establish a link between these mutations and the

development of pancreatitis.

Methods: Whole Exome Sequencing of 43 paediatric patients with idiopathic chronic pancreatitis identified in three of them a mutation in the ciliary/ciliogenic genes PKHD1, HNF1β, and NPHP3. We then focused on the NPHP3 gene and generated by CRISPR/Cas9 technique two transgenic mouse models: one replicating the NPHP3 gene mutations present in the corresponding patient (NPHP3mut1/mut2 model), while the other is a conditional inactivation of NPHP3 (NPHP3f/f model). Histological analyses of murine pancreas led us to come back to the patients' side. The pancreas of patients was analysed by magnetic resonance imaging and the organ fat content was determined using the IDEAL-IQ application, which enables volumetric fat-fraction mapping and quantification.

Results: Phenotypic analysis of these two models allowed us to conclude that loss of function of NPHP3 in pancreatic ductal cells led to inflammation and mild fibrosis associated with significant acinar atrophy and severe lipomatosis. In order to confirm the presence of pancreatic lipomatosis in patients NPHP3 mutations as well as in HNF1β, MRI was performed and confirmed a significant increase in fat percentage within the pancreas of these patients.

Conclusion: These findings suggest a new form of pancreatitis originating form a cilia dysfunction. Deeper analysis of mouse models, in particular to characterize the molecular mechanisms involved in the observed phenotypes, and the recruitment of a larger number of patients and control subjects, should allow us to confirm the existence of this new form of pancreatitis of ciliopathic origin.

IS and PJ serve as co-last authors

O-08

Acute pancreatitis is associated with gut dysbiosis in children

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Abstract

Background: Paediatric acute pancreatitis (AP) is associated with substantial morbidity and health care burden. Given these risks, improved understanding of children who are at risk of developing severe AP is critical. While previous studies have reported AP associated gut dysbiosis in adults, paediatric studies are lacking. The aim of our study was to determine if (i) stool microbial taxonomic and functional profiles differ between children with AP and healthy controls in the same geographic location (ii) stool microbial taxonomic and functional profiles differ between children hospitalized with mild AP compared to those with moderately severe and severe AP.

Methods: This study was a prospective pilot study (n=30) of children under 21 years hospitalized at Cincinnati Children's Hospital Medical Center (CCHMC) with first attack of AP. Faecal samples were obtained within 7 days of hospitalization. Healthy controls (HC, n=34) were recruited from the GI clinic and did not have any systemic organic disease or irritable bowel syndrome. Shotgun metagenomic sequencing was performed on extracted DNA and taxonomic and functional profiles obtained using the biobakery3 tool suite with default parameters.

Results: Baseline characteristics of age, sex, BMI did not differ between AP patients and HC. Diversity indices: Shannon (-.63±0.13, p-value < 0.001) and beta diversity (R2=0.13, p-value < 0.001) differed in children with AP when compared to HC with enrichment in numerous species previously associated with AP in adults and/ inflammatory bowel disease (IBD) in children including *R. gnavus*, *V. parvula, E. faecalis*, *C. innocuum* (FDR p-value < 0.05). There was enrichment in MetaCyc pathways involved in amino acid metabolism and fatty acid beta-oxidation (FDR p-value

< 0.05). Beta diversity (R2=0.06, p-value = 0.02) differed in severe and moderate AP when compared with mild AP with enrichment in *E. faecalis* and *C. citroniae* which has also been reported in IBD.

Conclusion: Paediatric AP shows an association with gut microbial dysbiosis. Several pro-inflammatory species were enriched in AP versus HC and severe versus mild AP. A multicentre study confirming these findings could potentially pave the way for well-designed clinical trials on interventions manipulating the gut microbiome to prevent severe AP.

O-09

Elevated pancreatic fluid and HCO_3^- secretion in diabetic mice is the result of increased CFTR function

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Abstract

Background: Type 1 diabetes is a disease of the endocrine pancreas, but it also affects the exocrine part, especially the ductal cells. Several studies have shown that secretin-induced ductal HCO_3^- secretion is reduced in diabetes, however, the underlying mechanism and the effect of diabetes on basal secretion is less known. Our aim is to investigate the effect of diabetes on pancreatic exocrine function.

Methods: Diabetes was induced in wild type and cystic fibrosis transmembrane conductance regulator (CFTR) knock out mice by i.p. administration of streptozotocin and disease development was confirmed by fasting blood glucose level measurement. Pancreatic ductal fluid and HCO_3^- secretion were measured by fluid secretion measurements and fluorescence microscopy, respectively. Expression of ion transporters were investigated by real-time PCR and immunohistochemistry, whereas TEM was used for the morphological characterisation of the pancreas.

Results: Basal fluid and HCO_3^- secretion are significantly elevated in diabetes. Acute or chronic glucose treatment did not affect HCO_3^- secretion, but inhibition of CFTR significantly reduced it in both normal and diabetic mice. Cl^- efflux and the expression of CFTR, ANO1, NHE-1 and AQP1 increased in diabetes. Secretin-stimulated fluid secretion was also significantly higher in diabetic mice.

Conclusion: Our results show that diabetes increases fluid and HCO_3^- secretion in ductal cells both under basal and stimulated conditions in which the increased function of ion and water transporters, especially CFTR, plays central role.

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O-10

DNGR-1 in dendritic cell limits pancreatic tissue damage during chronic pancreatitis via restraining IL-6-mediated Th17+ cell differentiation and persistent acinar-to-ductal metaplasia

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Abstract

Background: Chronic pancreatitis (CP) is defined as a progressive and irreversible fibroinflammatory disease of the exocrine pancreas, characterised by extensive loss of parenchymal tissue, persistent inflammation and fibrosis. The dendritic cell NK lectin group receptor-1 (DNGR-1), encoding by Clec9a, is a dendritic cell (DC)-specific sensor of tissue damage. In this study, we aim to investigate the effects and the underlying mechanism of DNGR-1 on pancreatic tissue damage during CP.

Methods: Peripheral blood and/or pancreatic tissue from patients (n = 33) and mice with CP were collected to detect DNGR-1 expression and frequency of DCs by flow cytometry. CP model were induced by six hourly injections of caerulein, 3 days a week for 6 weeks in Clec9a-/- and wild-type (WT) mice. The extent of pancreatic tissue damage and inflammation was assessed histologically. Subtypes of innate and adaptive immune cells in spleen and pancreas were analysed by flow cytometry. Cytokines (Tgfb and Il6) and transcription factor (RORγT and STAT3) responsible for Th17 differentiation were measured. The effect of IL-6 antagonist in CP model was assessed. Spatial transcriptome was performed to assess the interactions between persistent pancreatic acinar-to-ductal metaplasia and immune microenvironment.

Results: The frequency of DCs and its subtypes and the level of DNGR-1 were upregulated in patients and mice with CP. Deletion of DNGR-1 led to persistent pancreatic tissue damage, characterised by increased oedematous area by HE and accumulation of cleaved caspase-3+, CD45+ and CD19+ cells. Pancreatic proliferation (Ki67+ cells) was similarly increased. Innate immune cells, including macrophage and its subtypes, neutrophils, monocytes, DC and its subtypes in the pancreas, but not in spleen were all significantly increased in Clec9a-/- mice. T cells, including CD4 and its subtypes (Th1, 2), CD8 and γδT in pancreas remained unchanged. Th17+ cells was selectively elevated in Clec9a knockouts. Furthermore, IL-6 primarily released by cDC1 promoted Th17+ differentiation and IL-6 antagonist mitigated the severity of CP.

Conclusion: DNGR-1 protects against CP through Th17+ cell differentiation mediated by IL-6 released by cDC1 and persistent acinar-to-ductal metaplasia. Our data suggest that targeting cDC1 or cDC1-mediated cytokines, IL-6 is a promising therapeutic strategy for CP.

O-11

Pro-inflammatory cytokines of the IL-6 family induce regulatory T-cells and determine the severity of acute pancreatitis

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Abstract

Background: Acute pancreatitis is characterised by premature activation of pancreatic proteases which induce a local pro-inflammatory immune response. In parallel to the hyperinflammation, a systemic immunosuppression, characterised by the induction of regulatory T-cells (T_{regs}), occurs. Activated T_{regs} suppress T-effector cells and can promote intestinal bacterial translocation into pancreatic necrosis, thereby increasing the severity of acute pancreatitis. The aim of this study was to investigate the regulatory mechanisms behind activating T_{regs}.

Methods: Pancreatitis was induced in C57Bl/6 and DEREG mice by partial duct ligation and additional i.p. injection of caerulein (50 µg/kg/bodyweight). T_{reg} depletion was performed by i.p. injection of 1 µg diphtheria toxin 3 days before induction of pancreatitis. Bacterial translocation was determined in homogenized murine pancreatic tissue. Systemic T-cell differentiation was analysed by flow cytometry. Disease severity was determined by histological examination and analysis of serum amylase and lipase.

T_{regs} were isolated by FACS sorting and analysed for expression profiling using Affymetrix Chips and for their suppressive capacity. Naïve splenic T-cells were isolated and stimulated with IL-6 or Oncostatin-M for cell differentiation analysis. Cytokines of the IL-6 family were analysed in serum samples of pancreatitis patients.

Results: Activation of T_{regs} correlated with disease severity, and increased numbers of active T_{regs} significantly associated with infected pancreatic necrosis. Beside the number of T_{regs} also their suppressive capacity was increased. The absence of T_{regs} in a model of acute pancreatitis reduced the tissue damage and disease severity. *In vivo* T-cell stimulation experiments clearly showed that the T-cell differentiation towards T_{regs} was induced by cytokines of the IL-6 family. Transcriptome analysis of isolated T_{regs} revealed activated Oncostatin-M/IL-6 signalling. In serum samples of pancreatitis patients, a significant and severity-dependent increase of the IL-6 family members Oncostatin-M and IL-6 was detected.

Conclusion: Cytokines of the IL-6 family induce the differentiation of T_{regs}. in acute pancreatitis activated T_{regs} promote the development of infected pancreatic necrosis thereby significantly increasing the mortality. IL-6 is mainly released by pancreatic macrophages and links the local hyper-inflammation to the systemic immunosuppression. Intervention of the IL-6 pathway could be used as a therapeutic approach to limit the progression of acute pancreatitis.

O-12

Orai1 calcium channel inhibition prevents progression of chronic pancreatitis

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Abstract

Background: Patients with recurrent acute pancreatitis (RAP) are at significant risk of developing early chronic pancreatitis (CP), which progresses into irreversible, end-stage CP with severe symptoms. There is no specific therapy in RAP or in early CP that may hinder disease progression. The pathogenesis of CP is complex and involves interactions among multiple cell types, including pancreatic acinar, ductal, and stellate cells (PSC). Therefore, it is pivotal to identify common pathogenic pathways in these cells that could be targeted pharmacologically. The Orai1-mediated store-operated Ca^{2+} entry (SOCE) is a ubiquitous signalling mechanism, which may become over-activated in pathological states resulting intracellular Ca^{2+} overload. In this study, we used *ex vivo* and *in vivo* preclinical disease models to demonstrate that Orai1 inhibition prevents progression of RAP and early CP.

Methods: CP was induced in wild type FVB/N mice by repeated administration of caerulein (50 µg/kg) for two weeks, followed by administration of a selective Orai1 inhibitor (CM5480; 20 mg/kg) on the last five days, and histological parameters, fibrosis, pancreas weight/body weight ratio, and hydroxyproline (HyP) content were quantified. Functional and morphological assays were used to evaluate acinar and ductal functions. *In vitro* experiments were performed on PSCs.

Results: Our findings show that SARAF, an endoplasmic reticulum resident protein that inhibits Orai1 activity, is significantly reduced in pancreatic acinar cells from mouse and human CP tissue, leading to an increase in Orai1-mediated extracellular Ca^{2+} influx. In contrast, inhibiting Orai1 significantly reduced tissue damage during experimental CP in mice, as well as the extent of fibrosis and immune cell infiltration. Furthermore, CM5480-treated mice had significantly improved pancreatic acinar and ductal functions. Finally, Orai1 inhibition reduced PSC activation *in vitro* and *in vivo*, as well as migration and proliferation, while causing a cell cycle arrest and accumulation of PSCs in the S phase.

Conclusion: We suggest that the over-activation of Orai1 is a crucial pathogenetic event in the progression of early CP, and inhibition of Orai1 could prevent the development of end-stage CP.

O-13

Do infective complications of pancreatoduodenectomy affect recurrence and long-term survival rates?

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Abstract

Background: Recent studies have suggested that patients who experience an infective complication of pancreatoduodenectomy (PD) may be more likely to experience early disease recurrence. The mechanisms behind this are poorly understood. This study aimed to compare the outcomes of patients who developed infective complications to those who did not. The primary outcomes measured were one-year recurrence, five-year recurrence and five-year survival.

Methods: Data was extracted from the Recurrence After Whipple's (RAW) study, a multicentre retrospective cohort

study of outcomes of PD performed for pancreatic head malignancy (29 centres from 8 countries, n=1484). Patients with any of the following infective complications were identified: hospital acquired pneumonia, cholangitis, Clostridium difficile infection, intra-abdominal collection, liver abscess, sepsis of unknown origin, surgical site infection and urinary tract infection. The Mann-Whitney U test and Fisher exact test were used to perform the analyses.

Results: A total of 361 patients (24.3%) developed at least one infective complication. Patients with at least one infective complication had similar median age (67 vs 68 years, p=0.5) and 90-day mortality (5.3% vs 3.2%, p=0.08) to those with no infective complications. However, the former were more commonly American Society of Anaesthesiologists >grade II (40.2% vs 32.6%, p=0.01) and were more likely to have an unplanned return to theatre during their index admission (9.4% vs 3.6%, p<0.0001). Concerning long-term outcomes, once patients who died within 90-days of surgery were excluded, one-year recurrence (15.8% vs 14.4%, p=0.6), five-year recurrence (62.6% vs 62.6%, p=0.7) and five-year survival (33.6% vs 32.7%) rates were similar between the two groups.

Conclusion: In our multicentre study of PD patients, almost a quarter developed an infective complication postoperatively. These patients were more likely to be comorbid and have an unplanned return to theatre. However, long-term outcomes were similar to those who did not develop an infective complication.

O-14

Nerve-derived CXCL8 promotes perineural invasion and associates with poor survival in pancreatic cancer

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Abstract

Background: Myeloid derived suppressor cells (MDSC) are known mediators of T-cell immunosuppression and correlate with poor clinical outcome in many solid tumours, including pancreatic cancer (PCa). In this study, we aimed to uncover novel neuro-immune crosstalks in the pathogenesis of neural invasion in PCa.

Methods: MDSC were characterised within the tumour microenvironment (TME) and the perineural niche of PCa patients (n=40) using double immunofluorescence. In vitro migration and invasion assays and secretome arrays were used for the functional analysis of the invasive potential of pancreatic tumour cells towards DRG-neurons in the presence of MDSCs. Spatial transcriptomic technology (NanoString©) allowed us to determine the differential gene expression on nerve-invading tumour cells as well as on tumour-invaded nerves. In vivo depletion of MDSC in the highly innervated TPAC mouse model of pancreatic cancer further supported their role in tumour neurotropism.

Results: PCa patients with severe NI presented increased density of intratumoural MDSC. Furthermore, increased MDSC-infiltration was shown in the perineural niche of tumour-invaded nerves compared to non-invaded ones. Mechanistically, the migratory behaviour of PCa cells towards neurons was significantly enhanced by the interaction with MDSCs and it led to increased MDSC-proliferation and significantly higher secretion of several cytokines, including CXCL8. CXCL8-silencing in human Schwann cells (hSC) led to decreased MDSC-chemotaxis in vitro. Further, the expression of CXCL8 was notably higher on nerves invaded by tumour cells in PCa patients, whereas its expression on nerve-invading tumour cells remained constant. Enrichment analysis of bulk RNAseq from PCa samples demonstrated increased chemokine activity in the pancreatic microenvironment in context of NI. Finally, CXCL8 expression in the pancreatic microenvironment was associated with poor survival in PCa from the TCGA database.

Conclusion: CXCL8 derived from intrapancreatic nerves contributes to chemoattractive recruitment and proliferation of MDSC in the TME and constitutes an attractive target for immunotherapy for decreasing perineural pancreatic cancer spread.

O-15

Ideal outcome after pancreatoduodenectomy: a transatlantic evaluation of a harmonised composite outcome measure

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Abstract

Background: Assessing outcome after pancreatoduodenectomy among centres and countries requires a broad evaluation which cannot be captured by a single parameter. Previously, two composite outcome measures for pancreatoduodenectomy have been described from Europe and the United States. These composites were harmonised into one Ideal Outcome (IO).

Methods: This analysis is a transatlantic retrospective study (2018-2020) of patients after pancreatoduodenectomy within the registries from North America, Germany, the Netherlands, and Sweden. After three consensus meetings, IO for pancreatoduodenectomy was defined as the absence of: 1) in-hospital mortality, 2) severe complications - Clavien Dindo ≥3, 3) postoperative pancreatic fistula - ISGPS grade B/C), 4) reoperation, 5) hospital stay >75th percentile, and 6) readmission. Outcomes were evaluated using relative (RLD) and absolute largest differences (ALD), and multivariate regression models.

Results: Overall, 21,036 patients after pancreatoduodenectomy were included, of whom 11,845 (57%) reached IO. The rate of IO varied between 60% in North America, 53% in Germany, 52% in the Netherlands, and 53% in Sweden (RLD: 1.2, ALD: 8%, p<0.001). Individual components varied with an ALD of 4% for in-hospital mortality, 12% severe complications, 10% postoperative pancreatic fistula, 11% reoperation, 14% length of stay, and 9% readmission. Age, sex, country, absence of COPD, BMI, performance status, biliary drainage, absence of vascular resection, and histological diagnosis were associated with IO. In the subgroup of patients with pancreatic adenocarcinoma, neoadjuvant chemotherapy also was associated with improved IO.

Conclusion: The newly developed composite outcome measure 'Ideal Outcome' can be used for auditing and comparing outcomes after pancreatoduodenectomy. The observed differences can be used to guide collaborative initiatives to further improve outcomes of pancreatic surgery.

O-16

Artificial intelligence-based quantification of residual cancer burden to evaluate the impact of neoadjuvant therapy in resected pancreatic cancer in the PREOPANC randomised trial

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Abstract

Background: The effectiveness of neoadjuvant therapy (NAT) for pancreatic cancer is routinely evaluated by histopathologic examination of the resection specimen. The International Study Group of Pancreatic Pathologists (ISGPP) proposed that this should include the objective assessment of the residual cancer burden (RCB), but such systems are currently lacking. This study aims to determine whether artificial intelligence (AI)-based quantification of RCB can be used to evaluate the effects of NAT in resected pancreatic cancer and to investigate if RCB correlates with survival.

Methods: Post-hoc analysis of patients randomised in the PREOPANC trial for neoadjuvant chemoradiotherapy or upfront surgery. Patients with less than two tumour-bed H&E slides available or those deceased within 90 days after surgery were excluded. The ISGPP segmentation model was used to quantify the RCB for each patient, expressed as the average (mean) square millimetres (mm2) of cancerous tissue across all tumour-bed H&E slides. The patients were divided into groups based on medians. The prognostic value of RCB was assessed using Kaplan-Meier and log-rank analyses.

Results: Overall, 69 patients, 35 randomised to upfront surgery and 34 to neoadjuvant chemoradiotherapy and surgery were included. Patients after neoadjuvant chemoradiotherapy and surgery had significantly lower RCB compared to patients after upfront surgery (2.24 mm2 [IQR: 1.51–4.92] vs 10.3 mm2 [IQR: 6.8–18.6]; p-value=2.48*10-7). Among all 69 patients, those with below median RCB had a better overall survival than those with above median RCB (median OS of 30 months [95%CI: 22 - NA] vs. median survival of 23 months [95%CI: 13–32], p-value=0.018). When analysing patients by treatment status, the differences in median survival between those with below and above median RCB were not significant in neither the neoadjuvant group (44 months [95%CI: 17-NA] vs. 30 months [95%CI: 30-NA]; p-value=0.89) nor the upfront surgery group (24 months [95%CI: 18-33] vs. 15 months [95%CI: 18–33]; p-value=0.28)

Conclusion: This post-hoc analysis in a randomised trial suggests that neoadjuvant chemoradiotherapy for pancreatic cancer lowers RCB in resection specimens and that lower RCB correlates with improved overall survival.

O-17

Predicting response for each component of the FOLFIRINOX regimen in pancreatic cancer patients

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Abstract

Background: We recently developed a transcriptomic signature predicting gemcitabine response in resected PDAC patients and with metastatic disease (PMID: 36178036, 36496056), using preclinical PDAC models. The FOLFIRINOX regimen (FFX) (5FU, oxaliplatin, and irinotecan) is the more effective treatment option, but the high toxicity limits its use for all patients. As chemo-sensitivity prediction for each drug of FFX would optimize the combination of drugs, avoiding the adverse effect of an ineffective treatment, we developed and evaluated clinically three transcriptomic signatures for each drug separately.

Methods: Transcriptomic data from 14 patients derived xenograft and 31 patients derived cell cultures were associated with their corresponding chemotherapy response profiles. Three different predictive signatures were developed as previously reported for gemcitabine (GemCore; PMID: 36178036). The extracted signatures were validated in a pooled cohort of 167 patients with advanced/metastatic disease (94 patients from COMPASS and, 73 from a new cohort.

Results: One hundred and eleven patients were assessable for the progression-free survival (PFS) in the FFX arm (n=63). 1-For 5FU: 15 patients were identified as sensitive, median PFS 8.7 months (CI, 6.1- not reached) (HR, 0.25; CI, 0.11-0.57; P=0.001), and 48 resistant, median PFS 3.6 months (CI, 2.7-5.5). For oxaliplatin: 29 patients were sensitive, median PFS 8.5 months (CI, 5.3-12.4) (HR, 0.27; CI, 0.13-0.57; P <0.001), and 34 resistant (median PFS of 3.6 months (CI, 1.9-5.5)). For irinotecan 34 were sensitive, median PFS 6.1 months (CI, 4.4-9.9) (HR, 0.35; CI, 0.18-0.69; P=0.002) and 29 resistant (median PFS 3.2 months (CI, 1.6-5.7). We found a positive correlation between treatment response and the number of drugs predicted as sensitive. Patient's predicted as sensitive to 2 and 3 drugs displayed a HR of 0.32 (CI, 0.15-0.68; P=0.003) and 0.09 (CI, 0.03-0.32; P<0.001), respectively. On the contrary, patient's sensitive to one showed a HR of 0.65 (CI, 0.30-1.41; P=0.278).

Conclusion: The three signatures developed in this study provide a tool for predicting responsiveness to the individual therapeutic drugs of the FFX regimen. These signatures may ultimately lead to the development of a personalised FFX strategy combining only efficient drugs for increasing efficacy and reducing toxicity in PDAC.

O-18

Efficacy and safety of remimazolam versus propofol during endoscopic ultrasound: a multicentre randomised controlled study (an interim analysis)

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Abstract

Background: Propofol is widely used sedative drugs in gastrointestinal endoscopic procedures, but is associated

with cardiopulmonary suppression. Remimazolam is a novel ultra-short-acting benzodiazepine sedative with rapid onset and minimal cardiopulmonary depression. This study was aimed to compare the efficacy and safety of remimazolam and propofol during endoscopic ultrasound (EUS) procedures.

Methods: A multicentre randomised controlled study was conducted from October 2022 to February 2023 who underwent EUS procedures. The patients were randomly assigned to receive either remimazolam or propofol as the sedative agent. The primary endpoint was the quality of sedation during the procedure. The quality of sedation was evaluated by the satisfaction of both endoscopists and patients. Secondary endpoints included the time to achieve sedation, recovery time, and adverse events.

Results: A total of 198 patients enrolled in the study, with 100 receiving remimazolam (mean dose, 8.1±4.0 mg) and 98 receiving propofol (mean dose, 85.2±56.2 mg). The satisfaction score evaluated by endoscopist was significantly higher in the remimazolam group compared to propofol group (9.09±1.13 vs. 8.03±1.05, P<0.001). The satisfaction score evaluated by patients was also significantly higher in the remimazolam group (9.33±0.89 vs. 8.18±2.03, P<0.001). The induction time (47.42±38.73 sec. vs. 117.42±96.71 sec., P<0.001) and awake time (3.51±3.97 sec. vs. 6.78±7.02 sec., P<0.001) were much shorter in the remimazolam group compared to propofol group, respectively. The most common adverse event was tachycardia and there was no difference in the two groups.

Conclusion: Our results showed that remimazolam was non-inferior to propofol in terms of achieving deep sedation during EUS procedures. Additionally, remimazolam had a shorter induction time and awake time compared to propofol. These findings suggest that remimazolam could be a safe and effective alternative to propofol for sedation during EUS procedures.

O-19

Efficacy and safety of plastic, covered and uncovered self-expandable metal stents in the treatment of malignant biliary obstructions

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Abstract

Background: Endoscopic transpapillary biliary drainage (ETBD) is the gold standard to relieve jaundice caused by malignant biliary obstruction (MBO). Guidelines recommends the use of self-expandable metal stent (SEMS) over plastic stents (PS), but clinical practice is heterogeneous and an agreement about the most appropriate type of SEMS is lacking. Aim of the study was to highlight differences in efficacy and safety between PS and the three available SEMS designs.

Methods: This was a retrospective, multicentre evaluation of clinical success, need for reinterventions, stent dysfunction and adverse events (AEs) amongst consecutive patients undergoing ERCP for MBO. The inverse probability of treatment weights (IPTW) approach was adopted to handle for confounding.

Results: 2,752 ETBD were analysed: 636 received PS (23.1%), 606 uncovered (U-SEMS; 22.0%), 395 partially-covered (PC-SEMS; 14.4%) and 1115 fully-covered SEMS (FC-SEMS; 40.5%). After IPTW- adjustment, SEMS versus PS decreased the risk of additional ERCPs (p=0.001), debris accumulation (p=0.001) and migration (p=0.009). When comparing the three SEMS designs, FC-SEMS increased the clinical success over U-SEMS (odds Ratio [OR]: 2.20; p=0.001), but not over PC-SEMS (p=0.256). Compared to U-SEMS, FC-SEMS (OR: 0.17; p=0.001) and PC-SEMS (OR: 0.20; p=0.001) decreased stent ingrowth and FC-SEMS had higher migration rate (OR:2.14; p=0.001), despite no difference in redo-ERCP was registered. AEs, specifically post-procedural pancreatitis (OR: 1.83; p=0.036) was higher for FC-SEMS than U-SEMS.

Conclusion: In real-world clinical practice, PS adoption is still high despite guidelines' recommendations. SEMS provide longer patency, whilst each SEMS design has pros- and cons- deserving further prospective, comparative evaluation. (NCT05395013)

O-20

Re-shaping the pancreatic cancer tumour microenvironment: the metastasis suppressor NDRG1 inhibits pancreatic cancer exosome biogenesis, packaging and release

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Abstract

Background: Pancreatic cancer (PaC) cells can re-program surrounding stromal cells, including cancer associated fibroblasts (CAFs), to produce cytokines and extracellular matrix (ECM) proteins that fuel cancer growth, metastasis and form a barrier to current chemotherapies. Recent studies revealed that extracellular vesicles (EV) are a key mediator of communication between PaC cells and CAFs, contributing to chemotherapeutic resistance. We discovered that the metastasis suppressor N-myc down-stream regulated gene 1 (NDRG1) potently inhibits communication between PaC cells and CAFs. Herein, we investigate for the first time the effect of NDRG1 on the biogenesis, secretion and functional effects of EVs produced by PaC cells.

Methods: Using gradient ultracentrifugation, we isolated and characterised small and large EVs from PaC cells stably over-expressing wild-type NDRG1 (WT-NDRG1), mutant NDRG1 which lacks the protein-binding region (ΔCAP-NDRG1), or vector control (VC). EV cargo from the VC, WT-NDRG1 and ΔCAP-NDRG1 expressing PaC cells was examined using quantitative proteomics. PaC derived EVs were cultured with CAFs and immune cells to determine their functional effects on these key TME components. The effect of NDRG1 on key endosomal/lysosomal trafficking proteins, including endosomal sorting complexes required for transport machinery (ESCRT) and Rab GTPases, which control EV biogenesis and secretion, were also examined.

Results: We demonstrate that WT-NDRG1 potently attenuated production of small EVs (exosomes) from PC cells, with the protein binding CAP region being vital for this effect. NDRG1 re-programmed the endocytic pathway in PaC cells, diverting endosomes towards lysosomal maturation instead of EV release via direct inhibitory effects on multiple Rab GTPase and ESCRT proteins that control EV biogenesis. NDRG1 also substantially altered the PaC-derived EV protein cargo, leading to important functional effects on CAFs and immune cells to reduce their oncogenic re-programming.

Conclusion: By altering the endocytic pathway to favour lysosomal degradation, NDRG1 potently reduced the production of EVs and altered their protein cargo. Considering that EVs are a key contributor to oncogenic cross-talk between PC cells and surrounding stroma, targeting NDRG1 in PC cells may be a promising new approach to “uncouple” PC cells from the TME, enhancing their vulnerability to current chemo and immune-therapies.

O-21

Tunnelling nanotubes provide a route for mutant Kras spreading in pancreatic cancer

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Abstract

Background: Over 90% of pancreatic cancer, one of the most lethal tumours, harbour mutant K-RAS, the key oncogene on pancreatic cancer initiation. Transmission of oncoprotein is regards as the important ways of interacting between cancer cells recently. Tunnelling nanotubes (TNTs) is a newly discovered communication structure between cells even different types of cells. This study aims to explore the mechanisms of mutant Kras oncoprotein (mKras)

transmit via TNTs between pancreatic cancer cells (PCs) and normal acinar cells (ACs), and initiate its malignant transformation.

Methods: Immunostaining was performed to visualize the distribution of mutant Kras and Piezo1 expression in PCs and ACs. The observation of TNT formation and mutant Kras transmission were used by confocal microscopy, scanning electron microscopy and live cell workstation. In vivo, pancreatic specific Piezo1 knockout transgenic mice and spontaneous pancreatic cancer transgenic mice were adopted to show the role of Piezo1 on the formation of TNTs and the transmission of mutant Kras between PCs and ACs in vivo.

Result: In this study, we found that TNTs provide an "bridge" for transporting mKras from PCs to ACs, driving the transformation of acinar to acinar to ductal metaplasia (ADM) structure. Interesting, we found that this process was depended on the Piezo1, a mechanosensitive protein. Specifically, we found that during the progression of pancreatic cancer, Piezo1 is activated and is involved in cytoskeletal rearrangement, which regarded as the initiation of TNTs formation. When we knocked down Piezo1 in PCs, the number of TNTs between PCs and ACs was significantly decreased and the transport of mKras from PCs to ACs was also suppressed. In contrast, the number of TNTs and the transport of mKras were significantly increased after we treating PCs with Yoda1, a Piezo1 agonist. Moreover, we found TNTs promotion effect of Piezo1 may be related to its activating role on AKT/mTOR signalling pathway.

Conclusion: Our data highlighted a newly mechanism of mKras spreading between cells via TNTs, which provided a new way for pancreatic cancer cells to induce malignant transformation of surrounding normal acinar cells.

O-22

Small cyst size and slow growth rate are soothing features in individuals with pancreatic cysts undergoing surveillance

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Abstract

Background: Pancreatic mucinous cysts are increasingly discovered on imaging studies performed for unrelated conditions. Current guidelines do not stratify surveillance frequency by size, whereas repetitive imaging of (mostly)

small cysts imposes a substantial burden on health care recourses.

Methods: The PACYFIC-study is an international collaboration that investigates the yield of pancreatic cyst surveillance, performed at the discretion of the treating physician. We evaluated the risk of high-grade dysplasia (HGD) and pancreatic cancer (PC) for different cyst sizes and growth rates, in participants with ≥12 months of follow-up from 28 centres.

Results: 1049 of 1955 PACYFIC participants met predefined inclusion criteria of this study; mean age 66 years (SD 10), 63% female, median follow-up 26 months (IQR 25) and number of visits 3 (IQR 2). 197 individuals (19%) had a baseline cyst size <10mm, 454 (43%) of 10-19mm, 248 (24%) of 20-29mm, 91 (8.7%) of 30-39mm and 59 (5.6%) of ≥40mm.

46 individuals (4.4%) developed HGD (n=17) or PC (n=29). Based on a case-control analysis, cysts ≥40mm more often harboured HGD or PC (14%) than did cysts <20mm (3.1% for <10mm, p=0.002; 2.3% for 10-19mm, p<0.001). The prevalence of absolute indications for surgery was higher in individuals with a cyst ≥40mm (12%) than in those with cysts 10-19mm (4.4%; p=0.005), yet not higher than the other cyst size groups.

The risk of developing HGD or PC increased with baseline cyst size (HR 1.02 [95% CI 1.01-1.03], p=0.005; independent of presence of indications for surgery) and was 2-fold lower in individuals with cysts <20mm, as compared to those ≥20mm HR 2.2 [95% CI 1.2-4.0], p=0.01). Individuals with a growth rate of <5mm/year had a 14-fold lower risk of HGD/PC, as compared to those with faster growing lesions (HR 14 [95% CI 4.3-48], p=<0.001).

Conclusion: Cysts size <20mm and growth rate <5mm/year are 'soothing' features indicating a diminutive risk of malignant progression. For cysts with these features – and without indications for surgery ('trivial cysts') – a less intensive regime than the currently recommended yearly surveillance may suffice.

O-23

Surveillance for presumed BD-IPMN of the pancreas: stability, size, and age identify targets for discontinuation

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Abstract

Background: Currently, most patients with branch duct intraductal papillary mucinous neoplasms (BD-IPMN) are offered indefinite surveillance, resulting in health care costs with questionable benefits regarding cancer prevention. This study sought to identify patients where the risk of cancer is equivalent to an age-matched population, thereby justifying discontinuation of surveillance.

Methods: International multicentre study involving presumed BD-IPMN without worrisome features (WF) or high-risk stigmata (HRS) at diagnosis who underwent surveillance. Clusters of individuals at risk for cancer development were defined according to cyst size and stability for at least 5 years, and age-matched controls were used for comparison using standardised incidence ratios (SIRs) for pancreatic cancer.

Results: Of 3844 patients with presumed BD-IPMN, 843 (22%) developed a WF or HRS after a median surveillance of 53 (IQR 53) months and 164 patients (4.3%) underwent surgery. Of the overall cohort, 1617 patients (42%) remained stable without developing WF or HRS for at least 5 years. In patients 75 years or older, the SIR was 2.23 (95%CI 0.45-6.52), and in patients 65 year or older with stable lesions below 15mm in diameter after 5 years, the

SIR was 1.77 (95%CI 0.20-6.39).

Conclusion: The risk of developing pancreatic malignancy in presumed BD-IPMN without WF or HRS after 5 years of surveillance is comparable to that of the general population depending on cyst size and patient age. Surveillance discontinuation could be justified after 5 years of stability in patients older than 75 years with cysts < 30 mm, and in patients 65 years or older who have cysts ≤ 15 mm.

O-24

Predictive clinical and imaging features of high-grade dysplasia in mucinous cystic neoplasms of the pancreas

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Abstract

Background: Mucinous cystic neoplasms (MCN) are rare cystic pancreatic lesions with an evidenced malignant potential. Although the population who bear MCN is well characterised, the natural history of these lesions has not been elucidated as well as the risk features of malignancy. In a recent single centre study (Vullierme et al., 2021), we identified imaging features suggesting malignant MCN on MRI: 1) ≥ 5mm wall thickness, 2) mural nodule size ≥ 9 mm, and/or 3) enhancing intra-cystic septa. The aims of this study were to identify clinical malignancy predictive factors and to validate in a multicentre cohort, the imaging malignancy predictive factors identified previously.

Methods: In this multicentre retrospective study, patients who underwent pancreatic resection between January 2008 and December 2021 for MCN were included. Pathological review confirmed the presence of ovarian-type stroma. The preoperative imaging (CT and/or MRI) had to be available for a centralized expert radiological review. A multivariable logistic regression was performed to identify predictive factors of malignancy.

Results: A total of 199 patients were included from 13 participant centres. The cohort was constituted of 197 female patients (99%) with a median age of 46 (IQR 37-55) years. At diagnosis, 97 patients (49%) were asymptomatic. Low-grade dysplasia (LGD) was observed in 167 (84%) patients and at least high-grade dysplasia (≥HGD) in 32 (16%) patients, from which 14/32 had invasive carcinoma. The presence of symptoms at diagnosis was significantly associated with ≥HGD (p=0.011). Regarding imaging features: ≥ 5mm wall thickness, a mural nodule size of ≥ 9

mm and presence of enhancing intra-cystic septa, were all significantly associated with ≥HGD (p=0.008, p=0.005 and p=0.014, respectively). In multivariate analysis, symptoms at diagnosis (OR 2.66, CI95% 1.08-6.54; p=0.033), lesion size ≥4cm (OR 3.23, CI95% 1.03-10.1; p=0.044) and presence of mural nodule (OR 6.17, CI95% 2.62-14.55; p<0.0001) were independent predictive factors of ≥HGD.

Conclusion: MCN causing symptoms at diagnosis, measuring ≥ 4cm and with a mural nodule in imaging, should be addressed for surgical resection. The imaging features predictive of malignancy, that are confirmed in this cohort, should also be considered in surgical management decisions.

O-25

Long-term outcome of immediate versus postponed intervention in patients with infected necrotizing pancreatitis

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Abstract

Background: Patients with infected necrotizing pancreatitis did not benefit from immediate (<24h) catheter drainage in a recent randomised trial. Moreover, patients treated with a postponed-drainage approach using antibiotic treatment required fewer invasive interventions, and over a third of patients were treated without any intervention. However, it is unclear whether these relative benefits hold over time as conservatively treated patients may require interventions later.

Methods: Between Aug 2015 and Oct 2019, 104 patients with infected necrotizing pancreatitis were randomly assigned to either immediate catheter drainage or postponed catheter drainage in the multicentre randomised POINTER trial. Here, we re-evaluated all clinical data of patients who were still alive after the initial 6-month follow-up. The primary outcome was a composite of death and major complications.

Results: In total, 88 out of 104 patients were re-evaluated with a median follow-up of 51 months. After the initial 6-month follow-up, the primary outcome occurred in 7 of 47 patients (15%) in the immediate-drainage group and 7 of 41 patients (17%) in the postponed-drainage group (relative risk [RR] 0.87, 95% confidence interval [CI] 0.33 to 2.28; p=0.78). Additional drainage procedures were performed in 7 patients (15%) in the immediate-drainage group versus 3 patients (7%) in the postponed-drainage group (RR 2.03; 95% CI 0.56-7.37; p=0.34). New pancreatitis-related death occurred in 2 versus 0 patients. In the total follow-up period, the median number of interventions was 4 in the immediate-drainage group versus 1 in the postponed-drainage group (p=0.001). Eventually, 14 of 15 patients (93%) in the postponed group who were successfully treated in the initial 6-month follow-up with antibiot-

ics only without any intervention, remained without intervention at the end of the current follow-up. At the end of follow-up, pancreatic function and quality of life were similar.

Conclusion: Also during long-term follow-up, a postponed drainage approach using antibiotics to patients with infected necrotizing pancreatitis results in fewer interventions as compared to immediate drainage, and should therefore be the preferred approach.

O-26

Sarcopenia is associated with pancreatic exocrine insufficiency on laboratory and CT imaging findings in patients with chronic pancreatitis

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Abstract

Background: Sarcopenia has been reported to affect the clinical course and prognosis of various diseases including chronic pancreatitis (CP). However, clinical characteristics and imaging findings of the CP patients complicated with sarcopenia remain unclear.

Methods: In this single-centre cross-sectional study, 89 cases with definitive CP were enrolled. The skeletal muscle mass index (SMI) was measured by transverse computed tomography (CT) images at the third lumbar vertebra (L3). Sarcopenia was defined according to the cut-off value proposed by the Japan Society of Hepatology. SMI was also measured by bioelectrical impedance analysis method. Body composition analysis, grip strength, laboratory data including nutritional status and pancreatic functions, and pancreatic CT imaging findings were compared between the CP patients with sarcopenia and those without sarcopenia.

Results: Forty-nine of the 89 (55%) patients met the criteria for sarcopenia. Patients with sarcopenia had lower BMI (20.2 vs. 24.0 kg/m2, *P* <0.001), body fat percentage (20.5 vs. 25.4 %, *P* =0.009), lower SMI (male: 6.42 vs. 7.50 kg/m2, *P* <0.001, female: 4.72 vs 6.41 kg/m2, *P* =0.005), and grip strength (male: 30.3 vs 36.1 kg, *P* <0.001, female: 20.1 vs 24.7 kg, *P* =0.04). Assessment of nutritional status found that total peripheral lymphocyte count (1629 vs. 1965 /μL, *P* =0.014) and Controlling Nutritional Status score (1.25 vs. 2.06, *P* =0.023) were worse in patients with sarcopenia. Serum lipase level (28.7 vs. 41.7 U/L, *P* =0.034) and urinary PABA excretion rate in the pancreatic function diagnostant test (63.6 vs. 82.0 %, *P* =0.013) were lower in the patients with sarcopenia. Patients with sarcopenia had larger main pancreatic duct diameter (5.81 vs. 4.21 mm, *P* =0.002) and thinner pancreatic parenchyma (7.71 vs. 10.93 mm, *P* <0.001), both of which are associated with pancreatic exocrine insufficiency, on pancreatic CT imaging.

Conclusion: Our results suggest the association of sarcopenia with pancreatic exocrine insufficiency in CP patients. Further studies are warranted to clarify whether proper nutritional management would contribute to the improved prognosis of CP patients with sarcopenia.

O-27

Comparison of diagnostic rate for type 1 autoimmune pancreatitis between the Japanese clinical diagnostic criteria and the international clinical diagnostic criteria

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Abstract

Background: The International Consensus Diagnostic Criteria (ICDC) for autoimmune pancreatitis (AIP) are known to show an excellent diagnostic performance. Recently, the Japanese clinical diagnostic criteria for AIP (JPS2018), revision of the JPS2011, have been published. Our study aimed to clarify the diagnostic rate for type 1 AIP of the JPS2018 by comparing with the JPS2011 and the ICDC.

Methods: One hundred forty-five patients in Kansai Medical University hospital who fulfilled the Japanese clinical diagnostic criteria (definitive, probable, or possible AIP) or the ICDC (definitive, probable, or not otherwise specified AIP) were included in the current study. Furthermore, we studied the clinical features of patients who were diagnosed as AIP based on surgical specimen.

Results: The diagnostic rates for type 1 AIP (definitive and probable type 1 AIP) in the JPS2018, JPS2011, and ICDC were 91%, 82.4%, and 87.6%, respectively. One of the reasons why the diagnostic rate of the JPS2018 was improved was the new establishment of a procedure that includes magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) biopsy in the JPS2018. Six patients who were classified into definitive/probable AIP according to the JPS2018 were not diagnosed as AIP by applying to the ICDC due to the lacks of marked elevation of serum IgG4 (>2 times upper limit of normal) and administration of steroid. It was impossible to diagnose 6 patients undergoing pancreatic resection as AIP according to the JPS 2018 and the ICDC because of absence of elevated serum levels of IgG4 and/or typical radiological findings for type 1 AIP.

Conclusion: In the diagnosis of type 1 AIP, the diagnostic rate of JCDC was superior to that of the ICDC. The histological diagnosis based on EUS-FNA biopsy tissues is required for further improvement of diagnostic ability for AIP.

O-28

Defeating gemcitabine resistance in pancreatic tumours with antibody-based CDA degrader

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis that is notably due to the emergence of resistance mechanisms to conventional treatments such as chemotherapy. Gemcitabine, a deoxycytidine analogue, is one of the main chemotherapy drugs used for patients with PDAC but resistance mechanisms limit its efficacy. Among them, cytidine deaminase (CDA) has been identified as a key regulator of resistance to gemcitabine by promoting its deamination and inactivates about 90% of intracellular gemcitabine. Moreover, CDA is overexpressed at baseline in PDAC and is predictive of gemcitabine efficacy in experimental models of PDAC. However, current inhibitors targeting CDA active site have a poor bioavailability, a limited efficacy and/or off-target issues. Hence, to target CDA and overcome these resistances, alternative therapeutic strategies need to be explored and we choose the specificity of intracellular antibodies (i.e. antibodies expressed in the cells).

Methods: From a library of single domain antibodies, we selected anti-CDA antibodies by phage display. Next, these antibodies were cloned in fusion with an E3 ubiquitin ligase domain to generate antibody-based degraders. Then, a cell-based screening was performed to select functional intracellular antibody-based CDA degraders able to deplete CDA in cells. Finally, the effects of CDA degraders combined or not with gemcitabine on PDAC cells were assessed

in vitro and in vivo.

Results: We develop here 2 potent CDA degraders and show their potency to rapidly deplete endogenous CDA protein in several PDAC cell lines. Functionally, CDA degraders decrease gemcitabine's IC50 and inhibit PDAC cells proliferation by increasing the apoptosis. Finally, using a cell derived xenograft (CDX) mouse model, we show that the combined treatment of CDA degrader and gemcitabine strongly impedes tumour growth.

Conclusion: Collectively, CDA degraders are an innovative and potent approach to sensitise PDAC cells and tumours to gemcitabine. Future work will be dedicated to the intratumoural delivery of CDA degraders in experimental PDAC models, both in vitro and in vivo with the ultimate goal of bringing these therapeutic proteins closer to a clinical use.

O-29

Med12 promotes immune evasion by enhancing endogenous retroelements silencing in pancreatic ductal adenocarcinoma

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers with limited treatment options, including checkpoint blockade (ICB) immunotherapy. Epigenetic dysregulation is a defining feature of tumourigenesis and contributes to immune escape. However, little is known about whether and how epigenetic regulators evade immune surveillance in PDAC.

Methods: To identify the factors that modulate immune surveillance, we employed in vivo epigenetic-focused CRISPR-Cas9 screens in mouse PDAC tumour models engrafted in either immunocompetent or immunodeficient mice.

Results: Here, we identified Med12, a subunit of RNA polymerase II, as a mediator of immune escape in PDAC. In a murine PDAC models, Med12 loss effectively promotes the cytotoxicity of adaptive immune and sensitizes to immune checkpoint blockade. And the anti-tumour effects were largely reversed by depleting CD8+ T cells. Mechanistically, Med12 enhanced H3K9me3 modification to repress endogenous retroelements. Thus, loss of Med12 derepressed retroelements, triggered cytosolic RNA-sensing and DNA-sensing pathways and the downstream type I interferon pathways, leading to enhanced tumour rejection and responses to immune checkpoint blockade. Moreover, Med12 depletion induced H3K27Ac gain in the Med12-binding domains, further enhancing the interferon-related genes transcription.

Conclusion: Our results demonstrate the role of Med12 in suppressing tumour-intrinsic immunogenicity, thus providing a potential target for immunotherapy of PDAC.

O-30

Same-session double EUS-bypass versus surgical gastroenterostomy and hepaticojejunostomy: an international multicentre comparison

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Abstract

Background: Standard treatment of gastric outlet and Bbliary obstruction would be surgical gastroenterostomy and hepaticojejunostomy (i.e. 'double bypass'). Endoscopic ultrasound (EUS) has nowadays enabled the creation of an EUS-guided double bypass. However, same-session double EUS-bypass has been described in small proof-of-concept series and lack comparison with surgical double bypass.

Methods: A retrospective multicentre analysis was performed of all consecutive same-session double EUS-bypass procedures performed in 5 academic centres. Surgical comparators from the same time interval were extracted. Efficacy, safety, hospital stay, nutrition and chemotherapy resumption, long-term patency and survival were compared.

Results: In total, 154 patients were identified, of which 53 (34.4%) received treatment with EUS and 101 patients with surgery (65.6%). At baseline, patients undergoing EUS exhibited higher ASA scores and a higher median Charlson Comorbidity Index (9.0 [IQR 7.0-10.0] vs. 7.0 [IQR 5.0-9.0], p<0.001).

Technical success (96.2% vs. 100%, p=0.117) and clinical success rates (90.6% vs. 82.2%, p=0.234) were similar when comparing EUS and surgery. Overall (11.3% vs. 34.7%, p=0.002) and severe adverse events (3.8% vs. 19.8%, p=0.007) occurred more frequently in the surgical group. In the EUS group, median time to oral intake (0 [IQR 0-1] vs. 6 [IQR 3-7] day(s), p<0.001) and hospital stay (4.0 [IQR 3-9] vs 13 [IQR 9-22] days, p<0.001) were significantly shorter.

Conclusion: Despite being used in a patient population with more comorbidities, same-session double EUS-bypass achieved similar technical and clinical success, and was associated with fewer overall and severe adverse events when compared to surgical gastroenterostomy and hepaticojejunostomy.

O-31

Designing new targeted therapies against stress granules formation in Kras-dependent pancreatic cancer

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Abstract

Background: Stress granules (SGs) are membrane-less organelles formed by liquid-liquid phase separation (LLPS) that play a critical role in regulating RNA metabolism, and protein synthesis, in a wide range of stress responses. These granules are required to support pancreatic cancer (PDAC) transformation, cell survival, growth, and chemotherapy resistance, making them an attractive target for new cancer therapies. Here we report a novel mechanism for SG formation in response to oncogenic stress induced by $KRAS^{G12D}$, and provide a preclinical proof of concept for using small drug inhibitors of this new mechanism to inhibit PDAC initiation.

Results: We find that SG formation in response to $KRAS^{G12D}$ requires NUPR1, an intrinsically disordered protein overexpressed in PDAC. We observed that SGs become enriched in NUPR1 and proteomic interactors involved in RNA metabolism, splicing, and transport. By using genetic and pharmacological tools, we find that inhibition of NUPR1 abolishes the formation of SGs. Targeting NUPR1 with ZZW-115, an inhibitor that binds to residues A33 and T68, results in complete inhibition of SG formation in vitro. Moreover, SG inhibition deeply disrupts its functions such as RNA sequestration and regulation of protein synthesis. Consistent with a direct role in SG formation we find that recombinant NUPR1 can undergo liquid-liquid phase separation in vitro in a concentration-dependent manner, being actively involved the residues A33Q and T68Q. In addition, we demonstrate that NUPR1 overexpression, but not mutants at positions A33Q/T68Q, is sufficient for triggering SG formation in cells, highlighting the significant role of this protein in the development of these structures. We further reveal that SGs inhibition by ZZW-115 induces cell death in a concentration-dependent manner in the $Kras^{G12D}$-activated cells, while silencing the expression of this oncogene makes these cells resistant to ZZW-115-treatment. Meanwhile, inhibition of SG formation with ZZW-115 in Pdx1-Cre; LSL-$Kras^{G12D}$ mice completely blocks the developed of pancreatic intraepithelial neoplasia (PanINs), indicating that SG formation is necessary for PDAC development induced by the oncogenic $Kras^{G12D}$.

Conclusion: Our study provides new insights suggesting that targeting SGs can be utilised as a synthetic lethality therapeutic strategy in mutated $Kras^{G12D}$-dependent tumours to develop new therapies against PDAC.

O-32

Total pancreatectomy with islet autotransplantation as an alternative to high-risk pancreatojejunostomy after pancreaticoduodenectomy: a prospective randomised trial

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Abstract

Background: Criteria to predict the risk of Post-Operative Pancreatic Fistula (POPF) occurrence after pancreaticoduodenectomy (PD) are available. However, even when a high risk of POPF is predicted, total pancreatectomy (TP) is not currently accepted as an alternative to PD, because of its severe consequences on glycaemic control. Combining Islet AutoTransplantation (IAT) with TP may mitigate such consequences. The aim of this study was to compare PD and Total Pancreatectomy with Islet AutoTransplantation (TP-IAT) in patients at high risk of POPF.

Methods: This is a randomised, open-label, controlled, bicentric trial (NCT01346098). Candidates for PD with a high-risk of fistula of the pancreatic anastomosis (i.e., soft pancreas and duct diameter ≤3 mm) were randomly assigned (1:1) to undergo either PD or TP-IAT. The primary endpoint was the incidence of complications within 90 days after surgery.

Results: Between 2010 and 2019, 61 patients were assigned to PD (n=31) or TP-IAT (n=30). In the intention-to-treat analysis, morbidity rate was 90·3% after PD and 60% after TPIAT (p=0·008). According to complications' severity, PD was associated with an increased risk of grade ≥2 [OR 7·64 (95% CI 1·35-43·3), p=0·022], while the OR for grade ≥3 complications was 2·82 [(95% CI 0·86-9·24), p=0·086]. After TP-IAT, the postoperative stay was shorter [median 10·5 vs 16·0 days; p<0·001). No differences were observed in disease-free survival, site of recurrence, disease-specific survival and overall survival. TP-IAT was associated with a higher risk of diabetes [HR 9·1 (95% CI 3·76-21·9); p<0·0001], but most patients maintained good metabolic control and showed sustained C-peptide production over time.

Conclusion: TP-IAT may become the standard treatment in candidates for PD, when a high risk of POPF is predicted.

O-33

The effect of neoadjuvant chemoradiotherapy on the immune profile of pancreatic ductal adenocarcinoma: in-depth analysis of the PREOPANC-1 randomised controlled trial

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Abstract

Background: The randomised phase III trial (PREOPANC-1) that was performed in 16 centres in the Netherlands compared the effects of preoperative chemoradiotherapy (Gemcitabine and 2.4 Gy radiation) versus immediate surgery for resectable and borderline resectable pancreatic cancer. The outcomes of the secondary endpoints and predefined subgroup analyses suggest an advantage of the neoadjuvant approach. The aim of the present study was to investigate the changes in the immune microenvironment and infiltration caused by the neoadjuvant treatment.

Methods: To that aim, we collected formalin-fixed, paraffin-embedded pancreatic cancer samples from all centres that participated in the PREOPANC -1 trial. We performed targeted gene expression using the PanCancer Immune Profiling panel of NanoString.

Results: Comparing 50 samples of the patient who were subjected to neoadjuvant treatment to 46 treatment-naïve samples showed a distinct genetic profile induced by the neoadjuvant therapy. More than 250 immune-related genes were significantly differentially expressed between the two groups of samples. The results indicate that neoadjuvant therapy resets the innate immune activation in the tissue samples. A significantly higher infiltration of CD14+, CD33+, CSF1R+, and CD163+, MRC1+ cells was found in samples of the neoadjuvant arm. In contrast, B cells and various subtypes of T cells like CD8+ and FOXP3+ showed a significant decrease in the same samples. Pathway

analysis revealed that the neoadjuvant treatment stimulated the expression of genes related to complement activation, chemotaxis, and wound repair, while genes related to lymphocyte activation and adaptive immune responses were dominant in the treatment-naïve arm.

Conclusion: In conclusion, this is the first comprehensive study to describe the immune-molecular changes as a result of neoadjuvant therapy in a randomised clinical trial. The results reveal the enrichment of the myeloid compartment following neoadjuvant therapy which was significantly associated with a survival benefit for the patients. Studying the personalised effect of neoadjuvant therapy will guide choosing the appropriate combined therapy for pancreatic cancer.

O-34

How a PI3K interactor drives PDAC chemoresistance and metastasis while paving the way for PI3K-targeted therapy

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Abstract

Background: Pancreatic cancer is a major challenge in cancer treatment today. The initial steps towards invasive pancreatic cancer involve activating Kras mutations and activation of the PI3K/AKT pathway. It is unclear which signalling pathways allow these early cancer cells to gain metastatic abilities after Kras activation, giving rise to the early metastatic spread observed in pancreatic cancer and leading to the high recurrence rates seen in operable PDAC patients. Recently, we found that the p130Cas protein plays a pivotal role in activating the PI3K-AKT pathway downstream of mutant Kras. We believe that p130Cas is key to activating the PI3K-AKT pathway and enabling metastatic properties of pancreatic cancer cells.

Methods: Mouse models of PDAC (KrasG12D/Trp53R172H/CrePdx1 and KrasG12D/CrePdx1) were crossed with mouse strain carrying p130Cas floxed alleles. Functional 3D in vitro and in vivo experiments were performed with murine primary PDAC cells.

Results: We found that p130Cas is required for the activation of the PI3K-AKT pathway downstream of mutant Kras, which promotes acinar metaplasia and tumour progression. We discovered that p130Cas binds to the PI3K-p85 regulatory subunit, thereby releasing its inhibitory effect on the PI3K-p110 catalytic subunit and allowing full activation of the PI3K-AKT pathway. Analysis of RNAseq datasets revealed that circulating tumour cells from patients with metastatic PDAC display a significant upregulation of the p130Cas gene and PI3K-AKT gene signature, suggesting a crucial role of this axis in promoting metastasis. We demonstrated that p130Cas levels control the ability of PDAC cells to grow as 3D organoids and their metastatic potential in an in vivo zebrafish model. We observed that organoids with higher p130Cas levels are more resistant to gemcitabine and that these cells are addicted to p130Cas-dependent PI3K-AKT activation, as the inhibition of the pathway has a significant impact on cells with high levels of p130Cas.

Conclusion: Our data suggests that the p130Cas-PI3K pathway contributes to both primary tumour chemoresistance and metastatic cell chemoresistance. Elimination of p130Cas-dependent cells with PI3K inhibitors may present a novel therapeutic opportunity to target specifically aggressive metastatic cancer cells escaping from primary tumour or already in circulation and may potentially interrupt the way of tumour metastasis.

O-35

Development of a novel and safe NUPR1 inhibitor with efficient anticancer activity for pancreatic cancer treatment

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Abstract

Background: Pancreatic cancer is a deadly disease with the highest mortality rate. This is because there are no efficacious treatment options for pancreatic cancer. We previously developed a promising drug candidate, ZZW-115, a trifluoperazine-derivate, for the treatment of pancreatic cancer. ZZW-115 binds and inhibits the nuclear protein 1 (NUPR1), a stress-related protein essential for pancreatic cancer development and progression. However, the clinical translation of ZZW-115 appeared limited because it could bind to the potassium channel hERG, thus causing the potential risk of cardiotoxicity when administered to patients. As such, there is an urgent need to identify a novel and safe NUPR1 inhibitor.

Methods: We first applied a fluorescence thermal-denaturation approach-based screening on 10000 compounds (Maybridge chemical library) and 28 compounds were identified as binding to NUPR1. We systematically analysed the cytotoxic effect in vitro and identified AJO14 as a lead compound. We further studied this lead compound to test its anticancer activity in vivo using the Mia-PaCa-2 cell-based xenografts mouse model. We also assessed its hERG binding ability and dissected its mechanism of action. Finally, we applied an AI-based approach to improve the structure of the AJO14 to increases its anticancer efficiency, to optimize its safety and improving its biochemical characteristics such as its solubility.

Results: Among the 28 NUPR1 binding compounds identified in our screening AJO14 was retained because its low IC50 on several PDAC-derived cells and its absence of binding to the hERG channel. In addition, we found that AJO14 showed an excellent dose-dependent tumour reduction activity on xenografted mice. Mechanistically, we demonstrated that AJO14 induced cell death mainly through apoptosis and necrosis, accompanied by a mitochondrial catastrophe followed by a strong metabolism failure with a decrease in ATP production. This process seems to be mediated by hyperPARylation since it could be reversed by Olaparib. Finally, we tried to improve the compound using an AI-based approach and among the 55 candidates proposed and tested 6 showed a significant gain of efficiency and have been retained for further studies.

Conclusion: Collectively, AJO14-derived compounds are new potent NUPR1 inhibitors to treat pancreatic cancer without cardiotoxicity.

O-36

Spatial transcriptomic analysis of sensory neurons in murine pancreatic cancer reveals a potential role for neuron-mediated immune suppression in the tumour microenvironment

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is characterised by pronounced intratumoural nerve growth, neural invasion and neuro-inflammation. In our preliminary analysis, we demonstrated mutual trophic effects between myeloid derived suppressor cells (MDSCs) and dorsal root ganglia (DRG) neurons, which suggest a hitherto unconsidered, immunosuppressive role for sensory neurons in PDAC. To elucidate the role of neuron-mediated immune suppression, we characterised the transcriptional profile of DRG neurons innervating tumour bearing mouse pancreata using spatial transcriptomics.

Methods: DRG isolation and FFPE block preparation were performed from genetically engineered (Ptf1a-Cre; LSL-Kras+/G12D [KC], Ptf1a-Cre; LSL-Kras+/G12D; Trp53+/fl [KPC], and Ela-TGFα; Ptf1a-Cre; Trp53fl/fl; RelAfl/fl [TPAC] mouse models) and surgically induced (orthotopic KPC cell implantation and electroporation) mouse models of PDAC. The DRG neurons were subject to spatial transcriptomic profiling at the NanoString GeoMx Digital Spatial Profiling Technology.

Results: In our spatial transcriptome analysis, we identified an enriched expression of proteins related to endopeptidase inhibition pathway in tumour DRGs compared to their age-similar controls. Two of the most enriched ones of these molecules among KPC and TPAC DRGs were Wfikkn2 (fold change= 1,77 & p< 0,01 for KPC; fold change= 1,73 & p< 0,01 for TPAC) and Serpinb9b (fold change= 1,61 & p< 0,01 for KPC; fold change= 1,71 & p<0,01 for TPAC), both previously shown to regulate immune evasion in cancer (1, 2, 3). Furthermore, we also detected an altered expression of other immunomodulatory pathways, including the chemokine binding. For instance, CXCL15 was highly enriched in both KPC (fold change= 1,45 & p=0,04) and TPAC (fold change= 1,77 & p< 0,01) DRG samples. Taking the known MDSC recruiting role of this protein into account (3), its upregulation in tumour DRGs is another strong indication for the immunosuppressive role neurons play in PDAC.

Conclusion: Our spatial transcriptomic analysis of DRGs creates a broad perspective on the diverse roles neurons can play in PDAC and the immunomodulation. Further functional and mechanistic studies of targets of interest in PDAC will uncover the true translational potential of targeting sensory neurons for tumour control in PDAC.

O-37

The Italian Registry of Families At Risk of Pancreatic Cancer (IRFARPC): Long-term results of a prospective, multicentre trial

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Abstract

Background: Pancreatic cancer (PC) surveillance of high-risk individuals is diffusing worldwide. It aims at anticipating PC diagnosis in a pre-clinical stage. In 2015 the Italian Registry of Families At Risk of Pancreatic Cancer (IRFARPC) was created. We herein report yield, outcomes, and harms seven years after the registry inception.

Methods: High-risk individuals (subjects with family history –"FPC"- or with genetic predisposition with/without family history – Mutation carriers, "MC") have been enrolled in 18 Centres. They underwent magnetic resonance with cholangiopancreatography or endoultrasonography on annual basis. The yield and harms of surveillance were analysed. NCT04095195.

Results: During the study period (June 2015 – September 2022), 679 individuals were enrolled. Of these, 524 (77.2%) underwent at least a baseline imaging and represented the study population. Median age was 53 (IQR 14). FPC accounted for 75.6% of subjects enrolled. Only 69 (17.2%) of them were tested for at least a PC predisposition gene, and among such five (7.2%) individuals were revealed as harbouring pathogenic / likely pathogenic mutations (three ATM, one BRCA-1, and one BRCA2). Of the 93 constituting the MC group with family history, a predominance of BRCA2 and p16/CDKN2A was reported (40.9% and 30.1%, respectively.

Three-hundred-twenty-eight individuals (62.6%) were followed-up after the first evaluation. A total of 1,340 outpatient visits (median two visits/subject) were recorded. The rate of adherence to the annual surveillance was 79.9%, 83.1%, 85.3%, 90.9%, 100% for the second, third, fourth, fifth and sixth surveillance rounds, respectively.

Overall, malignant (n=7) and pre-malignant (1 PanIN3) lesions were found in eight individuals (1.5%). In 4 PC cases, a genetic background was present. Two of the 7 PC were Stage I; five and two were prevalent and incident cases, respectively. Six pancreatic neuroendocrine tumours (one resected) and one overtreatment (a low-grade mixed-IPMN) are reported as well. Pancreatic cysts did not significantly increase in size during surveillance. Median overall and disease-free survival of resected PC patients were 18 and 12 months (95%CI not computable).

Conclusion: PC surveillance in a fully public healthcare system is feasible, safe, and can lead to early PC diagnosis.

O-38

The impact of transcriptional subtyping on pathological staging and therapy response of pancreatic cancer

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Abstract

Background: Loss of GATA6 or HNF1A and increased expression of KRT81 in pancreatic cancer (PDAC) is associated with increased malignancy. Its effect on outcome of gemcitabine-based treatment of pancreatic cancer and on tra-

ditional staging criteria has not been studied yet.

Methods: The prognostic impact of GATA6 and combined KRT81 / HNF1A expression by immunohistochemistry was examined in the tumour tissue of 139 patients with advanced PDAC treated within the AIO-PK0104 trial or translational trials as well as in the specimens of 411 patients resected for PDAC. The findings were validated using RNAseq data of 178 resected PDAC patients.

Results: In the advanced PDAC cohorts, 39.6 % of all samples showed high GATA6 expression, which was not associated to progression-free survival (PFS, HR 0.65, p<0.21) and overall survival times (OS, HR 0.34, p= 0.34) in the gemcitabine-based treated patients. Instead, patients with GATA6 low tumours showed significantly improved survival when treated with gemcitabine-based chemotherapy (HR 0.60, p=0.04). Similar results were obtained for the combination of KRT81 and HNF1A. In the resected PDAC cohort, 54.5 % of all samples showed low GATA6 expression, which conferred significantly longer disease-free survival times (DFS, HR 0.52, p<0.001) and OS times (HR 0.44, p<0.001) restricted to patients treated with adjuvant gemcitabine. Similar results were obtained by KRT81 and HNF1A expression. RNAseq data from the validation cohort confirmed the findings. Moreover, based on molecular subtype, different parts of the TNM staging criteria influenced independently the outcome of the patients. Margin status only impacted on outcome in GATA6 low or KRT81 positive tumours.

Conclusion: The assessment of the transcriptional subtype based on expression of GATA6 or combination of KRT81 and HNF1A may serve as a marker for therapy stratification for gemcitabine-based palliative and adjuvant chemotherapy in PDAC and could be used to inform clinical therapy decisions.

O-39

Early versus late removal drainage in patients who underwent pancreatic resection: a comprehensive systematic review and meta-analysis using trial sequential analysis

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Abstract

Background: The superiority of EDR versus LDR after pancreatic resection has never been demonstrated. The study aims to compare early drainage removal (EDR) versus late (LDR) after pancreatic resection.

Methods: A systematic review was performed to identify RCTs comparing EDR versus LDR after pancreatic surgery. A meta-analysis was carried out using a random-effects model and trial sequential analysis. The critical endpoints were major morbidity, percutaneous re-drainage, relaparotomy, and clinically relevant post-operative pancreatic fistula (CR-POPF). Haemorrhage (PPH), delayed gastric emptying (DGE), length of stay (LOS), and readmission rates were also evaluated. Risk ratios (RRs) and mean differences (MDs) with a confidence interval of 95 % (CI) were calculated. Type I and Type II errors were excluded comparing the accrued sample size (ASS) with the required sample size (RIS). When RIS is superior to ASS, type I or II errors can be hypothesised.

Results: ASS was 786 for all endpoints except DGE (711 patients available). The major morbidity (RR=0.44; 0.23 to 0.83, CI) was lower in EDR groups. This result was not at risk of type I error (RIS=598). The CR-POPF rate was lower in EDR than in the LDR group (RR=0.36), but this difference is not statistically relevant (0.11 to 1.13, CI). The RIS to confirm or exclude these results can be reached by randomizing 262 patients. The need for percutaneous drainage, relaparotomy, PPH, DGE, and readmission rates was similar between the two groups. The related RISs were higher

than ASS, and type II errors cannot be excluded. LOS was inferior in EDR than in the LDR group (MD= -2.10; -2.99 to -1.21, CI). The RIS was 770, and type I errors can be excluded.

Conclusion: EDR, compared to LDR, is associated with lower major morbidity and shorter LOS. These results are robust and not at risk of type I errors.

O-40

Pharmacotyping, response prediction and tumour evolution in pancreatic cancer organoids

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Abstract

Background: Pancreatic cancer (PC) is characterised by an aggressive biology and high tumour heterogeneity causing considerable variations in therapy response. Patient-derived organoids (PDOs) reflect parental tumour features and represent a powerful preclinical tool to predict drug response and harness personalised treatment.

Methods: We have derived >40 PDOs from treatment-naïve and pre-treated PC patient primary tumour and metastases with a reliable efficacy. Drug response was evaluated using a cytotoxicity assay. Using Jenks natural breaks classification method, we clustered PDO responses (AUCs) and correlated it to patient response. A limited set of 7 PDO pairs were derived from the same patients at two distinct time points, followed by pharmacotyping and whole exome sequencing (WES).

Results: The implementation of an automated pipetting system and the subsequent miniaturization of drug screenings enhanced our process capacity, conferring the possibility to extend our panel to approved targeted substances and reducing the time before pharmacotyping. Following up our feasibility trial (Beutel, 2021), we validated the model accuracy in real-life in a higher number of PC patients. Our model allowed overall a successful drug-response prediction in naïve patients with an accuracy of 85.7% for first and second-line regimens. Prediction power was lower in pre-treated patients with a precision of 57.1% for subsequent chemotherapy lines. There was a trend towards a better performance of our system in prognosticating chemoresponsiveness vs unresponsiveness (89.5% vs 68.8%). Finally, administration of a regimen predicted to be efficient translated into a longer progression-free survival. The access to longitudinal biopsies allowed to conduct WES on 14 PDOs to capture a comprehensive genetic profiling over the time of treatment, notably revealing a CHEK2-mutated patient responding over time upon PARP-inhibitor maintenance therapy, in line with our PDO-based prediction, further highlighting the robustness of our method and algorithm. WES revealed a lower mutational burden und lower amount of nonsynonymous mutations upon chemotherapy. Tracking clonal evolution also revealed therapy-linked changes.

Conclusion: Overall, we report a robust and clinically-relevant preclinical tool for drug-response prediction, paving the way towards a PDO-based true precision medicine in clinical routine. Finally, WES of longitudinally-resolved PDO samples from the same patient under therapy unravelled genetic changes.

O-41

Surveillance for pancreatic cancer in high-risk individuals leads to improved outcomes: a propensity score matched analysis

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Abstract

Background: Recent pancreatic cancer surveillance programs of high-risk individuals have reported improved outcomes. This study assessed to what extent outcomes of pancreatic ductal adenocarcinoma (PDAC) in patients with a *CDKN2A/p16* pathogenic variant (PV) diagnosed under surveillance are better as compared to PDAC patients diagnosed outside surveillance.

Methods: In a propensity score matched cohort using data from the Netherlands Cancer Registry (NCR), we compared resectability, stage and survival between patients diagnosed under surveillance with non-surveillance PDAC patients. Survival analyses were adjusted for potential effects of lead time.

Results: Between January 2000 and December 2020, 43 762 patients with PDAC were identified from the NCR. Thirty-one patients with PDAC under surveillance were matched in a 1:5 ratio with 155 non-surveillance patients based on age at diagnosis, sex, year of diagnosis, and tumour location. Outside surveillance, 5.8% of the cases had stage I cancer, as compared to 38.7% of surveillance PDAC patients (OR 0.09; 95% CI, 0.04 – 0.19). In total, 18.7% of non-surveillance patients vs. 71.0% of surveillance patients underwent a surgical resection (OR 10.62; 95% CI, 4.56 – 26.63). Patients in surveillance had a better prognosis, reflected by a 5-year survival of 32.4% and a median overall survival (OS) of 26.8 months vs. 4.3% 5-year survival and 5.2 months median OS in non-surveillance patients (HR 0.31, 95% CI 0.19 – 0.50). For all adjusted lead times, survival remained significantly longer in surveillance patients than in non-surveillance patients.

Conclusion: Surveillance for PDAC in carriers of a *CDKN2A/p16* PV results in earlier detection, increased resectability and improved survival as compared to non-surveillance PDAC patients.

O-42

Pancreatitis - Microbiome As Predictor of Severity (P-MAPS): a prospective international multicentre translational study

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Abstract

Background: Acute pancreatitis (AP) is an inflammatory disorder that causes a considerable economic health burden. While the majority of AP shows a mild clinical course, about 10% of patients have moderate or severe disease with major local and systemic complications and a prolonged hospital stay. Still there is a lack of early biomarkers of severity while multiple complicated scoring systems fail to predict the course of disease. Here, we aim to investigate the role of the microbiome to predict the course of AP at admission.

Methods: 450 patients were prospectively enrolled in 16 centres from 8 European countries. Buccal and rectal swabs were collected to analyse the microbiome of AP patients within the first 72h of hospital admission. All samples were sequenced with Oxford Nanopore Technologies (ONT) a method belonging to 3rd generation of sequencing. Primary endpoints are the association of orointestinal microbiome with revised Atlanta classification and severity. Secondary endpoints are the association with mortality and length of hospital stay.

Results: In total, 832 samples from 424 patients were sequenced, 26 patients met exclusion criteria. After normalization of microbial data 409 buccal samples and 391 rectal samples remained for subsequent analysis. Significant differences were observed in beta diversities for all primary endpoints, rev. Atlanta classification (Bray Curtis, p-value 0.009**) and severity (Bray Curtis, p-value 0.008**) and for all secondary endpoints, mortality (Bray Curtis, p-value 0.006**) and length of hospital stay (Bray Curtis, p-value 0.043*) in rectal but not buccal swabs. Notably, these results remain significant after factoring in 74 potential confounding variables as alcohol consumption, smoking status, and antibiotic intake. No differences were observed in alpha-diversity. Classifiers are built with different abundant taxa.

Conclusion: The rectal microbiome has the ability to predict the course of acute pancreatitis at admission of the patient.

O-43

Prognostic significance of nodal micrometastases in patients with non-functioning pancreatic neuroendocrine tumours (NF-PanNETs) - a survival analysis from a prospective observational study

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Abstract

Background: Nodal metastases (N+) are one of the most powerful predictors of disease recurrence after surgery for non-functioning pancreatic neuroendocrine tumours (NF-PanNETs). However, the prognostic role of nodal metasta-

ses <5 mm, defined as micrometastases, has been poorly investigated so far. The aim of this study was to compare clinico-pathological features and survival outcomes between patients with NF-PanNETs without nodal involvement (N0), with nodal micrometastases (microN+) and with nodal metastases (macroN+).

Methods: Consecutive patients who underwent a formal pancreatic resection for NF-PanNETs at San Raffaele Hospital (Milan, Italy) between 2018 and 2021 and were enrolled in the DETECTYON trial were considered (NCT03918759).

Results: Overall, 100 patients were included. Of these, 58 had N0 PanNETs, 15 had microN+ and 27 had N+. Patients with macroN+ had significantly larger tumours [median 35 mm (IQR 28-47)] as compared to patients with microN+ [25 mm (IQR 24-35), *p*=0.040] and N0 neoplasms (26 mm (IQR 18-34), *p*=0.003]. The rate of G2-G3 neoplasms was comparable between patients with N0 and microN+ PanNETs (*n*=26/58 - 45% versus *n*=4/15 - 27%, *p*=0.203), whereas it was significantly higher among subjects with macroN+ tumours (*n*=21/27 - 78%). Patients with microN+ had a significantly lower Ki67 index as compared to those with macroN+ [2% (IQR 1-3) versus 6% (IQR 3-9), *p*=0.003]. Patients with N0 and microN+ neoplasms had microvascular invasion in 47% of cases (both), as compared to 82% of cases in patients with macroN+ (*p*=0.008). After a median follow-up of 37 months, 16 patients (16%) experienced disease relapse. Patients with N0 PanNETs had a 4-year DFS rate of 97% as compared with 88% and 43% in patients with microN+ (*p*=0.152) and macroN+ (*p*<0.001), respectively. At multivariable analysis, distant metastases (HR 5.826, *p*=0.026) and macroN+ (HR 6.281, *p*=0.034) were identified as independent determinants of disease relapse.

Conclusion: NF-PanNETs with microN+ seem to be associated with a risk of recurrence similar to N0 neoplasms upon their removal. MicroN+ may be regarded as a clinico-pathological entity separate from macroN+, with a possible impact on postoperative surveillance protocols.

O-44

A basal-like pancreatic cancer molecular subtype can be identified on EUS-acquired tissue and is associated to current smoking, lower Ca19.9 expression and worse prognosis

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Abstract

Background: Two pancreatic cancer(PDAC) transcriptome subtypes have been defined (basal-like and classical) that seem related to different prognosis. Nevertheless, RNA-extraction from pancreatic tissue is cumbersome and has been performed mainly on surgical samples, representative of<20% of cases. Most PDAC patients undergo endoscopic ultrasound (EUS)-guided tissue acquisition(EUS-TA),but RNA-sequencing on such samples has been rarely performed or limited to paraffin-embedded samples with low RNA quality. Furthermore, the association between molecular subtype and patient-related factors such as BMI, smoking, drug use, tumour location and Ca19.9 expression is uninvestigated. Our aim was to correlate PDAC molecular subtypes identified by RNA-sequencing on EUS-TA samples with prognosis and evaluate whether they are associated to patients' factors.

Methods: Consecutive patients with non-metastatic PDAC who underwent EUS-TA at diagnosis were enrolled in a prospective biobanking study with snap-frozen samples. Those with adequate quantity and quality of RNA underwent RNA-sequencing with Illumina Nova-Seq.PURIST score was applied to define transcriptional subtype and association with patient-related factors and overall survival(OS) investigated. Categorical and continuous variables were investigated by Fisher's exact test or Mann-Whitney test, correlation analyses with Pearson test.

Results: In 44/45 samples, RNA was of quantity/integrity allowing successful RNA-sequencing. According with PURIST score 3 patients were classified as basal-like(6.8%) and the other 41 as classical. Basal-like patients had a significantly lower median OS compared to classical (3 vs 16 months;p=0.01) and a basal-like phenotype was associated to increased risk of death (HR 7.79; p=0.006). PURIST score also significantly correlated inversely with OS (r=-0.6;p=0.0007). Concerning patients' variables, patients with basal-like tumours were more frequently current smokers (66.6% vs 12.2%; p=0.05) and had a lower baseline Ca19.9 (80 vs 1243 IU/ml; p=0.001). No differences were found concerning age, gender, BMI, diabetes history, disease stage, tumour location, use of aspirin or statins.

Conclusion: Molecular subtype identification on EUS-TA PDAC cases at diagnosis is feasible and a basal-like phenotype is rare but associated to worse prognosis. Furthermore, current smoking seems to be associated to a more aggressive molecular subtype, which in turn does not seem to express a high Ca19.9. Further studies on a larger cohort are needed to confirm such findings.

O-45

EUS-guided detective flow imaging (DFI): a new advanced imaging technique for the differential diagnosis of solid pancreatic tumours

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Abstract

Background: Differential diagnosis of solid pancreatic tumours (SPT) is a clinical challenge. Development of advanced imaging techniques associated with EUS, such as elastography and contrast enhancement, has been a step forward in this context. EUS-guided detective flow imaging (DFI) is a very recent technology allowing the evaluation of microvascularisation and low-velocity blood flow without the need of contrast agents. Aim of our study was to evaluate the findings obtained by EUS-DFI in SPT and compare them with contrast enhanced harmonic EUS (CEH-EUS).

Methods: A prospective, single-centre, observational study in patients who underwent EUS for the evaluation of SPT was designed. Procedures were performed with a linear echoendoscope (Fujifilm 740UT) attached to the ultrasound system Arietta 850. Lesions were characterised according to the vascularization pattern (hypervascular, isovascular and hypovascular) described with both methods. Final diagnosis was based on histology after EUS-guided biopsy. Data area shown as mean ± SD and percentage.

Results: 28 patients were included (mean age 64 years, range 24-88, 15 males). Mean tumour size was 27.5 ± 17.0 mm. 7 (25%) lesions were located in the head of the pancreas, 15 (53.6%) in the body, 5 (17.9%) in the tail and 1 (3.6%) in the uncinate process. Final diagnosis was adenocarcinoma in 15 patients (53.6%), neuroendocrine tumour in 10 (35.7%), inflammatory mass in 2 (7.1%), and accessory spleen in 1 (3.6%). Agreement regarding the vascular pattern of SPT between CEH-EUS and EUS-DFI was reached in 96.4% of the cases. All adenocarcinomas were hypovascular, inflammatory masses isovascular, and the accessory spleen hypervascular at both CEH-EUS and EUS-DFI. All ten neuroendocrine tumours were hypervascular at CEH-EUS, nine of them (90%) at EUS-DFI.

Conclusion: EUS-DFI allows evaluating the microvascular pattern of SPT with a similar accuracy than CEH-EUS, but without the need of using contrast agents.

O-46

Homologous recombination-deficient pancreatic cancer coordinates cancer-associated fibroblast programming to support cancer aggressiveness and chemoresistance

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Abstract

Background/Methods: Despite intensive basic and translational research, the complex biology of pancreatic ductal adenocarcinoma (PDAC) remains a significant challenge and limits overcoming its dismal prognosis. The tumour microenvironment (TME) actively contributes to PDAC pathogenesis via a dynamic tumour-stroma dialog where cancer-associated fibroblast (CAF) subpopulations orchestrate TME architecture and modulate disease progression and prognosis. Although our understanding of tumour-stroma crosstalk is continuously growing, the impact of specific gene mutations in the tumour epithelium on the programming of an oncogenic TME remains largely unknown. Homologous recombination deficiency (HRD), caused by mutations in genes such as ATM, not only promotes PDAC aggressiveness, mesenchymal phenotype, and desmoplastic reaction but also sensitizes towards platinum-based therapies and PARP1 inhibition. To investigate whether and how HRDness impacts TME biology, we examined murine ATM- and/or P53-knockout PDACs, as well as human counterpart tissues.

Results: Both human and murine systems revealed that ATM status significantly impacts TME composition with an αSMA+ myCAF enrichment in HRD tumours. Additionally, secretomics and proteomics investigations demonstrated a greater TGFβ release capacity and further in vivo and in vitro analyses a downstream activation of canonical TGFβ signalling in CAFs. Additional transcriptomic and in vitro analysis suggested a reactive oxygen species (ROS)-mediated phenomenon. Strikingly, we demonstrate in several ex vivo and in vivo models that combinatorial therapy with a TGFβRI inhibitor reverses cancer-promoting TME remodelling and exacerbates FOLFIRINOX cytotoxic effects in ATM-deficient HRD PDAC.

Conclusion: These findings suggest that ATM-deficient HRD malignant cells mediate a TGFβ-dependent myCAF fate switch, in turn promoting tumour chemoresistance. Overall, our study conceptualizes how genotype-specific tumour-stroma feedback and -forward signalling axes redraft TME towards a cancer-promoting outcome and introduces exploiting HRDness-specific vulnerabilities via multiple tumour-stroma interference strategies.

O-47

Metformin reduces the risk of hypoglycaemia, major cardiovascular events, and all-cause mortality in patients with postpancreatitis diabetes mellitus: a nationwide population-based cohort study

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Abstract

Background: Postpancreatitis diabetes mellitus (PPDM) is a frequent complication of acute and chronic pancreatitis and is associated with an increased risk of adverse diabetes-related outcomes. Metformin may promote beneficial effects in patients with PPDM, but evidence from large-scale studies is scarce. In a pharmacy-epidemiological study, we investigated the putative beneficial effects of metformin in patients with PPDM.

Methods: In a Danish nationwide population-based cohort study, we included adults (>18 years) with incident PPDM or type 2 diabetes between 2009 and 2018. PPDM was further categorised into acute and chronic subtypes (PPDM-A and PPDM-C). Associations between metformin treatment and severe hypoglycaemia, major adverse cardiovascular events (MACE), and all-cause mortality were examined across the diabetes subgroups using multivariate Cox regression analysis, with metformin and insulin treatment as time-varying exposures. Results are reported as adjusted hazard ratios (HRs) with 95% confidence intervals (CIs).

Results: We included 222,337 people with new-onset type 2 diabetes and 3781 with PPDM, of whom 2305 were classified as PPDM-A and 1476 as PPDM-C. Metformin was associated with a lower risk of severe hypoglycaemia (adjusted HR 0.42, 95% CI 0.27-0.64, P <0.001), MACE (HR 0.59, 95% CI 0.41-0.85, P 0.048), and all-cause mortality (HR 0.57, 95% CI 0.50-0.65, P <0.001) in patients with PPDM. Findings remained significant in the PPDM-C subgroup across all three outcomes. Treatment with metformin was also associated with a reduced risk of severe hypoglycaemia and all-cause mortality in the PPDM-A subgroup. In addition, we confirmed previously observed beneficial effects of metformin treatment for the type 2 diabetes subgroup.

Conclusion: The use of metformin is associated with a lower risk of adverse diabetes-related outcomes and all-cause mortality in individuals with PPDM. These findings have important clinical implications and support that metformin should be used as a glucose-lowering therapy (with or without concomitant insulin) in patients with PPDM.

O-48

Sodium valproate causes pancreatic injury in vitro and in vivo via dysregulation of one carbon metabolism

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Abstract

Background: To investigate the mechanisms of pancreatic sodium valproate (Na-VPA) toxicity *in vitro* and *in vivo*.

Methods: Freshly isolated murine pancreatic acinar cells (PACs) were used in vitro to test the toxicity of Na-VPA and its major metabolites using plate reader cell death and autofluorescence assays. Confocal microscopy was applied to measure cytosolic calcium signalling, mitochondrial membrane potential (MMP), and time-lapse cell death pathway activation in response to Na-VPA. Target metabolites were quantified by liquid chromatogram mass spectrometry (LC-MS); target mRNA and protein expression were measured by RT-qPCR and western blotting. *In vivo*, 500 mg/kg/day Na-VPA was given for 7 days together with four hourly intraperitoneal injections of 50 µg/kg caerulein in C57Bl/6 mice. Next generation mRNA sequencing was used to detect pancreatic transcriptomic changes induced by Na-VPA, with functional analysis using Ingenuity pathway analysis (IPA).

Results: *In vitro*, 1-20 mM Na-VPA or metabolites caused time and dose dependent PACs cell death, confirmed by confocal time-lapse imaging. NADH autofluorescence was reduced by Na-VPA and metabolites. Transient application of 10-20 mM Na-VPA did not elicit toxic cytosolic calcium signals or MMP depolarization. Notably, supplementation of methionine or S-adenosylmethionine (SAM) significantly reduced Na-VPA induced PACs cell death, while addition of ethionine showed contrary effects. LC-MS demonstrated that SAM and S-adenosylhomocysteine (SAH) levels in PACs were markedly reduced by Na-VPA exposure. mRNA and protein level changes induced by Na-VPA showed downregulation of methylenetetrahydrofolate reductase and methionine adenosyltransferase 2A, and upregulation of S-adenosylhomocysteine hydrolase and methionine synthase. mRNA levels of endoplasmic reticulum (ER) stress markers were significantly upregulated. In vivo, Na-VPA exacerbated CER-AP as shown by significant increases of pancreatic trypsin, myeloperoxidase, and necrosis; serum interleukin 6 was markedly increased by Na-VPA exposure. IPA analysis of mRNA-seq data (Na-VPA versus control) revealed oxidative phosphorylation, mitochondrial dysfunction, and the unfolded protein response were among the top 20 canonical pathways affected.

Conclusion: Na-VPA and Na-VPA metabolites are toxic to murine pancreatic acinar cells and Na-VPA exacerbates CER-AP. These data show pancreatic Na-VPA toxicity is mediated by dysregulated one carbon metabolism that induces ER stress and mitochondrial dysfunction.

Posters

P-01-01

Irisin/FNDC5 time-dependently and acutely regulate pancreatic lipase

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Abstract

Background: The myokine irisin, derived from Fibronectin type III domain-containing protein 5 (FNDC5), is known to regulate whole-body metabolism through increased thermogenesis and energy expenditure. Recently, we have shown that exocrine pancreas FNDC5 expression is regulated by the peroxisome proliferator-activated receptor gamma (PPARγ)-PPARγ coactivator-1-alpha (PGC1α) axis and involved in the regulation of pancreatic lipase (PL) expression and secretion. In this study, we aimed to investigate the time scale for irisin/FNDC5 effect on exocrine pancreas functionality related to lipid metabolism.

Methods: Exocrine pancreas cells (AR42J-B1) were exposed to exogenous irisin treatment (60 ng/ml, time scale; 0, 2, 4, 6, 24 hr), and the PPARγ-PGC1α-FNDC5 axis signal transduction, and PL expression and secretion were studied using molecular and biochemical methodology.

Results: Exogenous irisin significantly ($P<0.05$) and time-dependably inhibited PPARγ, PGC1α and FNDC5 transcript and protein expression levels, reaching peak inhibition of protein levels by 60%, 50% and 55%, respectively after 4 hr. Exogenous irisin significantly and gradually ($P<0.05$) down-regulated the expression of PL protein, transcript and secretion levels, reaching minimal reduction of 30%, 50%, and 50%, respectively after 4 hr.

Conclusion: Our findings demonstrate that exogenous irisin down-regulate the PPARγ-PGC1α-FNDC5 axis and PL expression and secretion in a time-dependent manner. The irisin inhibitory effect is short-term. Given irisin role as metabolic mediator, our recent findings point to the important role the exocrine pancreas plays in coordinated and orchestrated whole-body metabolism.

P-01-02

Irisin/FNDC5 regulate carbohydrate metabolism in the exocrine pancreas

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Abstract

Background: Irisin, a secreted myokine produced by Fibronectin type III domain-containing protein 5 (FNDC5), is known to play a role in muscle-adipose and whole-body metabolism by activating uncoupling proteins (UCPs). Previous studies have primarily focused on irisin's role in endocrine pancreas glucose metabolism. Our recent research showed that PPARγ-PGC1α axis regulates exocrine pancreas FNDC5 expression and participates in lipid digestion by regulating pancreatic lipase (PL) expression and secretion. In this study, we aimed to investigate the role of exogenous irisin on the exocrine pancreas' carbohydrate regulation.

Methods: Exocrine pancreas cells (AR42J-B13), were subjected to exogenous irisin (60 ng/ml, time scale; 0, 2, 4, 6, 24 hr), glucose (5.5mM, 25mM, 24hr), and insulin (glucose 25Mm + insulin; 10nM, 50nM, 100nM, 24 hr). The PPARγ-PGC1α-FNDC5 axis signal transduction, pancreatic amylase and UCP2 expression were studied using molecular and biochemical methods.

Results: Exogenous irisin significantly (P<0.05) down-regulated amylase transcript levels in a short, and gradual manner, reaching a minimal expression level of 50% after 6 hr. Glucose and insulin significantly and dose-dependently up-regulated the transcript and protein expression levels of PPARγ-PGC1α-FNDC5 axis. Glucose (25mM) maximally up-regulated protein levels by 1.8-fold (PPARγ), 2.2-dold (PGC1α), and 3.4-fold (FNDC5), after 24 hr. Addition of insulin (glucose 25mM+100nM), further up-regulated PPARγ and FNDC5 by 1.6 and 2.5-fold, respectively. Glucose (25mM) without and with insulin (100nM) significantly (P<0.05) elevated amylase transcript levels by 3 and1.7-fold, respectively. Exogenous irisin, glucose without/with Insulin treatments significantly (P<0.05) elevated UCP2 transcript expression levels in a time-dependable manner, reaching maximum of 200%, 180% and 160%, respectively after 24 hr.

Conclusion: Glucose and insulin significantly elevate the PPARγ-PGC1α-FNDC5 axis, amylase, and UCP2 exocrine pancreas expression levels in a synergistic manner. Furthermore, similar to the researchers' previous findings regarding lipid enzymes, irisin down-regulates amylase expression. Therefore, the results indicate the possible involvement of the exocrine pancreas in whole-body glucose metabolism mediated by irisin, given its beneficial role in the whole-body carbohydrate metabolism.

P-01-03

Development of a human model system for investigating pancreatic ducts

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Abstract

Background: There are several animal models to investigate pancreatic ductal function (i.e. bicarbonate secretion), but these have limitations because of differences between human and animal cells. Therefore, primary human tissues would be favourable, but their availability is restricted. Our aim was to characterize the structure and function of isolated foetal pancreatic ducts and organoid cultures. We also wanted to reveal whether these are suitable tissues for research.

Methods: Aborted human foetal pancreata were collected at 14-23 gestational weeks (GW). Ducts were isolated by microdissection. Organoids were cultured from the pancreatic tissue. Expression of ductal proteins (CFTR, SLC26A6, Na+/H+ exchanger [NHE], Na+/HCO3- cotransporter [NBC], and CK-19) was detected by immunohistochemistry. Measurements of ion transporter function (CFTR, NHE, NBC) were performed by determining intracellular pH (pHi), and applying specific agonists (forskolin) or inhibitors (CFTRinh-172, EIPA, S0859).

Results: CFTR and CK-19 protein expression was found in the same human foetal pancreatic cells from 14 GW onwards. CFTR expression was significantly higher at 22-23GW than at 14-15GW. SLC26A6 and NHE stainings were also detected in the tissue from 16GW. Organoids derived from a 22-GW foetus also showed CFTR, SLC26A6, NHE, and CK19 protein expression. Functional measurements on isolated duct cells revealed that recovery from alkali load was significantly higher at 20-23 GW than at 14-16 GW. Functional measurements on organoid cultures demonstrated CFTR activity during ammonium pulse treatment. Specific inhibitors indicated the presence of NHE and NBC

activity in organoids.

Conclusion: Ductal on transporters were shown to be active in isolated ducts derived from 14GW pancreata and those activities increased by GW. We could also establish organoid cultures which exhibited expression and function of ductal specific proteins (CFTR, SLC26A6, NHE). The results obtained so far provide a good basis for the use of human foetal pancreatic tissues for further studies of pancreatic ductal bicarbonate secretion.

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P-01-04

The importance of spatial transcriptomics in translational research: identification of druggable targets in PDAC tissue samples.

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Abstract

Background: The recent development of spatial transcriptomics/biology enabled studying tissue samples within their own 2D or 3D context. It is the new frontier of molecular biology. Spatial biology facilitates the creation of cellular and molecular maps within a given tissue sample. Pancreatic ductal adenocarcinoma (PDAC) is highly heterogeneous. The variability between tumours within a single patient and between patients is considerable. Understanding the diversity in cancer samples at the molecular level can aid in biomarker discovery and identification of drug targets. Moreover, understanding how the genetic makeup of cancer differs between various patients will lead to describing personalised therapy.

Methods: Pancreatic ductal adenocarcinoma samples of patients who benefited from receiving neoadjuvant chemo-radiotherapy (PFS > 36 months) and those who did not benefit from the same therapy (PFS < 6 months) were included in this study. One FFPE section of 5µm was used to profile and quantify 70 antibodies in a specific location within the tissue samples. The GeoMx Digital Spatial Profiler (DSP) of NanoString Technology was used for the measurement of the multiplex proteomics analysis. Tumour, desmoplastic, aggregations of immune cells, and tertiary lymphoid structures (TLS) were compared within a single patient's sample, and between different patients based on their PFS outcome.

Results & Conclusion: The results revealed distinct inflammatory responses in each group. Immune cells were rarely infiltrated within tumour cells. However, the number and composition of immune cells infiltrated in the desmoplastic areas showed different patterns based on the patient's outcomes. In addition, the number and composition of TLS showed significant variation between the two groups. The DSP proteomics data revealed the limited expression of various immune checkpoint proteins in PDAC samples. However, the findings may help to inform personalised therapeutic strategies in PDAC, including immunotherapeutic modalities.

P-01-05

Visualising pancreatic neural structures using Golgi-Cox staining method

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Abstract

Background: Pancreas is known to contain complex network of neurons, but their exact organization and function in this tissue remains poorly understood. The Golgi-Cox staining technique is a well-established method for visualizing the morphology of neurons in the brain, however its applicability to non-brain tissues, such as pancreas, has not been extensively explored. In this study, we adapted the Golgi-Cox staining to investigate the neural components of the pancreas.

Methods: Pancreatic tissue specimens were collected from wild-type and genetically engineered (Ptf1a-Cre; LSL-Kras+/G12D; Trp53+/fl [KPC] and Ela-TGFα; Ptf1a-Cre; Trp53fl/fl; RelAfl/fl [TPAC]) mice, as well as from human pancreatic ductal adenocarcinoma (PDAC) tissue samples, and processed using a modified Golgi-Cox staining protocol that involved impregnation with mercury chloride, potassium chromate and potassium dichromate. Tissues were cryosectioned at 50 micrometer thickness, and brightfield microscopy was used to image the stained tissues.

Results: Modified Golgi-Cox staining protocol allowed us to visualize morphology of neurons within the pancreatic tissue. The stained tissues exhibited high-quality staining of neuronal processes, including dendrites and axons.

Discussion: Our findings suggest that the modified Golgi-Cox staining technique can be successfully adapted for use in pancreatic tissue, providing a novel and alternative approach to studying the neural components of the pancreas. Further studies are needed to explore the potential of this technique in pancreas and other non-brain tissues, and to fully characterize the neural network in the pancreas.

P-01-06

Modelling PIEZO1-mediated pressure-induced pancreatitis by human organoids with artificially adjustable cell polarity

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Abstract

Background: Sustained intraductal pressure, caused mainly by endoscopic retrograde cholangiopancreatography (ERCP), a minimally invasive examination method, or by gallstones, often leads to inflammation of the pancreas. This transient pressure is proved to decrease tight junction integrity via calcineurin in mice. The mechanosensitive Ca^{2+} channel PIEZO1 is another effector protein of the intraluminal pressure as it senses cell elongation and increases Ca^{2+} influx and thus regulates both epithelial cell division and apoptosis. However, difficulties in *in vitro* modelling of pressure-related alterations in recent years have hindered the development of therapeutic options specifically targeting post-ERCP and gallstone-induced pancreatitis. Therefore, our aim was to reveal the pressure-related pathological processes *ex vivo* by using human pancreas derived apical-out organoids (hPOCs).

Methods: Pancreatic tissue samples were collected from 3 cadaver donors and used for establishment of hPOCs. Polarity switching of apical-in organoids was induced by extracellular membrane matrix (Matrigel) removal. Conventional and apical-out (polarity switched) hPOCs were compared by RNA-sequencing and fluorescent live cell imaging. Gene expression changes in response of 1 µM PIEZO1 activator (YODA1) treatment were measured by qRT-PCR in apical-out hPOCs.

Results: Polarity switching resulted in decreased *PIEZO1* expression while the reduction of intraluminal pressure and thus cell elongation led to reduced expression of cytoskeletal and cell cycle related genes such as *ACTB, VCL, LPXN, LMNA* and cyclin gene family members. In the same experiment, decreased expression of pro-inflammatory cytokines such as *CXCL1, CXCL2, CXCL3* and *CXCL8* were also observed. We showed that the polarity switching led to increased Cl^- efflux through *CFTR* and *ANO1* due to the lack of sustained intraluminal pressure maintained by basal secretion in the closed lumen of conventional organoids. Pharmacological activation of *PIEZO1* by YODA1 reversed the expression of pro-inflammatory cytokines in apical-out hPOCs, suggesting that inflammation-like pre-stimulated phenotype of apical-in hPOCs is developed by *PIEZO1*.

Conclusion: Altogether, our results suggest that conventional organoid cultures, previously used as physiologically relevant models, may represent a pressure-induced inflammatory state by overexpressing elements of the epithelial innate immune response, while polarity switching of organoids may overcome the previous limitations and open new perspectives in modelling pressure-induced pancreatitis in vitro.

P-01-07

Do mechanical forces induce a protumoural dialogue between the tumour and the adjacent healthy tissue?

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is characterised by an abundant stroma composed predominantly of activated fibroblasts (CAFs) and dense extracellular matrix (ECM). Tumour cell growth and ECM modifications generate forces named “solid stress” documented to promote tumour progression. While it is recognised that these forces also result in compression of surrounding healthy tissue, their impact on the biology of adjacent normal cells, especially normal fibroblasts (Pancreatic Stellate Cells, PSCs) remain poorly described.

Methods & Results: In order to mimic the mechanical force transmitted by the tumour to the surrounding healthy tissue, we have developed a 2D model in which a pad is added on the top of a monolayer of PSCs. We show that a low pressure (85 Pa) induces a strong expression of at least three of the main markers of activated fibroblasts. This phenomenon is associated with the activation of the mechanosensor FAK, drastic changes in cell morphology and a rearrangement of the mitochondrial network. Importantly, the mechanically-induced activation of the fibroblasts is a stable phenotype that persists for at least seven days after removing the pressure. In addition, fibroblasts submitted to pressure acquire the capacity to produce and deposit ECM, such as collagen I, a hallmark of myofibroblastic CAFs. This matrix secreted by the mechanically-activated fibroblasts promotes the induction of the epithelial-to-mesenchymal transition in tumour cells.

We are currently developing an original 3D device, allowing the application of a quantifiable and homogeneous pressure on cells embedded in a gelatin methacrylate (GelMA) hydrogel, to verify our results in a context more relevant to the pathology. This device, compatible with a wide range of techniques (IF, WB, RNAseq, live imaging…) will enable us to deeply characterise the impact of tumour-generated pressure on normal adjacent pancreatic fibroblasts

Conclusion: We obtained the proof of concept in 2D, and will verify it in 3D, that solid stress activates PSCs in a durable manner and confer them protumoural properties that most likely will support and favour tumoural progression.

P-02-01

A multicentre prospective study of exocrine pancreatic insufficiency at 3 months after acute pancreatitis attack

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Abstract

Background: The majority of patients with AP experience rapid resolution of abdominal pain, but the timeline of pancreatic exocrine function recovery and risks for persistent impairment are unknown. Exocrine Pancreatic insufficiency (EPI) following acute pancreatitis (AP) is thought to be secondary to reduced pancreatic enzyme secretion and pancreatic acinar cell damage. The aims of this study were to establish the incidence and predictors of EPI at 3 months after AP in a prospective cohort.

Methods: Adult participants (≥18 years) admitted to the hospital with AP were enrolled in the Post-Acute Pancreatitis Pancreatic Exocrine Insufficiency (PAPPEI) Study at the time of oral or enteral feeding attempt at three centres. AP was defined according to the Revised Atlanta Classification. Patients with pre-existing pancreatic cancer, chronic pancreatitis, EPI, or malabsorptive disease were excluded. Symptoms of EPI, along with blood and stool samples were collected at baseline and at 3-months after enrolment. EPI was evaluated using faecal elastase-1 (FE-1) levels from stool samples (FE-1 <200 µg/g indicating EPI).

Results: Total of 112 participants at enrolment provided stool samples, with 79 completing 3-month stool samples. At 3 months, EPI was seen in 29 (37%). At enrolment, 32/79 (40%) of the subjects had EPI and 25/32 (78%) had persistent EPI at 3 months. Of the 47 subjects without EPI at baseline, 4 developed new EPI at 3 months. Rates of EPI were significantly different between AP aetiologies: gallstone AP comprised only 17% of subjects with EPI at 3 months, but 52% of those without EPI at 3 months. Idiopathic aetiology contributed the largest group of subjects with EPI at 3 months (45%). Severity of AP and presence of pancreatic necrosis were both associated with EPI at 3 months after AP ($p \leq 0.05$.)

Conclusion: Approximately 37% of prospectively-enrolled AP patients were found to have EPI at 3 months post-AP. Idiopathic aetiology, severe AP, and presence of pancreatic necrosis were associated with EPI. Further studies are needed to understand the mechanisms of EPI following AP.

P-02-02

Perioperative management of pancreatic exocrine insufficiency - evidence-based proposal for a paradigm shift in pancreatic surgery

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Abstract

Background: Despite exocrine pancreatic insufficiency (EPI) being a significant postoperative consequence following pancreatic surgery, there is still no consensus on its perioperative management. This prospective observational study evaluated whether unselective pancreatic enzyme replacement therapy (PERT) is reasonable for all patients.

Methods: All patients who underwent partial pancreatectomy at the University Medical Centre Hamburg-Eppendorf from April 2021 to November 2022 were included. EPI status was assessed pre- and postoperatively, each time based on three independent faecal elastase measurements. Characteristic EPI symptoms were evaluated through a standardised questionnaire. In an additional 85 post-surgical patients, the subjective burden of PERT was measured.

Results: In total, 101 patients were followed prospectively. Preoperative EPI screening was available for 83 patients, of which 48% were diagnosed with pre-existing EPI. Of those patients with regular exocrine function, 54% developed EPI de novo; this rate being higher following pancreatic head resections (72%) compared to left-sided pancreatectomies (LP) (20%) ($p=0.016$). Overall postoperative EPI prevalence is significantly greater following pancreatic head resections (86%) than LP (33%) ($p<0.001$). Only young and female patients declare a significant burden related to PERT.

Conclusion: Patients with an indication for pancreatic head resection should receive PERT without testing already before surgery due to the subgroup's high pre- and postoperative EPI rate, difficulties associated with screening and the comparatively low burden of PERT. Patients with LP, which are at much lower EPI risk, should be pre- and postoperatively screened and then supplemented accordingly to avoid overtreatment, especially in young and female patients.

P-02-03

Lp-One Study: observational prospective study to assess the relationship between hepatic steatosis and pancreatic exocrine function

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Abstract

Background: Liver and pancreas are target organs of increased alcohol intake or impaired metabolic asset. Literature and clinical practice show correlation between liver cirrhosis and exocrine pancreatic insufficiency (EPI), while the relationship between non-cirrhotic chronic liver damage and EPI is less clear. Although studies show the role of alcohol-relate hepatic steatosis and NAFLD as precursors of chronic pancreatic damage, literature is heterogeneous, discordant and lacking. The aim of our study is to verify the frequency of EPI in patients (pts) with known diagnosis of hepatic steatosis.

Methods: Prospective, observational, monocentric study, not randomised. Pts with known diagnosis of alcohol-related hepatic steatosis (alcohol intake > 2-3 AU/day - *Group A*) and non-alcoholic-related (alcohol intake < 2-3 AU/day, insulin resistance with Homa Index > 2.5, Diabetes type II - *Group B*) were included. All pts were submitted to a clinical questionnaire, clinical and biochemical evaluation, hepatic ultrasound and elastometry; evaluation of exocrine pancreatic function was made by faecal elastase (FE-1) value (EPI < 200 µg/g). Pts with known diagnoses of chronic liver damage, chronic pancreatitis or EPI were excluded.

Results: This study included 37 pts in total, of whom 22 (59.4%) men and 15 (40.5%) women (median age of 57 years). Pts belonging to *Group A* were 10 (27.2%) while those of *Group B* were 27 (72.9%). They were also divided according to the degree of hepatic steatosis (mild:7 (18.9%), moderate: 15 (40.5%), severe: 5 (13.5%) and hepatic elastometry according to Metavir score (F0-F1:10 (27%), F2:25 (67.5%), F3:2 (5.4%). No pts had biochemical profile change, except 3 (8.1%) women with vitamin D values < 30 ng/ml. 34 (91.9%) pts had FE-1 value > 500 µg/g compatible with preserved pancreatic exocrine functionality while 3 (8.1%) pts (2 from *Group B* and 1 from *Group A*) had FE-1 value < 200 µg/g, of which only one with symptoms.

Conclusion: Only 8.1% of patients with hepatic steatosis had a condition of EPI. These data, although still preliminary, do not show a significant relationship between hepatic steatosis and EPI. It will be necessary to increase the study population with integration through radiological study with MRI and Elasto-MRI.

P-02-04

A patient support program complementing hospital care to enhance patients' ownership of pancreatic exocrine insufficiency treatment in the Netherlands

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Abstract

Background: Pancreatic enzyme replacement therapy (PERT) is the standard treatment for pancreatic exocrine insufficiency (PEI). The correct use of PERT may be challenging for patients. Essential to be compliant for patients is to know why, how, how much and when to take their pancreatic enzymes. A patient support program (PSP) for PERT was initiated in the Netherlands in 2019. Within this program nurses visit the patients at home to educate on PEI and PERT, enzymes are delivered at home, and nurses follow up on the patients, with the aim to improve access, usage and adherence to treatment. We present the use of a PSP to improve PERT usage and adherence in patients suffering PEI in The Netherlands.

Methods: The PSP is a nationwide, free of charge, educational support program for patients with exocrine pancreatic insufficiency due to chronic pancreatitis and pancreatic cancer, who are prescribed PERT in the Netherlands. Healthcare professionals with prescribing authority can register patients for the PSP, which is executed by a third party, and patients' informed consent is requested. Patients may withdraw from the program at any point. Although, the aim is to improve usage and adherence to the treatment, it is not directly measurable. Every week an update on the amount of newly included patients per hospital is received from the third party.

Results: From November 2019 until March 2023 a total of 659 patients was included in the PSP. In the beginning of 2020 four hospitals started to use the PSP complementary to the standard hospital care. The number of hospitals has increased up to 30. Four hospitals in the North included in total 203 patients, seven hospitals in the East included 100 patients, five hospitals in the South included in total 44 patients and fourteen hospitals in the West included in total 312 patients.

Conclusion: The use of a PSP program for patients suffering from PEI can be a useful tool to support the management of this condition in The Netherlands, while enhancing patient ownership of their treatment.

P-02-05

Correlation between endoscopic ultrasound features according to Rosemont criteria and exocrine pancreatic function in chronic pancreatitis

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Abstract

Background: Chronic pancreatitis (CP) is a pancreatic progressive disease in which inflammatory episodes result in replacement of the parenchyma by fibrous connective tissue leading to endocrine and pancreatic exocrine insufficiency (PEI). Endoscopic ultrasound (EUS) is the most sensitive method to diagnose CP in its early stage, and Rosemont criteria are used to classify its findings. Since data on the correlation between EUS features and PEI are scarce, our aim is to investigate them.

Methods: This is a retrospective, monocentric cohort study concerning patients prospectively enrolled and followed-up from 2016 to 2021, with definite/probable CP according to M-ANNHEIM diagnostic criteria. All patients had a EUS performed and known data about exocrine function, both within 12 months from the diagnosis of CP. PEI was diagnosed for faecal elastase (FE) values ≤200 mcg/g or when overt steatorrhea was reverted by pancreatic enzyme replacement therapy. Chi-square test, Fisher's exact test, Kruskal-Wallis test were used as appropriate. To evaluate the association between EUS features and PEI, logistic regression analyses and Rank correlation were performed. ROC curve and area under the curve (AUROC) were calculated to determine accuracy of Rosemont criteria in predicting PEI. P<0.05 was considered statistically significant.

Results: 128 patients were examined (63.3% male, mean age 47 years; 95% CI 44-50). Aetiology was exotoxic in 43.7%. 69.5% had diagnosis of PEI (69.7% based on reduced FE). At multivariate logistic regression among all the Rosemont features, only the presence of lithiasis in main pancreatic duct (MPD) was associated with increased risk of PEI (OR 2.92, 95% CI 1.29-6.61; p=0.01); autoimmune aetiology was the only other statistically significant factor (OR 8.48, 95% CI 1.04-69.40; p=0.04). Rank analysis showed a weak significant inverse correlation between Rosemont categories and FE values (Spearman's rho=-0.02; p=0.03). Accuracy of Rosemont in predicting PEI was moderate with AUROC: 0.62 (p=0.014, sensitivity 69.7%, specificity 53.8%).

Conclusion: EUS structural findings seem of limited help identifying patients at risk for PEI but for lithiasis of the MPD. Dynamic and functional tools used during EUS, such elastography and pancreatic function tests (secretin), could improve the usefulness of EUS in evaluating PEI.

P-02-06

Pancreatic exocrine insufficiency is a risk factor for kidney stones in patients with chronic pancreatitis

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Abstract

Background: Most patients with chronic pancreatitis (CP) develop pancreatic exocrine insufficiency (PEI) over the course of the disease. PEI may lead to hyperoxaluria and development of urinary oxalate stones. It has been postulated that the patients with CP may be at increased risk of kidney stone formation, but the data is scarce. We aimed to estimate incidence and risk factors for nephrolithiasis in a Swedish cohort of patients with CP.

Methods: We performed retrospective analysis of an electronical medical database of patients diagnosed with definite CP during 2003–2020. We excluded patients <18 years of age, those with missing relevant data in medical charts, patients with probable CP (according to the M-ANNHEIM classification system) and those in whom kidney stones were diagnosed before CP diagnosis.

Results: Some 632 patients with definite CP were followed over a median of 5.3 (IQR 2.4–6.9) years. There were 41 (6.5%) patients diagnosed with kidney stones, of whom 33 (80%) were symptomatic. Comparing to patients without kidney stones, patients with nephrolithiasis were older, with median age of 65 (IQR 51–72) years, and a male predominance (80% vs 63%). Cumulative incidence of kidney stones was 2.1%, 5.7%, 12.4% and 16.1% at 5, 10, 15, and 20 years after CP diagnosis, respectively. Multivariable cause-specific Cox regression analysis revealed PEI as independent risk factor for nephrolithiasis (adjusted HR 4.95, 95%CI 1.65–14.84; p=0.004). Another risk factors were increase in BMI (aHR 1.16 95% CI 1.04–1.30; p=0.001 per unit increment), and a male sex (4.51, 95% CI 1.01–20.3, p=0.049).

Conclusion: PEI and increase in BMI are risk factors for kidney stone development in patients with CP. Male CP patents are particularly at increased risk of nephrolithiasis. This should be taken into consideration in general clinical approach to raise awareness among patients and medical workers.

P-02-07

Diagnostic accuracy of faecal elastase-1 test for the diagnosis of pancreatic exocrine insufficiency: a systematic review and meta-analysis

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Abstract

Background: Pancreatic exocrine insufficiency (PEI) has been recently defined as a reduction of pancreatic exocrine secretion and/or intraluminal activity of pancreatic enzymes below a level that prevents normal digestion of nutrients. For diagnosis, quantification of the coefficient of fat absorption (CFA) is considered the gold standard. Faecal elastase-1 test (FE-1) is the most widely used pancreatic function test in clinical practice. However, the efficacy of this test for the diagnosis of PEI is debatable. Aim of our study was to evaluate the accuracy of FE-1 test for the diagnosis of PEI using CFA or 72-h faecal fat quantification as reference methods.

Methods: A systematic review and meta-analysis was performed. Major databases were searched for studies reporting accuracy of FE-1 test using the above mentioned reference methods for the diagnosis of PEI. Sensitivity (S), Specificity (E), Positive Predictive Value (PPV) and Negative Predictive Value (NPV) were calculated globally and individually for cystic fibrosis (CF) and chronic pancreatitis (CP) based on cut-off points of 200 µg/g and 100 µg/g. Results are shown with 95% confidence interval.

Results: Nineteen studies (948 patients) were included (8 studies in CF, 5 in CP, 2 after pancreatic surgery, 2 in pancreatic cancer, 1 in diabetes mellitus and 1 in neuroendocrine tumours). The overall S, E, PPV, and NPV of FE-1 test for PEI were 86% (76-94), 55% (36-73), 72% (55-86) and 44% (21-67), respectively, for a cut-off point of 200 µg/g. In the studies that used a cut-off point of 100 µg/g, values were 92% (87-96), 65% (52-76), 55% (22-85) and 59% (31-84), respectively. In CF, the studies using the cut-off point of 200 µg/g showed S and E of 88% (73-98) and 65% (31-93). In CP, with the same cut-off point, results of S and E were 83% (63-96) and 54% (18-88).

Conclusion: Independently of the cut-off used for diagnosis, FE-1 test is a rather sensitive but nonspecific method for PEI. A low FE-1 result supports the diagnosis of PEI in just 55-72% of the patients with pancreatic disease, whereas a normal FE-1 result does not rule out PEI.

P-02-10

The association between the severity of pancreatic exocrine insufficiency and computed tomography-based morphological severity in patients with chronic pancreatitis

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Abstract

Background: The association between pancreatic exocrine insufficiency (PEI) and morphologic findings in chronic pancreatitis has not been fully studied. The aim of this study was to investigate the correlation between PEI severity and computed tomography (CT)-based morphological severity in patients with chronic pancreatitis.

Methods: This multicentre retrospective study included 180 patients with chronic pancreatitis aged 18 years or older between January 2018 and December 2021. PEI severity was measured by PEI questionnaire (PEI-Q), and morphological severity was measured using a CT-based scoring system including pancreatic duct calibre, pancreatic duct stricture or intraductal obstructing calculus, pancreatic atrophy, and pancreatic calcification. In addition, 35 patients who received pancreatic enzyme replacement therapy (PERT) were evaluated by PEI-Q whether PEI improved after PERT.

Results: PEI severity was normal (n = 89), mild (n = 69), moderate (n = 14), and severe (n = 8). The severities of pancreatic duct calibre and pancreatic duct stricture or intraductal obstructing calculus had significantly small associations with PEI severity (Cramer's V = 0.121 and 0.141, respectively). The severities of pancreatic atrophy and pancreatic calcification were not significantly associated with PEI severity. PEI severity showed a significant improvement after PERT ($P < 0.001$).

Conclusion: PEI severity had a significant association with CT-based morphological severity, including pancreatic duct calibre and pancreatic duct stricture or intraductal obstructing calculus. In addition, PEI-Q could be a useful indicator for evaluating the therapeutic effect of PERT in clinical practice.

P-02-11

The positive nutritional and gastrointestinal effects of elexacaftor/tezacaftor/ivacaftor in the treatment of cystic fibrosis

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Abstract

Background: Highly effective modulator therapy improves both nutritional status and quality of life. Clinical trials have even shown pancreatic insufficiency conversion, but mostly in paediatric patients treated with ivacaftor. Studies with elexacaftor/tezacaftor/ivacaftor (ETI) in older patients have not suggested the restoration of exocrine pancreas function, but quality data in adults are still lacking. Our aim was to show the effect of ETI therapy on the nutritional status and digestive function in adult patients with cystic fibrosis (CF). We hypothesized the improvement of nutritional parameters and gastrointestinal symptoms, and the reduction of pancreatic enzyme replacement therapy, but uncertain improvement in exocrine pancreatic function.

Methods: This prospective study enrolled adult patients with CF treated with ETI from August 2021 to June 2022. We measured anthropometric parameters, laboratory nutritional markers, change of faecal elastase, changes in pancreatic enzymes replacement therapy needs, and gastrointestinal symptoms.

Results: In the cohort of 29 adult patients with CF (mean age 29.1 years), 82.8% suffered exocrine pancreatic insufficiency. After ETI therapy, the mean BMI increased by 1.20 kg/m2 ($p < 0.001$), mean body weight by 3.51 kg ($p < 0.001$), albumin by 2.81 g/L, and prealbumin by 0.06 (both $p < 0.001$). One patient (4.5%, $p < 0.001$) developed pancreatic sufficiency, indicated by faecal elastase > 200 µg/g. The mean change in lipase substitution decreased by 1,969 units/kg/day ($p < 0.001$) and stool frequency by 1.18 per day ($p < 0.001$). No acute pancreatitis was observed.

Conclusion: Our data suggests increased nutritional parameters, a restoration of exocrine pancreatic function, lower pancreatic substitution requirements, and improved defecation in adult CF patients on ETI therapy. Improvement in exocrine pancreatic function might be mutation-specific and requires further study.

P-03-01

Discovery of pancreas enhancers and their respective target genes with an activity-by-contact model

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Abstract

Background: Distant enhancers regulate gene expression in a tissue-specific manner by physical interaction with respective target gene promoters. Mutations within enhancer sequences can alter transcription factor binding affinities, leading to aberrant gene expression and disease. Various studies have discussed a functional impact of enhancer variants in the context of pancreatic agenesis, pancreatic cancer and pancreatitis. A number of different enhancer-target gene prediction approaches exist, but the overlap among them is limited. A recently published activity-by-contact model has been shown to outperform other approaches in detecting enhancer-gene relationships.

Methods: To determine promoter elements, we generated ±250 bp windows at the transcriptional start sites of MANE transcripts, representing the most biologically relevant transcripts of protein-coding genes. We defined genome-wide pancreas candidate enhancer elements by a lenient thresholded peak calling of open chromatin (DNase-seq) from ENCODE pancreas tissue. Next, we integrated for each enhancer its DNase-seq signal strength with pancreas-specific enhancer histone modification (H3K27ac) and chromatin interaction (HI-C) data from the ENCODE project by the recently published Activity-by-Contact model to assign our discovered enhancers to their respective potential target gene promoters.

Results & Conclusion: We generated a genome-wide enhancer-to-gene dataset from pancreas-specific chromatin activity and HI-C data, which we consider a valuable resource for further understanding pancreatic gene regulatory function and for prioritizing disease-associated variants in pancreatic disorders.

P-03-02

Genetic association analysis of variants in CUZD1 with chronic pancreatitis

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Abstract

Background: Chronic pancreatitis (CP) is a multifactorial disease characterised by recurring inflammation of the pancreas. Genetic risk factors for the development of CP were mainly identified in genes with a relatively high expression in pancreatic cells. *CUZD1*, which encodes the CUB and Zona pellucida like domains protein 1, is highly expressed in pancreatic acinar cells and has recently been suggested to represent a potential genetic risk factor which for CP. Here we investigated *CUZD1* as a possible chronic pancreatitis risk factor.

Methods: The entire coding sequence of *CUZD1* was sequenced in 338 German pancreatitis patients using Sanger sequencing. Control data were taken from a non-Finnish, European cohort at the gnomAD database. Variants were analysed for pathogenicity by prediction tool analysis SIFT, CADD, Provean and PredictSNP. Prevalence differences of CUZD1 variants between cases and controls were analysed by two tailed Fisher's exact test. A p-value below 0.05 was considered to be significant.

Results: Seven non-synonymous variants were identified in the German case cohort. Six of these variants were missense mutations and one was a non-sense mutation. The non-sense variant is not present in any of the online database and has not been described, yet. Two variants were predicted to be deleterious by all used online prediction tools. Both variants were significantly more frequent in CP patients compared to controls.

Conclusion: The prevalence of two variants seems higher in our cohort of German patients with chronic pancreatitis. However, the statistical power is limited due to the extreme rareness of these variants. Our knowledge about the biological CUZD1 function in pancreatic acinar cells is scarce and a potential disease-causing mechanism of *CUZD1* variants should be further explored.

P-03-03

CEL-HYB1 haplotypes confer varying risk for chronic pancreatitis

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Abstract

Background: The hybrid allele 1 of carboxyl-ester lipase (*CEL-HYB1*) created by the recombination of *CEL* and its pseudogene *CELP* has been linked to the development of chronic pancreatitis (CP) in German and French populations. However, a Polish study failed to replicate a significant association with CP. Moreover, recent observations suggested that polymorphic variants within *CEL-HYB1* determine its effect on CP risk. Thus, the Thr488-Ile548 haplotype was designated as pathogenic while the Thr488-Thr548 haplotype was considered relatively benign. Our aim was to investigate the association of *CEL-HYB1* and CP in a Hungarian cohort and re-assess the role of *CEL-HYB1* haplotypes in European CP cohorts.

Methods: The *CEL-HYB1* allele was screened in 319 CP patients and 618 healthy controls from the Hungarian National Pancreas Registry by melting curve analysis and PCR. To investigate the *CEL-HYB1* haplotypes, Sanger sequencing was used in Hungarian, and previously reported German, French and Polish *CEL-HYB1* positive subjects. HEK 293T cells were transfected with *CEL-HYB1* constructs containing the Thr488-Thr548 and Thr488-Ile548 haplotypes and expression of *BiP* mRNA was measured as a marker of endoplasmic reticulum (ER) stress.

Results: The *CEL-HYB1* allele was significantly overrepresented in the Hungarian CP cohort (9/319, 2.82%) relative to controls (5/618, 0.81%) (P=0.0239, OR=3.56, 95% CI=1.18-10.71). Haplotype analysis revealed that all Hungarian (9 patients and 5 controls) and French (17 patients and 9 controls) *CEL-HYB1* positive subjects carried the Thr488-Thr548 haplotype. Interestingly, 7/19 (37%) German and 2/6 (33%) Polish CP patients carried the Thr488-Ile548 haplotype, while the haplotype of German (19) and Polish (8) controls was exclusively Thr488-Thr548. *BiP* mRNA levels in cells expressing the Thr488-Thr548 or Thr488-Ile548 *CEL-HYB1* haplotypes were significantly higher in comparison to cells transfected with empty vector (P<0.0001). Notably, cells expressing the Thr488-Ile548 haplotype had significantly higher levels of *BiP* transcripts than cells transfected with the Thr488-Thr548 *CEL-HYB1* haplotype (P=0.006).

Conclusion: The *CEL-HYB1* allele is a relatively strong risk factor for CP in Hungary. We observed ethnic differences in the *CEL-HYB1* haplotype distribution among European cohorts. The higher CP risk associated with the Thr488-Ile548 haplotype might be explained by the stronger ER stress response it triggers in pancreatic acinar cells.

P-03-04

Exposome and genome interactions and pancreatic ductal adenocarcinoma susceptibility in the UK Biobank

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is a complex disease that arises from the interplay of many independent variables, such as lifestyle and environmental exposure, but also common low penetrance and high penetrance mutations. Gene environment interactions studies have also been attempted but only considering a small group of SNPs or few environmental risk factors. This limited knowledge, paired with the lack of successful treatment options, is partially the cause of the meagre survival of the disease. The aim of this study was to analyse the exposome on PDAC susceptibility and identify possible genome-exposome (GxE) interactions, in order to establish preventive and screening programs to identify high-risk individuals.

Methods: A total of 371 exposome variables, grouped in 30 categories, were analysed in 816 PDAC cases and 302,644 controls in the UK Biobank cohort, to test their association with PDAC risk. Correlation matrixes were used to calculate intra and inter category correlation (r^2<0.80) and in this way 346 independent variables were identified. In addition to exposome variables, weighted polygenic risk score (PRS) was computed using all susceptibility SNPs with P of association with PDAC risk <$5x10^{-8}$. A total of 347 independent variables were analysed and considering multiple testing the P-value threshold used to declare statistical significance was P<1.45×10^{-4}. Finally, GxE interactions were calculated using multiplicative models for all significant variables and PRS.

Results: A total of 54 associations under the Bonferroni corrected threshold were observed. The PRS showed very significant association, for the highest versus lowest quintile of the weighted score, OR=2.25 (95%CI: 1.73-2.95), P=2.09×10^{-9}. Considering the exposome variables a clear indication for an association with PDAC risk was observed for heavy alcohol drinking (P=3.39×10^{-7}), smoking (P=7.31×10^{-17}), heavy weight (P=3.39×10^{-10}), high percentage of fat free mass in body composition (P=2.39×10^{-22}), sedentary behaviours (P=5.72×10^{-4}) and stress related factors (P=2.00×10^{-16}). We did not observe any statistical interaction in the GxE interaction analysis.

Conclusion: Our results show very clear associations for the genome and the exposome with PDAC risk. However, there are no interaction between the two.

P-03-05

Complement system genetic variability shapes pancreatic cancer risk

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Abstract

Background: The complement system (CS) is a multistep cascade consisting of three distinct but interconnected pathways that play a key role in innate response. Its relevance in cancer development, growth, and metastasis, along with its relation with chemotherapy/immunotherapy outcomes have been renewed in recent years. However, its importance in pancreatic cancer (PC) development and therapy outcome remains unclear, owing to its etiological complexity, fast evolution, and resistance to therapy.

Our objectives were to assess the role of the CS on the genetic susceptibility to PC risk, at the SNP and gene levels, and to shed light on the biological mechanisms involved.

Methods: We employed the resources of PanGenEU, a case-control study (1317 cases and 700 controls), and the UK Biobank, a prospective cohort study (761 cases and 95,050 controls). The association between the SNPs in 111 genes related to the CS and PC risk was assessed through logistic regression models. The association was also tested at the gene level by applying the SKAT-O test within each study population. We meta-analysed the summary statistics of both models by employing a random-effect model. Finally, a functional in-silico analysis was performed to get further insight into the genes significantly associated after multiple test correction.

Results: Genetic variation in FCN1 and PLAT was significantly associated with PC risk after correcting for multiple-testing, whereas variation in CD46, F2RL2, VTN, and A2M displayed borderline significant associations. Most of these genes have been previously associated with mental health and digestive diseases. Additionally, 8/11 VTN SNPs were associated with differential expression (eQTLs) in normal pancreas, while one SNP in CD46 was associated with differential splicing (sQTL). Interestingly, CD46 is the target of over 20 clinical trials conducted in different tumour sites. Moreover, all genes but VTN exhibited higher expression levels in PC tumours when compared to normal pancreas.

Conclusion: Our study suggests that the CS might be involved in the development of PC and paves the way for further studies to understand its role in pancreatic carcinogenesis.

P-03-06

Decitabine reactivates gene expression of silenced genes in PDAC preclinical models

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Abstract

Background: Epigenetic deregulation is a critical factor in the development and progression of PDAC. Understanding these changes may lead to the development of new therapies targeting these epigenetic modifications to improve patient outcomes. This study evaluates the effectiveness of decitabine (DAC), a DNA methyltransferase inhibitor, in modulating the expression of key genes implicated in PDAC progression in vitro and in vivo.

Methods: Changes induced by exposure to DAC were assessed in three PDAC cell lines, BxPC-3, MIA PaCa-2, and SU.86.86. Subcytotoxic DAC concentrations were added every 24 h for a total of 72 h (6 µM for BxPC-3 and SU.86.86; 8 µM for MIA PaCa-2). DNA methylation was evaluated by pyrosequencing. The orthotopic in vivo xenograft model was derived from MIA PaCa-2 cells. A DAC concentration of 0.125 mg/kg was administered by intraperitoneal injection five days per week for a total of three weeks.

Results: DAC efficiently decreased DNA methylation of several studied genes, TWIST1, CDH2, and NID2 in BxPC-3; all studied genes in MIA PaCa-2 and TWIST1 in SU.86.86. Simultaneously, gene expression of all studied genes except for STEAP1 increased significantly in BxPC-3 cells, KRT19, TSPAN13, FN1, and ITGA5 were upregulated in MIA PaCa-2 and OCLN, CDH2, FN1, ITGA5, BMP2, NID2, and DSC2 in SU.86.86 cell line. Although DNA methylation decreased slightly in vivo, the upregulation of CDH2 (FC 309), FN1 (FC 11), and NID2 (3.6), was observed in tumour xenografts.

Conclusion: This work shed light on the role of DNA methylation in the transcriptional regulation of genes involved in PDAC progression. DNA methylation-mediated reactivation of silenced genes has a critical translational impact. However, further studies are warranted to investigate epigenetic drug efficacy in synergy with other anticancer therapies and possible off-target effects.

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P-03-07

The CEL gene in chronic pancreatitis: characterisation of a new humanised compound heterozygous Cel$^{16R/HYB1}$ mouse model

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Abstract

Background: The *CEL* gene encodes the digestive enzyme carboxyl ester lipase, expressed by pancreatic acinar cells. *CEL-HYB1*, a hybrid allele of *CEL* and its adjacent pseudogene *CELP*, is associated with 5-fold increased risk for chronic pancreatitis (CP) (1). Recently, we reported a new *Cel-HYB1* mouse model that spontaneously develops CP, confirming the pathogenicity of the *CEL-HYB1* risk variant (2). The aim of the present study was to characterize a humanized compound heterozygous $Cel^{16R/HYB1}$ mouse strain and to compare its phenotype with that of heterozygous $Cel^{+/HYB1}$ mice.

Methods: We established a knock-in mouse where the VNTR region of the endogenous mouse *Cel* gene was substituted with the normal human *CEL* VNTR region containing 16 repeats (16R). The *Cel-16R* mice were bred with *Cel-HYB1* mice to create a compound heterozygous $Cel^{16R/HYB1}$ mouse strain. These animals have a genetic constitution similar to human *CEL-HYB1* carriers, with one normal (*16R*) and one pathogenic (*CEL-HYB1*) VNTR allele. The $Cel^{16R/HYB1}$ mice were monitored for six months and analysed with respect to bodyweight, pancreas weight, pancreas histology and endocrine function.

Results: Successful construction of the *Cel-16R* strain and breeding with the *Cel-HYB1* mouse were confirmed by DNA and protein analyses. Preliminary data indicated that there was no difference in bodyweight or pancreas weight between $Cel^{+/HYB1}$ and $Cel^{16R/HYB1}$ mice. Pancreas histology showed features of inflammation and fat infiltration of the pancreas in both strains. However, we observed a tendency that $Cel^{16R/HYB1}$ mice presented with less exocrine tissue volume, more widespread inflammation and intracellular vacuolation than $Cel^{+/HYB1}$. We detected high levels of serum amylase for two $Cel^{16R/HYB1}$ mice (167 and 950 mOD/min), compared to maximally 29 mOD/min for $Cel^{+/HYB1}$ animals. Glucose tolerance tests showed no sign of diabetes development for either mouse strains at six months.

Conclusion: High levels of serum amylase and more severe pancreas pathology may indicate that the phenotype of the compound heterozygous $Cel^{16R/HYB1}$ mouse strain is more in line with acute than with chronic pancreatitis. However, the number of animals were limited and the experiments are now being expanded.

P-03-08

Early onset of abnormal glucose tolerance in patients with cystic fibrosis: a systematic review and meta-analysis

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Abstract

Background: Basic science results suggest that abnormalities of the endocrine pancreas in cystic fibrosis (CF) occur earlier than hitherto estimated. All stages of the abnormal glucose tolerance (AGT) spectrum are associated with declining pulmonary function and increased mortality which could be reduced by early recognition and treatment. Despite, screening for AGT is recommended only from 10 years of age (yoa) according to the current guidelines.

Methods: We registered our systematic review and meta-analysis protocol via PROSPERO (CRD42021282516).

Literature search was conducted in MEDLINE (via PubMed), Embase and Cochrane Register of Controlled Trials (CENTRAL) for studies reporting data on the prevalence of AGT or its subtypes in CF populations. General and superselected populations (e.g.: pancreas exocrine insufficient, ΔF508 homozygous) were separately analysed. Pooled proportions, risk and odds ratios with 95% confidence intervals (CI) were calculated in at least three age subgroups (paediatric, adult, mixed/unknown). One-stage dose-response random effect meta-analysis was used to assess the effect of age on CF- related diabetes (CFRD).

Results: 457 studies and data from 520 544 patients were involved in the quantitative analysis. More than one third of the patients were affected by AGT in childhood (0.31 [95% CI 0.25-0.37]), even under the age of 10 0.33 [95% CI 0.23-0.44], and half of the adults had AGT (0.51 [95% CI 0.45-0.57]). The prevalence of prediabetes remained unchanged (impaired glucose tolerance in chwCF: 0.14 [95% CI 0.10-0.18]) vs. awCF: 0.19 [95% CI 0.14-0.25]), while the proportion of CFRD increased by age (<5 yoa: 0.005 [95% CI 0.0001-0.15]; 5-10 yoa: 0.05 [95% CI 0.01-0.27]; 10-18 yoa: 0.11 [95% CI 0.08-0.14]; >18 yoa: 0.27 [95% CI 0.24-0.30]).

Conclusion: Accurate knowledge of the global prevalence of AGT and its subtypes is essential to develop a better screening strategy. Reconsideration of the current guidelines and better awareness are needed for screening and treating AGT in CF, especially under 10 yoa, to delay the disease progression and maintain a better life quality.

P-03-09

Hereditary pancreatitis - report of 73 paediatric patients

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Abstract

Background: Hereditary Pancreatitis (HP) is a rare inherited condition. We reviewed our experience over the last 30 years. The aim of our study was to evaluate the clinical course of HP in children.

Methods: 495 children with chronic pancreatitis, hospitalized since 1990 to 2022, were enrolled into the study. The medical records of these patients were reviewed for data on the presentation, diagnostic findings and endoscopic treatment. All children were screened for the PRSS1 gene mutations.

Results: Hereditary pancreatitis was diagnosed in 73 patients (14.5%) (47 girls and 26 boys). PRSS1 gene mutations were found in 62 patients (85%). We detected R122H/- in 23, R122C/- in 21, N29I/- in 6, A16V/- in 6, E79K/- in 5, E190K/- and N29T/- in 1 patient. Family history was positive in 57 children with HP (88%). In 11 patients without mutations diagnosis of HP was made when the patients satisfied the requirements of the family history. In 3 patient we found SPINK1 mutation (N34S/-). In 2 children CFTR mutation (delF508/- and M470V/M470V) was present. There was no difference in age of the disease onset between HP group and non-HP group (7.5 vs. 9.1 years; NS). In children with PRSS1 mutation ERCP had mean 2,2o Cambridge grade, vs. 1.6o, $p<0.05$. 44% patients with HP had calcifications in the imagine studies vs. 31%, $p<0.05$. Therapeutic intervention, including both surgical and endoscopic intervention, was more frequent in the HP group (59% vs. 35%; $p<0.05$). Pancreatic duct stenting was done in 33% children with HP vs. 26%; $p<0.05$.

Conclusion: Hereditary pancreatitis is a common cause of CP in children and has worse clinical course than CP in children without PRSS1 mutations.

P-03-10

Characteristics of BRCA2 families in a familial pancreatic cancer registry

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Abstract

Background: As 5-year survival rates from pancreatic ductal adenocarcinoma (PDAC) remain poor, strategies to detect it at an early or pre-malignant stage are key to try and improve this. Individuals with a pathogenic germline *BRCA2* mutation and a family history of pancreatic cancer have an elevated risk of developing pancreatic cancer and secondary PDAC surveillance with endoscopic ultrasound (EUS) or magnetic resonance imaging (MRI) is recommended for such individuals. Although germline *BRCA2* mutations have been associated with a family history of pancreatic cancer, it remains unclear to what extent this is conveys a pancreatic cancer risk on carriers unaffected by PDAC, as not all families with a *BRCA2* mutation will have a history of PDAC. We intend to describe the characteristics of families in the EUROPAC registry with *BRCA2* mutations.

Methods: Families registered with EUROPAC up to March 2023 were classified against diagnostic criteria for familial pancreatic cancer (FPC) and hereditary breast ovarian cancer (BOv). Demographic and mutation data were extracted from the registry.

Results: 131 families were identified, in which there were 203 cases of pancreatic cancer. 38 (29%) families met diagnostic criteria for HBOC, 30 (23%) families met diagnostic criteria for FPC, 14 (11%) families met criteria for both FPC and BOv and 49 (37%) families met criteria for neither. 103 (79%) families had genetic data available. Most mutations were either deletions (65, 63%) or single nucleotide variants (23, 22%). There was no significant difference in age of onset of pancreatic cancer and no significant difference in the type or location of the mutation between the groups.

Conclusion: Despite the phenotypic heterogeneity of *BRCA2* families registered with EUROPAC, there is no significant difference between age of onset of pancreatic cancer or between the type or location of the *BRCA2* mutation. This suggests that it may not only be the *BRCA2* mutation contributing to the increased incidence of pancreatic cancer in these families.

P-03-11

A comprehensive gene-based analysis of uncommon genetic polymorphisms and risk of pancreatic ductal adenocarcinoma

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Abstract

Background: Despite the extensive investigation of common germline variants, uncommon variants remain poorly understood due to the limited coverage of genome-wide association studies (GWAS) for polymorphisms with minor allele frequency (MAF)<1%, which represent most of the human genome variation, and the high cost of whole genome/exome sequencing that hinders comprehensive analyses of these variants at the whole genome scale. However, the recent TOPMed reference panel enables GWAS imputation of non-genotyped polymorphisms with MAFs as low as 0.01%. Our aim is to investigate the contribution of the uncommon variants in all known gene regions on genetic susceptibility to pancreatic ductal adenocarcinoma (PDAC).

Methods: The study utilised two GWAS datasets, PanScan/PanC4 (over 7,000 PDAC cases and 7,000 controls), which were imputed with TOPMed, and UKBiobank (1,466 PDAC cases and 296,184 controls), which were imputed with the UK10K reference panel. A gene burden test (via MAGMA software) was performed for each of the 18,279 known autosomal coding genes and a meta-analysis method was performed between the results of PanScan/PanC4 and UKBiobank. Also, a functional annotation-based gene-burden test (via the STAARpipeline R package) was performed for known gene regions by using FAVOUR, a comprehensive whole genome variant annotation database (study-wide statistical significance threshold, $p=2.6x10^{-6}$).

Results: Meta-analysis of the gene-burden test for uncommon variants (MAF<1%) showed a study-wise statistically significant gene, *MBD3L5*, with $p=4.5x10^{-7}$. According to the functional annotation-based gene-burden test, none of the tested genes resulted to be associated with PDAC risk. However, promising associations ($p<10^{-4}$) were found for *CXCL10*, *ART3*, *ZNF382*, *SIPA1L2*, *CNBD2* and *CLDN6* with missense uncommon variants. Although the *MBD3L5* gene is not known to be directly implicated in cancer, it has synthetic lethal genetic interaction with the *KRAS* gene, which is mutated in most pancreatic cancer cases.

Conclusion: Initial analyses revealed encouraging links between uncommon variants in multiple genes and PDAC susceptibility, although most of those fell short of achieving study-wide statistical significance; functional annotation-based methods with additional annotations (e.g. methylation, miRNA, lncRNA) will be employed to refine the analysis of the PanScan/PanC4 and UK Biobank datasets, as well as of additional datasets with upcoming GWAS data.

P-03-12

Impact of genetically driven inflammation on early pancreatic carcinogenesis

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Abstract

Background: Hereditary chronic pancreatitis (CP) is a well-known risk factor for pancreatic cancer. A recent study using a genetic mouse model showed that the p.N256K mutation of carboxypeptidase A1 (Cpa1) is sufficient to cause CP. We aim to elucidate the impact of Cpa1-induced CP on the early steps of pancreatic cancer development using the novel mouse model KC-Cpa1, combining Cpa1 mice with a pancreas-specific K-RasG12D/+ genotype.

Methods: The pancreata of KC-Cpa1 mice, as well as Cpa1, KC, and wild type (WT) mice, were analysed histologically and using multispectral imaging, at early time points. Furthermore, pancreatic acinar cell line 266-6 expressing the mutant Cpa1 was used to elucidate the impact on ADM (acinar ductal metaplasia) using diverse approaches such as qRT-PCR, immunofluorescence, and immunoblotting.

Results: At 10 weeks, KC-Cpa1 mice showed massive remodelling of the pancreas. In addition, immune cells, predominantly macrophages, showed increased infiltration at 10 weeks as compared to the KC and control mice. In 266-6 acinar cells overexpressing mutant or WT Cpa1, we observed differences in ADM transdifferentiation.

Conclusion: These results demonstrate that the combined impact of oncogenic mutant K-Ras and mutant Cpa1 as exhibited in the KC-Cpa1 mouse model enhances features of early pancreatic carcinogenesis, specifically ADM and pancreatic intraepithelial neoplasia (PanIn). In further studies, we aim to identify the underlying molecular mechanism of mutant Cpa1 for these features using in vitro, ex vivo, and in vivo techniques.

P-03-13

The role of TRPV6 variants in chronic pancreatitis in Hungary

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Abstract

Background: The transient receptor potential channel family, vanilloid subfamily member 6 (TRPV6) protein is a constitutively active calcium channel expressed on the apical membrane of polarized epithelial cells. TRPV6 facilitates trans-epithelial calcium absorption and thereby contributes to calcium homeostasis. Recently, a number of studies reported that loss-of-function *TRPV6* gene variants are associated with non-alcoholic chronic pancreatitis. Our aim was to investigate the role of *TRPV6* variants in chronic pancreatitis in an adult Hungarian cohort.

Methods: Patients were recruited from the Hungarian National Pancreas Registry. Exons 4-8, 11, 14, and 15 of the *TRPV6* gene were analysed by PCR and Sanger sequencing in 144 non-alcoholic chronic pancreatitis patients and 300 controls.

Results: We identified 3 novel variants (p.T159I, p.R194C, p.G501C), 5 previously reported functionally benign TRPV6 variants (p.R220W, p.L299Q, p.T309M, p.T309=, p.P352=), and 7 common variants (p.C197R, p.T400=, p.N504=, p.T641=, p.G666=, p.M721T, p.N734=). Among the novel rare variants, p.T159I and p.R194C were present in 1 patient each, while the p.G501C variant was identified in 1 control subject. In silico analysis using Meta SNP classified all 3 novel rare variants as potentially pathogenic. The p.R220W variant occurred in 1 patient, while the p.L299Q and p.P352= variants were identified once and twice, respectively, in controls. Variants p.T309M and p.T309= were found both in patients (once each) and controls (twice each). The T allele of the c.1512C>T (p.N504=) variant was significantly overrepresented in cases (40/224, 29%) relative to the control group (44/442, 21.5%) (OR=1.79; P=0.0; 95% CI=1.1-2.8).

Conclusion: None of the previously reported functionally impaired *TRPV6* variants were found in this Hungarian chronic pancreatitis cohort. We identified 3 novel potentially pathogenic rare variants (p.T159I, p.R194C, p.G501C). The common variant p.N504= was significantly associated with the disease, however, independent replication will be required to confirm this finding.

P-03-14

Significance of chymotrypsinogen C (CTRC) mutations c.180C>T and c.493+51C>A in Hungarian patients with chronic pancreatitis

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Abstract

Background: Chymotrypsinogen C (CTRC) has significant physiological role in preventing early, intrapancreatic trypsin activation. Impairment of this molecular defence mechanism (e.g. loss-of-function mutations of the CTRC gene) can eventually cause chronic pancreatitis (CP). Interestingly, the silent mutation c.180C>T (p.G60=) in the CTRC gene is associated with CP in European and Indian cohorts. Moreover, this mutation is very rare in Japanese and Chinese populations. Another intronic CTRC variant c.493+51C>A having a protective effect for CP was reported recently, however, no further confirmation of this statistical observation was published. Investigation of genetic associations with uncertain clinical significance is needed to understand their effect more comprehensively. We aimed to determine the allele frequency of known mutations of the CTRC gene in patients and controls to evaluate their frequency and association with chronic pancreatitis in the Hungarian population.

Methods: We selected 141 patients with non-alcoholic (NACP), 176 patients with alcoholic chronic pancreatitis (ACP) and 400 controls recruited by the Hungarian Pancreatic Study Group (HPSG). Mutations in exons 2, 3 and 5 and their harbouring intronic regions of the CTRC gene were analysed by Sanger sequencing.

Results: The allele frequency of the c.180C>T (p.G60=) silent mutation was significantly overrepresented in patients with chronic pancreatitis in all subgroups compared to controls (all patients vs. controls: OR=2.07, 95% CI=1.5-2.8, p<0.0001, NACP vs. controls: OR=2.13, 95% CI=1.5-3.1, p=0.0001, ACP vs. controls: OR= 2.02, 95% CI=1.4-2.9, p=0.0001). The intronic variant c.493+51C>A was not accumulated significantly in patients or controls (all patients vs. controls: OR= 0.84, 95% CI: 0.7-1.1, p=0.2, NACP vs. controls: OR= 0.9, 95% CI: 0.7-1.3, p=0.7, ACP vs. controls: OR= 0.8, 95% CI: 0.6-1.1, p=0.14).

Conclusion: We confirmed in the Hungarian cohort that the c.180C>T (p.G60=) mutation of the CTRC gene is associated with chronic pancreatitis. The CTRC intronic variant c.493+51C>A is slightly overrepresented in controls, but the measure of accumulation was not statistically significant, therefore this variant is not protective against chronic pancreatitis in the Hungarian population.

P-04-01

Altered gut microbiota in the early stage of acute pancreatitis predicts the occurrence of acute respiratory distress syndrome

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Abstract

Background: Acute respiratory distress syndrome (ARDS) is the most common cause of organ failure in acute pancreatitis (AP) patients, which associated with high mortality. Specific changes in the gut microbiota have been shown to influence progression of acute pancreatitis. We aimed to determine whether early alterations in the gut microbiota is related to and could predict ARDS occurrence in AP patients.

Methods: In this study, we performed 16S rRNA sequencing analysis in 65 AP patients and 20 healthy volunteers. The AP patients were further divided into two groups: 26 AP-ARDS patients and 49 AP-non ARDS patients based on ARDS occurrence during hospitalization. We also conducted a combination analysis using lung microbiota data between ICU-ARDS patients and ICU-non ARDS patients with publicly available data.

Results: Our results showed that the AP-ARDS patients exhibited specific changes in gut microbiota composition and function as compared to subjects of AP-non ARDS group. Higher abundances of Proteobacteria phylum, Enterobacteriaceae family, Escherichia-Shigella genus, and Klebsiella pneumoniae, but lower abundances of Bifidobacterium genus were found in AP-ARDS group compared with AP-non ARDS groups. Random forest modelling analysis revealed that the Escherichia-shigella genus was effective to distinguish AP-ARDS from AP-non ARDS, which could predict ARDS occurrence in AP patients. Higher abundance of Escherichia-shigella genus was also found in the lung of ICU-ARDS patients compared with ICU-non ARDS patients.

Conclusion: Our study revealed that alterations of gut microbiota in AP patients on admission were associated with ARDS occurrence after hospitalization, indicating a potential predictive and pathogenic role of gut microbiota in the development of ARDS in AP patients.

P-04-02

Disease and death of Alexander the Great: pancreatic necrosis?

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Abstract

Alexander the Great is considered one of the greatest commanders in history who created a world empire. The circumstances of his death remain the subject of scientific discussion in the historical and medical communities. We looked at documents in the historical literature to figure out what might have caused the death of the statesman. The Indian wise man Kalanos predicted Alexander's death in Babylon within one year, so in Babylon the king became suspicious of his friends and lost heart. Alexander's drinking problem, which his contemporaries had already no-

ticed, got worse as soon as he got to Babylon in November of 331 BC. From party to party, on the occasion of every success, he was gradually but steadily becoming a heavy drinker.

In the last years of his life, Alexander the Great, under the influence of a fatal prophecy about his own demise, was angry, systematically abusing alcohol, and overeating during lavish feasts. Such historians as Aristobulus, Haret, and Plutarch tried to justify the king's bad habits with his love for feast talks and "body heat." Alexander the Great died in June of 323 BC. At different times, many hypotheses were put forward. Greek scholars say that the most likely cause of Alexander the Great's disease was his addiction to "heavy food" and alcohol, which led to pancreatic necrosis. According to the ruler's contemporaries, the onset of symptoms was characterised by severe abdominal pain after heavy food and wine, accompanied by fever, and daily progressive worsening for 14 days. Despite his bad condition, Alexander the Great kept overeating and drinking too much wine, even though doctors tried to induce vomiting and give him cold baths. This resulted in a rapid rise in temperature, increased sweating, fever, and difficulty breathing. Before his death, Alexander was tormented by severe pain and numerous painful symptoms. He died in Babylon at the age of 33 from severe sepsis.

P-04-03

Machine learning improves prediction of severity and outcomes of acute pancreatitis: a prospective multi-centre cohort study

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Abstract

Background: Up to 20% of patients with acute pancreatitis (AP) develop severe pancreatitis (SAP), presenting persistent organ failure with considerable mortality. Previous scoring models such as the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHI-II), Bedside Index for Severity in Acute Pancreatitis (BISAP), and other scoring systems do not precisely predict clinical outcomes of patients at the onset of the illness.

Methods: Data including demographic characteristics, laboratory tests, vital signs, physical examinations, aetiology, prognosis, and others are collected from 915 AP patients within 48 hours of onset in a multi-centre prospective cohort study (2018-2022). We randomly divided data into the training set (80%, n=732) and the test set (20%, n=183). Multiple machine learning (ML) algorithms were trained. The primary outcome was grades of AP severity such as SAP, MSAP (moderately severe acute pancreatitis), and MAP (mild acute pancreatitis). Secondary outcomes included mortality, infected pancreatic necrosis, ICU admission, and length of hospital stay. The performance of these models was evaluated using the area under the receiver operating characteristic curve (AUC). Importance of predictors is estimated using Shapley additive explanations.

Results: Six common ML algorithms showed ideal prediction effect and the Ensemble Model had the highest AUC for both primary and secondary outcomes. Different from traditional ML systems that divided acute pancreatitis into SAP or non-SAP, we innovatively built a ML model that made three-category prognosis prediction with AUC of 0.920, 0.843, and 0.929 for SAP, MSAP, and MAP, respectively. AUC and calibrations confirmed superiority for ML

model compared with five traditional scoring systems such as APACHE-II, Marshall, and BISAP et al. For ICU admission, mortality, infected pancreatic necrosis and hospital stay, AUC of ML prediction was 0.958, 0.913, 0.922, and 0.849. Temperature, heart rate, respiratory rate, serum calcium, serum glucose, and serum creatinine were important prognosis predictive factors.

Conclusion: By using admission clinical predictors, ML model accurately predicted severity and outcomes of acute pancreatitis.

P-04-04

Prevalence of islet cell autoimmunity in paediatric patients in index cases of acute pancreatitis

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Abstract

Background: The natural course of diabetes mellitus (DM) that develops after acute pancreatitis (AP) in children is unknown. We hypothesized islet cell autoimmunity is involved in DM development in index AP cases. The aim of our study was to describe the prevalence abnormal glucose testing and islet cell autoantibodies (ICA) in paediatric patients during and in the year following their index case of AP.

Methods: Data was obtained from a single-centre observational cohort study of patients with their first episode of AP. Baseline demographics, and clinical factors were recorded. Diagnosis of pre-DM or DM was determined using American Diabetes Association criteria. ICA titres were measured on stored plasma collected from AP diagnosis, within the first 6 months and at 12 months post-AP attack.

Results: Eighty-six patients with AP and ICA data were included, 73 had available glucose measures. Median age at first AP attack was 14.1 (IQR 8.7-16.4), 46/86 (53%) were females. Twenty-one patients out 73 (29%) developed abnormal glucose testing (pre-DM or DM combined); 5/21 DM, 16/21 pre-DM in the first year after first-AP attack. Demographics and baseline clinical characteristics were not different between those with or without abnormal glucose testing. However, a higher proportion (38%, 8/21) with abnormal glucose testing had severe AP compared to those with normal DM testing (13%, 7/52) (p=0.03). Twenty-six patients (30%) were positive for at least one of four ICAs (IAA, GADA, IA-2, ZnT8), 7 (8%) with two or more positive ICAs. For patients who had two or more positive ICAs, there was no significant difference between those with normal DM testing (8%, 4/52) compared to abnormal DM testing (5%, 1/21) (p=1.00). Fourteen patients had islet cell testing at multiple time points, of which 2/14 (14%) were positive across multiple time points.

Conclusion: Pre-DM and DM is higher than previously described in the paediatric literature post AP. Islet cell autoimmunity is more common in patients in the first year after their index AP attack than the general population (7-8%). Future studies are needed to delineate DM prevalence, assess long-term outcomes, and investigate mechanisms of

DM in AP.

P-04-05

Acute pancreatitis increases the risk of gastrointestinal cancer in type 2 diabetic patients: a Korean nationwide cohort study

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Abstract

Background: The association between acute pancreatitis (AP) and gastrointestinal cancers in diabetic patients is currently not well understood. The study aim was to investigate the association between AP and gastrointestinal cancers in diabetic patients.

Methods: Data from the Korean National Health Insurance Service database were analysed. Participants with diabetes who underwent a health examination between 2009 and 2012 were followed up till December 2018. The primary outcome was the occurrence of gastrointestinal cancer. A total of 2,263,184 patients were included in the final analysis.

Results: Patients with a history of AP (n = 2390) were found to have a significantly higher risk of gastrointestinal cancer except for oesophageal cancer, as follows: gastric cancer (aHR = 1.637, 95% CI: 1.323–2.025), colorectal cancer (aHR = 2.183, 95% CI: 1.899–2.51), liver cancer (aHR = 2.216, 95% CI: 1.874–2.621), pancreatic cancer (aHR = 4.558, 95% CI: 4.078–5.095), bile duct cancer (aHR = 3.996, 95% CI: 3.091–5.269), and gallbladder cancer (aHR = 2.445, 95% CI: 1.459–4.099). The history of AP is associated with the increased risk of gastrointestinal cancer in diabetic patients.

Conclusion: It is necessary to investigate the history of AP and more actively recommend screening for gastrointestinal cancers in such patients.

P-04-06

Serum phosphate levels in acute alcoholic pancreatitis

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Abstract

Background: After gallstones, alcohol is the second most common cause of acute pancreatitis (AP). Experimental studies found a relationship between phosphate serum levels and severity in acute alcoholic pancreatitis (AAP). The aim of the study was to figure out this association in our AAP human cohort.

Methods: Fifty-seven AAP patients were retrospectively assessed from our prospective-maintained AP database. 2 cohorts of patients were created according to normal (≥2.5 mg/dl) or low (< 2.5 mg/dl) serum phosphate levels performed within 24 hours of admission. Clinical, analytical and radiological data were recorded. Our primary outcome was the severity of AAP. Secondary outcomes studied were: mortality, organ failure, local and systemic complica-

tions, intensive care unit (ICU) admission, necrosectomy and length of hospital. The research was approved by our Ethics Committee Board (PI 22-2931).

Results: Serum phosphate levels were quantified in 55/57 patients. Phosphate levels were normal in 21 patients (38.18%) and low in 34 patients (63.63%) . 42 patients suffered from mild AAP and 15 developed moderately severe or severe AAP. On univariate analyses high blood pressure (HBP), SIRS, waist circumference, albumin, blood urea nitrogen, creatinine, phosphate, RAMSON and BISAP classifications as well as pleural effusion were related with the severity of AAP. On forward stepwise multivariate regression, the risk of suffering from a moderately-severe or severe AAP was higher for those patients with lower serum phosphate levels OR 10.56 (95% IC 1.98-56.36 p 0.006) as well as patients suffering from HBP OR 11,85 (IC 95% 2,003-70,077 p 0.006). The area under the receiver operating curve (AUROC) for phosphate levels was 0.723 (IC95% 0.551-0.895 p 0.013); <2.35 mgs/dl were the best cut-off point for phosphate level to predict severity in AAP (sensitivity 0.78; specificity 0.71). In the model HBP+phosphate, AUROC was 0.801 (IC95% 0.659-0.942 p 0.001) with 0.20 the bet cut-off value (sensitivity 0.85; specificity 0.61). No relationship was found between phosphate and secondary outcomes.

Conclusion: Our study suggests that serum phosphate level on admission can be used as a reliable prognostic marker in AAP patients. A cut-off value of phosphate <2.35 mgs/dl, is accurate to predict severity.

P-04-10

Systematic review of volume and methodological quality of randomised trials in acute pancreatitis

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Abstract

Background: This systematic review assessed the volume and methodological quality of Randomised Controlled Trials (RCT's) in relation to management of acute pancreatitis (AP).

Methods: The PUBMED, MEDLINE, CENTRAL databases were systematically searched for RCTs published across 3 time periods: <1996(P1), 1996-2008 (P2), >2008(P3). RCT quality was analysed with Cochrane Risk of Bias (ROB)-II, sample size recalculation, and Spin (interpretation of non-statistically significant results as relevant, making the study appear to be positive).

Results: Overall, 265 RCTs with 23,472 patients with AP were included. The average number of RCTs per year increased from 1.3, 6.1 to 10.9 in P1, P2, and P3, respectively. The clinical domains were nutrition (27%), drug treatment (21%), pancreatic necrosis management (13%), antibiotic prophylaxis (10%), and fluid management (7%). The ROB assessment showed low, some, and high concerns in overall ROB in 21%, 55% and 24% of all RCTs. Selective reporting bias was low in P3 (P1 10%, P2 19%, P3 42%, P<0.005). Measurement bias was 76%, 90% and 82% in P1, P2, P3 (P=0.014). Sample size calculations were reported in 106 RCTs and sufficient data to recalculate sample size in only 67 of the 106 (63%) RCT's. Sample size calculation reporting significantly increased through the three time periods (17%, 38% and 47%, p<0.05). Spin was identified in 70 RCTs (26% of all RCTs).

Conclusion: The quantity of published RCTs relating to the management of AP has increased eightfold over time. Nearly three quarters of all RCTs had some or high overall ROB. Misleading reporting was identified in over a quarter of trials and only 25% reported reproducible sample sizes. Significant improvements in the conduct and reporting of randomised trials in AP are required to improve the evidence base in this field.

P-04-11

Discharge protocol in acute pancreatitis: an international survey and cohort analysis

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Abstract

Background: There are several overlapping clinical practice guidelines in acute pancreatitis (AP), however, none of them contains suggestions on patient discharge. The Hungarian Pancreatic Study Group (HPSG) has recently developed a laboratory data and symptom-based discharge protocol, which needs to be validated.

Methods: A survey was conducted by involving all members of the International Association of Pancreatology (IAP) to understand the characteristics of international discharge protocols. We investigated the safety and effectiveness of the HPSG discharge protocol.

Results: According to our international survey, 87.5% (49/56) of the centres had no discharge protocol. Patients discharged based on protocols have a significantly shorter median length of hospitalization (LOH) (7 (5;10) days vs 8 (5;12) days) p<0.001), and a lower rate of readmission due to recurrent AP episodes (p=0.005). There was no difference in median discharge CRP level among the international cohorts (p=0.586). HPSG protocol resulted in the shortest LOH (6 (5;9) days) and highest median CRP (35.40 (13.78; 68.40) mg/l). Safety was confirmed by the low rate of readmittance (n=35; 5%).

Conclusion: Discharge protocol is necessary in AP. The discharge protocol used in this study is the first clinically proven protocol. Developing and testifying further protocols are needed to better standardize patient care.

P-04-12

Development of pancreatic diseases during long-term follow-up of patients with acute pancreatitis in a prospective nationwide cohort

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Abstract

Background: Identification of acute pancreatitis patients at high-risk for development of recurrent acute pancreatitis, chronic pancreatitis and pancreatic cancer would offer opportunities for improvements in disease management and patient counselling. This study aims to gain insight into the natural course and factors associated with disease progression following a first episode of acute pancreatitis.

Methods: A long-term follow-up study of a nationwide prospective unselected cohort of patients with acute pancreatitis (2008-2015) was performed. Primary endpoints were recurrent acute pancreatitis, chronic pancreatitis and pancreatic cancer. Cox-proportional hazards and logistic regression models were used for cumulative incidence calculations and risk analyses.

Results: Overall, 1,184 patients with a median follow-up of 9 years (IQR 7–11) were included. Recurrent acute pancreatitis and chronic pancreatitis occurred in 301 patients (25%) and 72 patients (6%), with the highest rates among patients with alcoholic pancreatitis (40% and 22%), and for chronic pancreatitis among patients with recurrent acute pancreatitis (15%). Pancreatic cancer was diagnosed in 14 patients (1%) after a median time of 24 months (IQR 4–84). Independent predictive factors for recurrent acute pancreatitis were alcoholic and idiopathic pancreatitis (OR 2.70, 95% CI 1.51–4.82 and OR 2.06, 95% CI 1.40–3.02) and no pancreatic interventions (OR 1.82, 95% CI1.10–3.01). In biliary pancreatitis patients, endoscopic retrograde cholangiopancreatography (OR 0.33, 95% CI 0.20–0.55) and cholecystectomy ≤ 3 months (OR 0.16, 95% CI 0.11–0.25) were protective factors for recurrent acute pancreatitis. Male sex (OR 2.06, 95% CI 1.05 – 4.05), non-biliary aetiology (alcohol: OR 5.24, 95% CI 1.94–14.16, idiopathic: OR 4.57, 95% CI 2.05–10.16 and other: OR 2.97, 95% CI 1.11–7.94), smoking (OR 2.33, 95% CI 1.14–4.78), pancreatic interventions (OR 3.10, 95% CI 1.20–8.02) and recurrent acute pancreatitis (OR 4.93, 95% CI 2.84–8.58) were independently associated with chronic pancreatitis.

Conclusion: One in four patients after a first episode of acute pancreatitis will develop recurrent acute pancreatitis, chronic pancreatitis, or pancreatic cancer. We identified several risk factors that may be helpful to devise personalised strategies with the intention to reduce the impact of disease progression after a first episode of acute pancreatitis.

P-04-13

Anaemia predicts organ failure and mortality in acute pancreatitis

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Abstract

Background: Anaemia is a risk factor for poor evolution in several diseases. Haematocrit (HCT), the percentage of red blood cells, is a common parameter performed on admission. This study aims to investigate the relationship between anaemia and prognosis in Acute Pancreatitis (AP).

Methods: We included patients admitted to our unit for AP from March 2014-2022. Data were analysed retrospectively using our prospectively collected database on AP. HCT levels were considered as follows: normal (≥36 ♀ / ≥38 ♂) and low (<36 ♀ / < 38 ♂). A propensity score matching was performed to reduce bias of confounding variables. Clinical, demographic, analytic, and radiologic data were recorded, which included age, sex, abdominal perimeter, body mass index (BMI), Charlson Comorbidity Index, smoking and alcoholic status, high blood pressure (HBP) and diabetes mellitus (DM); HCT, leucocytes, C-reactive protein (CRP), systemic inflammatory response syndrome (SIRS), creatinine, blood ureic nitrogen (BUN) and pleural effusion on admission were also recorded. Outcome variables studied were: mortality, organ failure, local and systemic complications, intensive care unit (ICU) admission, necrosectomy, length of hospital stay and severity.

Results: A total of 775 patients were initially enrolled. Finally, after propensity score matching, two cohorts of 109 each were created according to normal/ low HCT levels, and analysed. On univariate analysis organ failure OR 2.36 (95% IC 1.05-5.29) p 0.037 and mortality OR 3.708 (95%IC 0.75-18.27) p 0.107 were associated with low HCT. A multiple linear regression model was performed adjusted for confounding variables: DM, Charlson comorbidity index, HBP, albumin, BUN, creatinine, CRP, SIRS, BISAP and pleural effusion. Multivariate analysis showed that organ failure (OR 2.84, 95%IC 1.12-7.18 p 0.027) and mortality (OR 3.88; 95%IC 0.77-18.51; p 0.099) were 2.84 times and 3.88 times respectively more frequent among anaemic patients than among non-anaemic ones.

Conclusion: In our series, AP patients with low HCT developed organ failure more frequently and had higher rates of mortality than AP patients without anaemia. Therefore, HCT, an easily checked parameter on admission, must be taken into account to predict worse prognosis in AP.

P-04-14

Predictors of pain evolution in acute pancreatitis. Post-hoc analysis of WATERFALL clinical trial

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Abstract

Background: Pain is the main symptom of acute pancreatitis (AP). Most patients have relatively rapid pain relief, but

some others may experience more severe and long-lasting pain. Early prediction of those patients who will suffer more pain would allow decisions to be made regarding greater power of analgesic treatment.

Methods: Post-hoc analysis of the international open-label randomised clinical trial WATERFALL, which compared aggressive fluid therapy (20 ml/kg bolus followed by 3 ml/kg/h) versus moderate (1.5 ml/kg/h preceded by 10 ml/kg bolus only in case of hypovolaemia) based on Lactated Ringer solution. Pain was assessed using the PAN-PROMISE scale (numerical scale with range 0 to 10, absence or maximum pain reported by the patient respectively) at baseline, 12, 24 and 48 hours. The predictive effect of 16 baseline variables (at study enrolment) on the evolution of pain were analysed using a general linear model for repeated measures.

Results: A total of 228 patients were included out of 249 from the WATERFALL trial. Younger age, blood leukocyte count, presence of signs or symptoms of dehydration, and alcohol aetiology of AP were predictors of pain evolution in the first 48 hours ($p<0.05$). With the combination of these variables we obtained regression lines to predict 0-10 pain in the first 12, 24 and 48 hours. Baseline variables such as sex, smoking, body mass index, comorbidity, haematocrit, creatinine, temperature, heart rate, respiratory rate, biliary aetiology, or randomization to aggressive or moderate fluid therapy did not independently predict pain intensity in the first days after AP.

Conclusion: Pain management could be scaled according to characteristics, habits and clinical variables to achieve better results during AP admission. Further studies are needed to validate these results.

P-04-15

Early predictors for infected necrotizing pancreatitis: a systematic review and a meta-analysis

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Abstract

Background: Infected necrotizing pancreatitis (INP) raises the possibility of organ failure and mortality. Patients with INP might benefit from an early diagnosis that would allow for prompt antibiotic treatment. Procalcitonin (PCT) was found to have the strongest correlation with IPN in a recent meta-analysis. In this study, our goal was to find early indicators of IPN.

Methods: On October 27, 2022, a thorough search was performed in three databases: Medline (through Pubmed), Embase, and Central (PROSPERO no.: CRD42022370672). The included studies used CT imaging to detect gas in the necrotic collection or examined samples obtained after interventions using Gram staining or culture to confirm infection. Any laboratory biomarkers that were analysed between sterile necrotizing pancreatitis and INP were included in the index test. The random effect model was used to gain pooled estimates with 95% confidence interval (CI) and we fitted the SROC curve and heterogeneity among the studies was evaluated.

Results: Fourteen observational studies with 1591 patients were included. The C-reactive protein (CRP) area under

the ROC curve (AUC) resulted in 0.70 (95% CI = 0.63, 0.77), while the AUC of PCT is 0.70 (95% CI = 0.57, 0.83), during the disease's early phases during the first 72 hours after admission. The AUC of CRP indicated a higher level of 0.88 (95% CI = 0.75, 1.00) after the first 72 hours, while the AUC of PCT is 0.86 (95% CI = 0.60, 1.00). There was no discernible heterogeneity found.

Conclusion: In conclusion, in the early phases of the disease, the serum measurements of CRP and PCT could be elevated without the presence of infection, and in clinical settings could not predict the risk of developing infection. However, their elevated level in the late phase could be associated with infection. These results may contribute to the use of antibiotics in cases when inflammatory markers remain continuously elevated.

P-04-16

Age-based comparison of the late complications and lifestyle factors after acute pancreatitis

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Abstract

Background: Acute pancreatitis (AP) is a severe inflammatory condition which can lead to late complications, which are expected to develop in higher rate in the elderly population. The aim of our study is to compare the rate of severe AP, late complications of AP; as well as the smoking habits and alcohol consumption in patients under (A) and above (B) 65 years of age.

Methods: The GOULASH-PLUS is a longitudinal observational clinical study, which data of the first year follow-up were analysed. Endocrine functions were tested with HbA1C and oral glucose tolerance test, exocrine insufficiency was measured with stool elastase test. Data about lifestyle factors were gained from questionnaires. Statistical analysis was performed using Chi Square Test.

Results: From the 223 patients 151 belong to group A and 72 to group B. The rate of smokers was 49% (n=74) in group A, while 13% (n=9) in group B ($p<0.001$). Alcohol consumers were 56% (n=84) and 37% (n=27) in group A and B respectively. Severe AP occurred in 3% (n=4) of group A, and 11% (n=8) of group B ($p=0.028$). The rate of diabetes was 12% (n=17) in group A, and 21% (n=15) in group B; the rate of prediabetes was 23% (n=34) in group A and 51% (n=37) in group B ($p<0.001$). Exocrine insufficiency was detected in 20% (n=31) and 11% (n=8) of group A and B patients respectively.

Conclusion: In the elderly population, the rate of severe AP, diabetes and prediabetes was found to be higher. The follow-up of AP in older patients requires more attention.

P-04-17

Sarcopenia in acute pancreatitis: a scoping systematic review

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Abstract

Background: Sarcopenia has been shown to have adverse outcomes in several benign and malignant conditions. The impact of sarcopenia is poorly explored in acute pancreatitis (AP). We undertook a systematic review on reporting of sarcopenia in AP and its impact on post pancreatitis complications.

Methods: A literature search was performed, and relevant articles were retrieved using PUBMED, MDELINE and EMBASE databases. Full text articles reporting on sarcopenia in AP and showing relationship between severity of acute pancreatitis and sarcopenia/sarcopenic obesity were included.

Results: A total of 8 studies with 2,272 patients with a median age of 56 years were included.. The number of patients with mild , moderate and severe AP were 771, 545 and 258 respectively. Seven studies used skeletal muscle mass, skeletal muscle index, skeletal muscle attenuation, and one study used visceral fat/muscle mass ratio as indicators of sarcopenia. These were measured using CT scan to measure the muscle mass/visceral fat at L3 vertebra or measuring the psoas muscle volume. Five studies showed a direct relationship between sarcopenia and the severity and prognosis of AP. Three studies showed that patients with severe pancreatitis had lower muscle mass than those with mild pancreatitis). Two studies showed that high visceral fat and low skeletal muscle volume strongly correlated with higher risk of developing severe AP . One study showed that higher amounts of visceral fat and muscle mass were positively associated with fewer hospitalizations after AP episode. One study showed that skeletal muscle density was independently associated with in-hospital mortality in necrotizing pancreatitis.

Conclusion: This systematic review suggests a direct association between Sarcopenia and severity of AP in addition to worse post pancreatitis outcomes in patients with sarcopenia. However, sarcopenia assessment in AP is not standardised with a variety of sarcopenia indicators used in the literature making comparisons difficult. Further prospective studies are needed with standardised definitions for sarcopenia with longitudinal follow up to determine long term impact.

P-04-18

Post-discharge mortality in acute pancreatitis: A prospective international cohort analysis of 2613 patients

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Abstract

Background: In-hospital mortality of acute pancreatitis (AP) is 2-5%. There is growing evidence, that patients may have a serious risk of mortality and morbidity after discharge as well, but there is no comprehensive analysis of the post-discharge period. In this study, we aimed to investigate the risk, causes, and predictors of post-discharge mortality following AP.

Methods: The Hungarian Pancreatic Study Group included and followed 2,613 well-characterised AP patients from 25 centres between 2012 and 2021. For control group, general population data was obtained from the relevant central statistical office. Data on mortality and time of death of patients after discharge were provided by the Ministry of the Interior. Causes of death were investigated retrospectively based on autopsy and/or pre-mortem clinical reports. All data handling and analyses was done in the R (v4.03) statistical environment.

Results: Patients after an AP episode have more than three-fold higher incidence rate of mortality than the general population (0.0454vs.0.0130 person-years). First-year mortality after discharge was almost double than in-hospital mortality (5.5% vs. 3.5%), with 3.0% occurring in the first 90-day period. Male gender, higher age, comorbidities, local complications (HR: 1.73, CI: 1.15, 2.60, p=0.008) and organ failure (HR: 1.89, CI: 1.16, 3.07, p=0.010) were the most significant independent risk factors for death following AP. A multivariate analysis identified creatinine, glucose, and pleural fluid on admission as independent risk factors associated with post-discharge mortality. Cardiac failure and AP-related sepsis were the main causes of death in the first 90-day period, while cancer-related cachexia and non-AP-related infection were the key causes in the later phase.

Conclusion: Almost as many patients die in the first 90-day period after discharge as during their hospital stay. It is essential to revise follow-up practises in AP. Evaluation of cardiovascular status, follow-up of local complications, and cachexia-preventing oncological care should be an essential part of post-AP patient care. Future study protocols in AP must include at least a 90-day follow-up period after discharge.

P-04-19

The degree of obesity has a serious effect on the outcome of acute pancreatitis and the development of other comorbidities: analysis of an international prospective cohort of 2244 cases

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Abstract

Background: Acute pancreatitis (AP) is a potentially severe or even fatal gastrointestinal disease requiring hospitalization. Obesity is a major risk factor for several chronic comorbidities and is associated with worse outcome in acute inflammatory conditions. Our objective was to investigate the characteristics and role of obesity in the outcome of acute pancreatitis.

Methods: Clinical data of 2461 AP cases were collected in the Acute Pancreatitis Registry run by the Hungarian Pancreatic Study Group. Data on body mass index (BMI) were available in 2244 cases. Patient groups were formed based on BMI categories according to the World Health Organization definitions. Anamnestic, admission and outcome parameters were analysed. Depending on the type of variables, Pearson's Chi-squared test, Kruskal-Wallis rank sum test, univariate linear regression and binary logistic regression model was used.

Results: In our cohort, 3% of the patients were underweight, 30% had normal weight, 35% were in the pre-obesity, 20%, 8% and 4% were in the obesity class I, II and III groups, respectively. Odds ratio (OR) for comorbidities are higher in the underweight (OR=2.00; p=0.40), pre-obesity (OR=1.28; p=0.039) and in obesity class I, II and III groups (OR=2.00, 2.11 and 4.63, respectively; p <0.001 in all three). The odds for diabetes, hypertension, liver steatosis and hyperlipidaemia increases substantially according to the degree of obesity. Higher odds for systemic complications were found in the pre-obesity, obesity class I, II and III groups (OR=1.61, OR=2.51, OR=2.85, OR=3.53; all significant). The odds for renal failure were higher in all four groups compared to the normal BMI group (OR=2.66, OR=5.64, OR=5.34, OR=7.74; all significant), while only in obesity class I, II and III groups had higher odds for respiratory and heart failure. Accordingly, the three obesity groups had higher odds for severe acute pancreatitis (OR=3.73, OR=4.24, OR=3.39; p<0.001, p<0.001, p=0.008, respectively).

Conclusion: Not only obesity, but also the degree of obesity has a significant role in the development of pancreatitis complications and other comorbidities. Gradual weight loss can also have a significant positive effect and should be included in patient reports and education.

P-04-20

Comparing gut microbiota results of patients with one attack of acute pancreatitis and with chronic pancreatitis

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Abstract

Background: In 7% of patients after acute pancreatitis (AP), chronic pancreatitis (CP) will develop. Gut microbiota alterations were shown in connection with developing several diseases, and were observed in CP patients as well.

However, it is not known if this change is the cause or the consequence of the disease. Our aim was to compare the faecal microbiota in patients after one AP attack and diagnosed with CP in this pilot study.

Methods: GOULASH-PLUS is an observational follow-up study, where yearly faecal samples are collected. Stool samples of 12 AP (age, gender, AP-severity based control) and 13 CP patients were analysed during follow-up through 16S ribosomal RNA third-generation sequencing. During the bioinformatics analysis, QIIME2 was used. Core diversity parameters (Shannon, evenness, Simpson, cao, etc.) were calculated as well. To compare the two groups Wilcoxon ranged sing tests were applied.

Results: The α-diversity did not differ in AP and CP patients (p=0.82). On the phylum level, 7 phyla were identified in both groups, and no difference was seen in the relative abundances, however, the Firmicutes/Bacteriodota ratio was higher in AP patients (36.9 vs. 12.1). A lower relative abundance of Eubacterium halli (2.8% vs 4.7%; p=0.029) and Dorea genera (1.6% vs. 4.6%; p=0.025) was showed in the CP vs. AP group respectively.

Conclusion: The current findings indicate reduced relative abundance in 2 genera in CP patients. Further investigation with a higher sample size and follow-up is needed to clarify the connection between CP development and microbiome changes.

P-04-21

The risk factors of acute pancreatitis progression into recurrent acute pancreatitis and chronic pancreatitis

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Abstract

Background: Acute pancreatitis (AP) can progress to recurrent acute pancreatitis (RAP) or chronic pancreatitis (CP). This systematic review and meta-analysis aimed to identify risk factors associated with this progression.

Methods: The protocol was registered on PROSPERO (CRD42022368931). A comprehensive search was conducted in three (Medline, Embase, Cochrane) databases on October 25th, 2022. Articles reporting AP – RAP or RAP – CP patient groups comparisons and risk factors associated with AP progression into RAP or CP were included. Pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated using the random effects model. Heterogeneity was evaluated using the I^2 statistic. The risk of bias assessment was performed using the Quality in Prognostic Studies (QUIPS) tool.

Results: A total of 71 articles were included in the meta–analysis, and several risk factors were identified for the progression of AP into RAP and CP. We found the following risk factors of AP recurrence: younger age, male gender, smoking, alcoholic aetiology, hypertriglyceridemia, diabetes mellitus, pseudocyst, etc. The pooled OR for the male gender was 1.45 (95% CI: 1.29-1.64, I^2=24%), for smoking was 1.45 (95% CI: 1.16-1.81, I^2=62%), for alcoholic aetiology was 1.76 (95% CI: 1.38-2.25, I^2=81%), for hypertriglyceridemia was 2.45 (95% CI: 2.07-2.90, I^2=9%), for diabetes mellitus was 1.49 (95% CI: 1.24-1.80, I^2=0%), for pseudocyst was 2.19 (95% CI: 1.52-3.15, I^2=0%). We also found risk

factors of RAP progression into CP, which were the following: male gender, alcoholic aetiology, alcohol consumption, smoking, etc. The risk of bias was low in the majority of the included studies.

Conclusion: Our study identified multiple modifiable risk factors which can be treated to prevent the progression of pancreatitis.

P-04-22

Acute pancreatitis and the risk of dementia in diabetes: a nationwide cohort study

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Abstract

Background: Diabetes is a major risk factor for the development of dementia, which has been proven to be associated with systemic inflammation. Acute pancreatitis, also a local and systemic inflammatory disease, is the most common gastrointestinal disease requiring acute hospitalization. The effect of acute pancreatitis on dementia was investigated in type 2 diabetic patients.

Methods: Data was collected from the Korean National Health Insurance Service. The study sample included type 2 diabetes patients who received general health examination from 2009 to 2012. Cox proportional hazard regression analysis was used to evaluate the association between acute pancreatitis and dementia with adjustment of confounders. Stratified subgroup analysis by age, sex, smoking, alcohol consumption, hypertension, dyslipidaemia, and BMI was conducted.

Results: Amongst the 2,328,671 participants in total, 4,463 patients had a history of acute pancreatitis before the health examination. During a median follow-up of 8.1 (range, 0–10) years, 194,023 participants (8.3%) developed all-cause dementia. Previous history of acute pancreatitis was the significant risk factor for dementia after adjustment of confounding variables (HR 1.39 [95% CI 1.26–1.53]). In the subgroup analysis, patient characteristics such as age under 65 years, male, current smoker and alcohol consumption were significant risk factors for dementia in patients with a history of acute pancreatitis.

Conclusion: The history of acute pancreatitis was associated with the development of dementia in patients with diabetes. Because the risk of dementia increases with alcohol consumption and smoking in diabetic patients with history of acute pancreatitis, abstinence from alcohol and smoking should be recommended.

P-04-24

Pancreatic necrosis infection as a determinant of multiple organ failure and mortality in patients with acute pancreatitis using a step-up approach and the concept of enhanced recovery after surgery

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Abstract

Background: Acute pancreatitis is one of the most pressing and complicated issues in emergency abdominal surgery

and is the most common pancreatic disease in the world. Several recommendations and data on treating of acute necrotizing pancreatitis (ANP) are conflicting, and different surgical approaches continue to exist.

The primary aim of the study was to determine the effectiveness of Enhanced Recovery After Surgery (ERAS) principles in reducing complications and 30-day mortality during the ANP treatment stages. The secondary objective of the study was to evaluate the microbiological characteristics of ANP and the antibiotic sensitivity of all isolated bacteria to understand local epidemiology better and define the most effective antibiotics.

Methods: We conducted a study on 148 patients with ANP. All the patients were divided into two groups: the main group (n = 95) when the tactics of the step-up approach were applied with the principles of the ERAS concept in order to determine the effectiveness of this approach in reducing complications and 30-day mortality (2017–2022); the comparison group (n = 53) when the same tactic of the treatment was used without ERAS principles (2015–2016).

Results: Treatment time for the main group in the intensive care unit was minimized ($p \leq 0.004$); it has been shown to reduce the frequency of complications in these patients ($p \leq 0.001$) requiring conservative or surgical treatment without general anaesthesia (Clavien-Dindo I-IIIa); no statistically significant differences were observed for the total incidence of Clavien-Dindo IIIb-IVb complications ($p > 0.05$); the median duration of treatment for patients in the primary group was 23 days, and in the reference group — 34 days ($p \leq 0.003$). Pancreatic infections have been observed in 92 (62.2%) patients, and gram-negative bacteria predominate in the overall pathogen structure with 222 (70.7%) strains.

Conclusion: The only evidence of multiple organ failure before (AUC = 0.814) and after surgery (AUC = 0.931) was found to be predictive of mortality. Antibiotic susceptibility testing of all isolated bacteria has helped to better understand local epidemiology and determine the most effective antibiotics for treating patients.

P-04-25

Bacteriology of infection complications in acute pancreatitis

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Abstract

Background: Severe acute pancreatitis is associated with elevated mortality, with infectious complications being the most common cause of death. The aim of the study was to analyse the prevalence and features of pancreatic and extrapancreatic infection in patients with acute infected pancreatitis.

Methods: A retrospective study over a five-year period in 92 patients examined the presence of pancreatic and extrapancreatic infections in patients with infected acute pancreatitis and their effect on disease outcome.

Results: Based on 217 microbiological studies, growth of microflora was absent in 22 cases (10.1%). Of the 195 strains, monomicrobial infections were isolated from 114 (58.5%) and 81 (41.5%) polymicrobial strains. The total number of strains identified was 314. Gram-negative bacteria predominated in the general structure of pathogens with a share of 222 (70.7%) strains, of which 112 (50.5%) were represented by enterobacteria and 110 (49.5%) were non-fermenting gram-negative bacilli (NFGNB). The total proportion of gram-positive microorganisms was 92 strains (29.3%), among which enterococci predominated with 46 strains (50%). It has been established that the main initiating etiological factor of the pancreatogenic infectious process is the autochthonous flora, the main part of which is primarily representative of the *Enterobacteriaceae*. In the treatment of pancreatic and extrapancreatic infections, 164 microbiological studies of discharge were taken for culture from the blood, urine, throat, intravenous

cannula tip, urinary catheter tip, tracheal aspirate, drain fluid, and bile, and 240 cultures of microorganisms were isolated. An increase in microbial associations was observed: a total of 74 polymicrobial associations were detected on 240 crops (30.8%); in gram-negative microorganisms, NFGNB began to prevail. One to two weeks after the start of treatment, 51.1% of cases of wound discharge were contaminated with hospital antibiotic-resistant strains. The antibiotic sensitivity pattern showed that most of the bacteria were sensitive mostly to several beta-lactam antibiotics at the beginning and then tigecycline, linezolid, etc.

Conclusion: Pancreatic infections are more often monomicrobial, with the prevalence of gram-negative bacteria at the beginning, and a shift from gram-negative to gram-positive, including hospital bacteria, as pancreatitis progresses. Extrapancreatic infections are more often polymicrobial.

P-04-26

Biliary sludge, microlithiasis and gallstone-induced acute pancreatitis are associated with comparable clinical outcome: a single-centre analysis and narrative review of the literature

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Abstract

Background: By using endosonography, idiopathic acute pancreatitis can be relabelled to a biliary aetiology in 30% of cases. Biliary sludge and microlithiasis account for the largest proportion of biliary concrement. However, unlike “classic” gallstone-induced pancreatitis, the course of sludge- and microlithiasis-induced pancreatitis in comparison to gallstone-induced pancreatitis has not been studied. Using a newly established consensus definition for sludge and microlithiasis, the aim of this study was to compare the course of pancreatitis in different biliary entities with respect to outcome, EUS concrement detection rate and cholestasis patterns.

Methods: A total of 601 biliary pancreatitis patients treated between 2005 - 2021 at LMU University Hospital were identified retrospectively. Stratified into the different entity groups using the new consensus definition, 84 gallstone-induced pancreatitis cases, 40 microlithiasis-induced pancreatitis cases and 50 pure sludge-induced pancreatitis cases were analysed. In the case of possible secondary aetiologies patients were excluded from the analysis to not contaminate the cohort.

Results: According to the revised Atlanta classification, there was no difference in pancreatitis severity between the three groups (gallstone-induced pancreatitis: 40.4 % moderate, 9.5 % severe; microlithiasis-induced pancreatitis: 23.2 % moderate, 9.3 % severe; sludge-induced pancreatitis: 36.0 % moderate, 10 % severe; p = 0.41). There was also no difference in the percentage of SIRS, percentage of ICU stays or length of hospital stay. In summary, the sludge- and microlithiasis-induced pancreatitis groups showed gallstone-equivalent cholestasis on admission (bilirubin: 3.5 mg/dl ± 2.9 (gallstone-induced pancreatitis group) vs. 2.8 mg/dl ± 3.1 (microlithiasis-induced pancreatitis group; p = 0.98) vs. 2.7 mg/dl ± 2,3 (sludge-induced pancreatitis group; p = 0.40)). In all three groups, early endosonography on day 1 of hospitalisation achieved the highest diagnostic accuracy for biliary pathology (gallstone group (n=29): 44.8% detection rate; microlithiasis group (n=15): 46% detection rate; sludge cohort (n=27): 40.7% detection rate).

Conclusion: Sludge and microlithiasis as triggers of acute biliary pancreatitis lead to gallstone-equivalent elevated

cholestasis and show no difference in clinical outcome compared to gallstone-induced pancreatitis. Prospective studies are warranted to assess the pathophysiological risk of sludge and microlithiasis to induce pancreatitis.

P-04-27

Role of unknown significance (VUS) and non-disease-causing (NDC) CFTR gene mutations in the pathogenesis of acute pancreatitis

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Abstract

Background: Acute pancreatitis (AP) can be associated with *CFTR* gene mutations. Several mutations have been described and classified based on the type of protein changes. The CFTR-France database classifies variants in disease-causing (DC), variants of unknown significance (VUS) and no-disease-causing (NDC), according to their clinical consequences. The role of VUS and NDC mutations in AP patients was not clearly defined. The aim of this study is to determine the role of VUS and NDC mutations in patients suffering from AP.

Methods: We enrolled retrospectively patients with AP observed in our Centre between 2013 and 2020 and tested for *CFTR* gene mutations. Patients were divided in *CFTR* wild type, DC, VUS and NDC. We evaluated epidemiological, clinical, and instrumental characteristics at the disease onset and the clinical outcome in terms of progression to chronic pancreatitis, onset of pancreatic calcifications, development of exocrine and endocrine pancreatic insufficiency.

Results: We tested 322 patients (199 males and 123 females, age at onset 35.4±15.8 years). We compared 99 patients with *CFTR* mutations (65 males and 34 females, age at onset 29±13 years) with 223 wild type patients (134 males and 89 females, age at onset 38.2±15.7 years), showing significant differences in terms of age at onset, BMI, smoking and drinking habits, chronic pancreatitis, and pancreatic calcifications at the onset of the disease. The clinical course of the wild type patients was characterised by an earlier progression to chronic pancreatitis, onset of calcifications and exocrine pancreatic insufficiency. VUS and DC patients had a similar clinical outcome of the disease. NDC group was excluded from the analysis due to the low number of patients.

Conclusion: Patients carrying VUS mutations of the *CFTR* gene have a clinical outcome like patients carrying DC mutations.

P-04-28

Risk of acute alcohol pancreatitis is not increased in patients with previous biliary pancreatitis in a long-term follow-up

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Abstract

Background: Recurrence after acute pancreatitis (AP) is common, about 20% regardless of the aetiology. Abstinence has been shown to protect from recurrences after the first episode of acute alcohol pancreatitis. It is not known, however, whether abstinence is beneficial in preventing recurrences after AP when aetiology was other than alcohol. Our aim was to investigate whether the patients with an earlier episode of biliary pancreatitis have an increased risk to develop acute alcohol pancreatitis in a long-term follow-up.

Methods: All patients treated for AP in Tampere University Hospital during 2004-2005 were collected from the hospital register. Patient files were studied and the patients with biliary acute pancreatitis (BAP) were included in the study database for analysis. From these patients, data on demographics, course of disease and data of any recurrences of AP was collected. From the hospital registry, we followed whether these patients had been treated for AP after the initial episode of BAP.

Results: From 434 patients who were treated for AP, 339 (78.1%) had their first episode. From all AP patients, the aetiology was biliary in 136 (31.3%), and these were included in the study database. Most of the patients were not abstinent after the first biliary AP. In up to 19 years of follow-up, 9 episodes of recurrent AP (RAP) was detected in 8 (5.9%) patients, none for aetiology of RAP being alcohol. The aetiologies for recurrences were 5 biliary, 3 post-ERCP and 1 non-specified.

Conclusion: Previous episode of biliary AP does not seem to increase the risk for alcohol AP in a long-term follow-up. Total abstinence might not be necessary after biliary AP.

P-04-29

Effect of serum vitamin D levels on the severity of acute pancreatitis: a prospective study

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Abstract

Background: Acute pancreatitis (AP) is a serious and complex disorder with varying disease course and severity. Early and prompt interventions are crucial in management of AP and commonly used scoring systems such as BISAP, Ranson's, CTSI, APACHE-II and Atlanta classifications help the clinician define the under-the-risk population with a probable severe disease course.

Vitamin D, being a prominent actor in calcium metabolism, also takes part in immunity and thus in immune-system related disorders, ranging from infections to cancer. Vitamin D deficiency is being thought and studied as an independent determinant of disease prognosis in various clinical pictures. In this study, the role of vitamin D status of a patient on the severity of AP was investigated.

Methods: This prospective study was conducted between June 2021 to August 2022. A total of 315 patients were enrolled in the study. Blood samples were obtained upon admission and laboratory analysis was performed including vitamin D levels. A 25-(OH)D3 level less than 10 ng/ml was defined as vitamin D deficiency. 10 to 19 ng/ml was defined as vitamin D insufficiency whereas 20 ng/ml or above was considered to be sufficient. Scoring systems (Ranson score, CTSI, BISAP, Atlanta classification) were applied.

Results: Serum 25-(OH)D3 levels of patients with AP were found to be negatively correlated with severity of the disease according to Atlanta classification and this relationship was found to be statistically significant. In concordance to this finding, both Ranson score and BISAP were found to be statistically significantly related to 25-(OH)D3 levels. Both scoring systems revealed higher scores in patients with insufficient or deficient levels of 25-(OH)D3. CTSI was not found to differ significantly between patients with varying 25-(OH)D3 levels. Serum 25-(OH)D3 levels were not

found to be related to ICU admission or mortality.

Conclusion: This study revealed that serum 25-(OH)D3 level is related to the severity of AP. In the future, interventional studies with vitamin D therapy in otherwise serum 25-(OH)D3 deficient AP patients might reveal a new potential therapeutic agent in this mechanically complex, burdensome disorder.

P-04-31

Acute pancreatitis: leave no stone unturned

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Abstract

Background: Hypercalcaemia is a seldom diagnosed condition that can cause pancreatitis. The most frequent cause is primary adenoma-related hyperparathyroidism (PHPT).

Patient: We present the case study of a 42-year-old man who had a history of myocarditis five years prior and did not exhibit any risk factors for pancreatitis.

Results: The patient presented at the Emergency Department complaining of abdominal pain and vomiting for four days. Blood tests showed leukocytosis with marked neutrophilia; elevated CRP; amylase and lipase >2000IU/L; normal transaminases, no signs of cholestasis or obstruction; normal renal function; normal triglycerides. Interestingly, total calcium was 2.46mmol/L (2.20-2.65) with severe albumin depletion, but ionized calcium was 1.3mmol/L (<1.35), stable at reevaluation; PTH was in range. A CT scan of the abdomen revealed moderate oedematous pancreatitis. The patient was placed on supportive care with additional albumin supplementation. After a few days, the clinical picture deteriorated dramatically, with pleural effusion, ascites, and severe paralytic ileus developing. On CT, necrotic-haemorrhagic pancreatitis with extensive peripancreatic and pericolic collections was seen. Later, polymicrobial sepsis developed. On the 32nd day of hospitalization, the patient underwent endoscopic drainage of a voluminous walled-off necrotic collection with signs of superinfection via trans gastric LAMS, with clear improvement of the situation. A follow-up MRI incidentally revealed a resorption of the bony structure of the pelvis, suspicious for manifestation-location of a malignant pathology. The patient was discharged with indications for outpatient assessments. After 4 months, he went back to the ED due to pancreatitis recurrence: marked hypercalcemia (ionized calcium up to 1.58) and PTH increase (up to 200pg/ml, <88) were found. Bisphosphonates and cinacalcet were administered. PET scans and neck ultrasounds revealed hyperenhancement swelling in the right lower parathyroid site. Six months after the first episode of pancreatitis, the patient underwent parathyroidectomy, which resulted in serum calcium and PTH normalisation (histology: parathyroid adenoma). However, he developed chronic pancreatitis with pancreatic insufficiency.

Conclusion: Acute pancreatitis may be the only and primary sign of PHPT. Diagnosis is essential for pursuing the appropriate treatment. In patients with elevated or normal blood calcium, hyperparathyroidism should be suspected, especially if other contributing factors of pancreatitis are not present.

P-04-32

Social deprivation increases the risk of acute pancreatitis but does not impact on disease severity and mortality

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Abstract

Background: The incidence of Acute Pancreatitis (AP) in increasing in the UK. Patients with severe AP require a significant amount of resources to support them during their admission. The ability to predict which patients will develop multi-organ dysfunction remains poor leading to a delay in the identification of these patients and a window of opportunity for early intervention is missed. Social deprivation has been linked with increased mortality across surgical specialties. Its role in predicting mortality in patients with AP remains unclear but would allow high-risk patients to be identified early and to focus resources on high-risk populations.

Methods: A prospectively collected single centre database was analysed. English Index of Multiple Deprivation (IMD) was calculated based on postcode. Patients were grouped according to their English IMD quintile. Outcomes measured included all-cause mortality, ITU admission, overall length of stay (LOS) and local pancreatitis specific complications.

Results: 398 patients with AP between 2018 and 2021 were identified. There were significantly more patients with AP in Q1 (IMD 1-2) compared to Q5 (IMD 9-10) (156 vs. 38, p<0.001). Patients who were resident in the most deprived areas were significantly younger (52.4 in Q1 vs 65.2 in Q5, P <0.001), and more often smokers (39.1% in Q1 vs 23.7% in Q5, P = 0.044) with IHD (95.0% vs 92.1% in Q5, P < 0.001). In multi-variate modelling, there was no significance difference in pancreatitis related complications, number of ITU visits, number of organs supported and overall, LOS by IMD quintile. Multivariate analysis demonstrated significantly poorer survival outcomes for patients with older age (HR- 1.064, P= 0.003), higher prothrombin time (HR- 0.868, P= 0.05) and need for ventilation support in the ICU (HR- 0.319, P= 0.036).

Conclusion: Social deprivation increases the risk of admission with acute pancreatitis but does not impact on disease severity and mortality. Increasing age and the development of organ failure are the strongest predictors of mortality in patients with AP.

P-04-33

Lactated Ringer's solution reduces severity, mortality, systemic and local complications in acute pancreatitis: systematic review and meta-analysis

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Abstract

Background: Fluid therapy is the cornerstone of early supportive therapy in acute pancreatitis (AP). Fluid choice is

still debated among clinicians, and the incorporation of recent evidence from randomised controlled trials (RCTs) is necessary. Aims: Quantitative synthesis of data from RCTs comparing lactated Ringer's solution (LR) with normal saline (NS) in adult and paediatric AP patients focusing on clinically relevant outcomes.

Methods: RCTs comparing intravenous fluid resuscitation with LR to NS in adult or paediatric AP patients were eligible. The study protocol was prospectively registered (CRD42021224542). Moderate-to-severe AP (MSAP), mortality, length of hospitalization (LoH), need for intensive care, the incidence of systemic (organ failure, OF) and local complications (in total), necrosis and pseudocyst formation, systemic inflammatory response and C-reactive protein levels were analysed. Risk ratio (RR) and median difference (MD) were calculated with 95% confidence intervals (CI) using a random effect model. Risk of bias and quality of evidence were assessed using the RoB2 and GRADE tools.

Results: Eight studies (557 patients) were found eligible, including one paediatric study. The risk of MSAP was reduced by 31% (RR: 0.59, 95% CI: 0.36-0.97, 3 studies, high quality), and the risk of mortality by 62% (RR: 0.48; 95% CI: 0.24-0.98, 5 studies, very low quality) in the LR group. LR fluid therapy was associated with significantly lower risk of need for intensive care (RR: 0.50, 95% CI: 0.33-0.77, 4 studies, low quality), OF (RR: 0.78, 95% CI: 0.61-0.99, 6 studies, low quality) and local complications (RR: 0.64, 95% CI: 0.46-0.89, 4 studies, moderate quality). No significant risk reduction was observed for LoH (MD:-0.57 days, CI:-1.33-0.19, 8 studies, moderate quality), necrosis (RR: 0.70, 95% CI: 0.40-1.23, 7 studies, low quality), pseudocyst formation (RR: 0.96, 95% CI: 0.11-8.68, 3 studies, low quality), C-reactive protein and systemic inflammatory response syndrome.

Conclusion: LR reduces severity, mortality, need for intensive care, systemic and local complications in AP, therefore LR should be used for initial resuscitation in AP.

P-04-34

Pancreatitis bundles: useful tools for acute pancreatitis

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Abstract

Background: To examine the usefulness of the Pancreatitis Bundles for acute pancreatitis.

Methods and Results: Pancreatitis Bundles were first presented in the Japanese Guidelines 2010 for the management of acute pancreatitis (AP). Those consist of 10 statements extracted from the Japanese guidelines for AP, specify the management and treatment within the first 48 h after the diagnosis of AP for the purpose of improving the mortality of severe AP (SAP) patients.

Using the data of the nationwide survey of patients who developed AP in 2011 in Japan, the implementation of statement number 6, which refers to initial fluid therapy, was associated with a significant reduction in mortality (9.5% vs 19.4%, P = 0.028). Moreover, the patients whose treatment satisfied eight or more statements showed a significantly lower mortality rate than those whose treatment satisfied seven or fewer statements (7.6% vs 13.7%, P = 0.042).

Those Bundles were a little modified in Japanese guidelines 2015 for AP. Using the data of the nationwide survey of patients who developed AP in 2016 in Japan, the mortality rate was lower when eight statements or more were im-

plemented than when less than 8 statements were implemented (1.0% vs 7.1%, P = 0.02). The statistical significance was also observed when the cut-off value was set to 7 implemented bundle statements (4.1% when implemented vs 8.7% when not implemented; P = 0.039).

Since low rate of early enteral nutrition and high rate of preventable antibiotics in the 2016 national survey, the pancreatitis bundles were modified in 2021 guidelines.

Conclusion: A high rate of implementation of the pancreatitis bundles might contribute to improving the mortality of patients with SAP.

P-04-35

Splenoportal veins thrombosis in severe acute pancreatitis: should we anticoagulate?

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Abstract

Background: Intraabdominal deep vein thrombosis (DVT), predominantly affecting the splenoportal veins, is a recognized complication of acute pancreatitis (AP), estimated incidence of 15%. There is not consensus on its management, as spontaneous recanalization has been described and anticoagulation is not exempt from complications. However, we can´t forget that complications due to the portal hypertension may arise, such as collateral circulation or ischaemia.

Methods: We conducted a retrospective observational study. Inclusion criteria were moderately-severe and severe AP according to revised Atlanta Classification, of any aetiology, hospitalized between 01/01/2018 and 31/12/2021. Exclusion criteria were previous DVT. The objective was to analyse usefulness and safety of anticoagulation in AP-associated DVT.

Results: A total of 845 APs were examined, including 181 patients (61.8% male, median age 65 years). Of them, 17 developed splenoportal DVT (9.4%). Patients characteristics, aetiology, severity, local and systemic complications of AP were analysed among those patients with DVT versus those without. No statistically significant differences were found except in male sex (p=0.02), and certain positive trend in severity (p=0.082).

Of those who develop DVT, toxic aetiology predominated (47%) followed by biliary (41%), and 59% of patients developed moderately-severe AP.

14 patients with DVT were admitted to intensive care units, and 1 died due to unfavourable course.

The most frequent location of DVT was the splenic vein (29.4%), followed by the superior mesenteric (23.5%) and the portal veins (17.6%).

All patients received treatment with Low Molecular Weight Heparins (LMWH) followed by Acenocoumarol, obtaining a recanalization rate of 52.7%. Associated with treatment, 3 non-severe haemorrhagic complications were observed (17.6%).

During follow-up, 9 patients developed complications associated with DVT (52.9%), being the collateral circulation the most frequent (77.8%). Patients who resolved DVT had statistically significantly lower rates of complications

than those who did not (p=0.016).

Conclusion: DVT in AP is more common in men. Anticoagulation therapy resolves DVT in half of patients, but it is associated with a non-negligible percentage of bleeding complications. Nevertheless, those patients who resolve DVT develop fewer secondary complications compared to those who do not. Prospective studies are needed to clarify whether DVT in AP should be anticoagulated and, if so, in which patients.

P-04-36

Cost analysis of moderately-severe and severe acute pancreatitis

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Abstract

Background: Acute pancreatitis (AP) is the first cause of hospitalization in Gastroenterology, with increasing incidence. Associated with significant morbidity and mortality, it might require prolonged hospitalization, even in intensive care units (ICU), and its complications may need invasive procedures (endoscopy, drainage or surgery) and/or long-term treatment (nutrition, antibiotics). Consequently, it's management is associated with high health care costs. Our objectives were to analyse the clinical characteristics of included patients and to quantify the resources consumed by those AP by extracting data from an internal data source.

Methods: Retrospective observational study. Inclusion criteria were moderately-severe and severe AP according to revised Atlanta Classification, of any aetiology, hospitalized from 01/01/2018 to 31/12/2021.

Results: A total of 845 APs were examined, including 181 patients with moderately-severe (76.3%) and severe APs (61.8% male, median age 65 years). Mean duration of hospitalization was 15 days (median=11), reaching 25 days (median=18) if admission to ICU required (11% of patients). Eleven patients required care by Hospital-at-Home after discharge (6%). A cost comparison analysis was made according to sex, aetiology, severity, presence of thrombosis, need for ICU, systemic and locoregional complications requiring treatment. A mean cost of 10,257€ (median=5,853€) was obtained, reaching 36,060€ of mean (median=22,284€) in those patients admitted to the ICU. Statistically significant differences appeared in the comparison of costs with respect to the previously mentioned variables (p=0.001), except for sex and aetiology. Predominant aetiology was biliary (50.6%), followed by toxic (23.7%). 142 patients developed systemic complications (76.4%), being multiple in more than 1/3 of the cases. 150 patients presented locoregional complications (83%), 19 requiring specific treatment (12%): 6 by endoscopy, 6 by percutaneous access, 3 in combination, and 4 by surgical approach. Sixteen patients died due to unfavourable course of AP and/or concomitant pathologies (8.6%), most of them advanced aged and/or with comorbidities.

Conclusion: AP is a frequent and potentially severe pathology that entails significant morbidity and mortality in addition to consumption of health care resources. The most severe pancreatitis with admission to the ICU, those with splenoportal thrombosis, and those requiring specific interventions, represent a greater cost to the health care system.

P-04-37

Ineffectual process concerning the initiation of enteral tube feeding in acute pancreatitis. a prospective, international, multicentre cohort analysis of 1088 cases.

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Abstract

Background: Enteral feeding (EF) is recommended in the severe or predicted severe forms of acute pancreatitis (AP) to reduce mortality. We aimed to investigate the factors leading to initiating EF in the acute phase (first three days of hospitalization) and the associations between EF and the disease outcome.

Methods: 1429 prospectively collected cases from 31 centres and 12 countries were included in the analysis. EF and Non-EF patient groups were formed concerning tube feeding in the first three days of the hospital stay. We investigated the associations between pancreatic and inflammatory laboratory parameters (amylase, lipase, CRP, WBC, LDH), imaging alterations (necrosis, fluid collections, etc.), and clinical symptoms influencing the initiation of EF (abdominal pain, vomiting, etc.). We used Fisher's exact test for categorical variables and the Mann-Whitney U test for not normally distributed continuous variables. A p-value <0.05 indicates a statistically significant difference.

Results: EF was applied during hospitalization in 30%, 41%, and 55% of mild, moderately severe, and severe cases, respectively. Significantly higher WBC (p=0.042 p=0.019, p=0.002 on D1, D2, and D3), CRP (p<0.001 on D3), and LDH (p=0.004, p=0.036 on D1 and D3) were detected in the EF group before nutritional support compared to the non-EF cases. The frequency of necrosis, pseudocyst, abdominal fluid collection (all with p<0.004), and the intensity of abdominal pain (p<0.001) were also significantly higher in the EF group before nutrition initiation. The overall mortality in this cohort was 2.8%. Notably, the mortality in the non-EF severe group was 10% higher than in the EF severe group (38% vs. 28%, p=0.384).

Conclusion: All parameters influencing the EF initiation here are not part of the current guidelines. In conclusion, decision-making mechanisms for initiating EF rely on personal preferences; therefore, there is still a substantial proportion of patients with severe AP without EF (45%). Since EF is cost-effective and has a very low complication rate if applied correctly, it should be introduced to all AP cases regardless of laboratory parameters and imaging findings.

P-04-38

Metabolic-associated fatty liver disease is associated with more severe acute pancreatitis: a prospective cohort analysis of 2053 cases

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is a proven risk factor in acute pancreatitis (AP). However, NAFLD has recently been redefined as metabolic-associated fatty liver disease (MAFLD). In this prospective cohort analysis, we quantified the effect of MAFLD on the outcomes of AP.

Methods: We identified our cohort from the multicentre, prospective International Acute Pancreatitis Registry of the Hungarian Pancreatic Study Group. Next, we compared AP patients with and without MAFLD and the individual components of MAFLD regarding in-hospital mortality and AP severity based on the revised Atlanta classification. Lastly, we calculated odds ratios (ORs) with 95% confidence intervals (CIs) using multivariate logistic regression analysis.

Results: MAFLD had a high prevalence in AP, 39% (801/2,053). MAFLD increased the odds of moderate-to-severe AP (MSAP) (OR=1.43, CI:1.09-1.89). However, the odds of in-hospital mortality (OR=0.89, CI:0.42-1.89) and severe AP (SAP) (OR=1.70, CI:0.97-3.01) were not higher in the MAFLD group. Out of the three diagnostic criteria of MAFLD, the highest odds of SAP were in the group based on metabolic risk abnormalities (OR=2.68, CI:1.39-5.09). In addition, the presence of one, two, and three diagnostic criteria dose-dependently increased the odds of MSAP (OR=1.23, CI:0.88-1.70, OR=1.38, CI:0.93-2.04, and OR=3.04, CI:1.63-5.70, respectively) and SAP (OR=1.13, CI:0.54-2.27, OR=2.08, CI:0.97-4.35, and OR=4.76, CI:1.50-15.4, respectively). Furthermore, in patients with alcohol abuse and aged ≥60 years, the effect of MAFLD became insignificant.

Conclusion: MAFLD is associated with AP severity, which varies based on the components of its diagnostic criteria. Furthermore, MAFLD shows a dose-dependent effect on the outcomes of AP.

P-04-39

COVID-19 and acute pancreatitis: not increased risk but reduced care

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Abstract

Background: Several reports explored the relationship between Covid-19 and acute pancreatitis (AP), but it is unclear whether pancreatic injury is truly caused by SARS-CoV-2 or represent a casual association due to pandemic.

We aim to evaluate AP features during the first year of Covid-19 pandemic (2020) and compare them with pre-Covid period (2008-2019), to identify any differences and clarify a potential causative role of SARS-CoV-2.

Methods: Monocentric retrospective study among 132 AP patients during 2020 and 1987 during 2008-2019. Diagnosis and severity were classified according to Revised Atlanta Criteria. We performed outcome analysis both in the whole sample and in a statistically matched group according to epidemiological features, aetiology, lipase and severity.

Results: Total number of AP cases in 2020 is one of the lowest in the last 13 years, ranking below the second quartile (132 cases, compared to 161 cases/year during 2008-2020, IQR 146-183). No major differences are noted regarding sex (p=0.058), age (p=0.669), lipase levels at presentation (p=0.234). A slight decrease of comorbidity at diagnosis was seen in 2020 (79.5% vs 93.4%, p<0.001). During 2020 we observed a significant modification of distribution of aetiologies (p<0.001) mainly by a decrease of biliary forms (43.2% vs 59.6%) and increase of alcoholic and IPMN-related forms (12.9% vs 6.9% and 9.1% vs 2.2% respectively). Idiopathic forms remain unchanged (20.5% vs 21.9%). During 2020, 7 AP patients (5.3%) tested positive for SARS-CoV-2: among these, 6 had a clear AP cause, while one (0.008%) had idiopathic AP. Comparing 2020 to 2008-2019, there were no differences regarding severity distribution (mild 83.3% vs 79.3%, moderately severe 9.6% vs 15.9%, and severe 6.8% vs 4.8%, p=0.127), length of stay (10 vs 9 days, p=0.916), need for ICU (6.1% vs 3.4%, p=0.139) and mortality (2.3% vs 4.4%, p=0.462). Even between the statistically matched subgroups, no significant differences in outcome were observed.

Conclusion: The unchanged proportion of idiopathic forms support the hypothesis that SARS-CoV-2 is not an AP trigger. Moreover, any relevant outcome has been affected during pandemic. The lower AP diagnoses indicate delayed and likely missed diagnoses, probably due to both hesitancy and organizational problems during pandemic.

P-04-40

Chronic liver diseases is an important risk factor in acute pancreatitis: systematic review and meta-analysis

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Abstract

Background: Chronic liver diseases (CLD) affect 1.5 billion patients worldwide, with incidence increasing dramatically in the last decades. Evidence suggests that particular chronic liver diseases unfavourably affect the outcomes of acute pancreatitis (AP). However, the lack of comprehensive data, restrains the validity of chronic liver disease as a potential prognostic factor in acute pancreatitis. Our aim is to fill the gap in the knowledge regarding the underlying risk that CLD poses on the outcomes of AP.

Methods: Systematic search was conducted until October 2022 in Embase, Medline, and Central databases. Studies investigating patients with acute pancreatitis and with or without CLD were included in the meta-analysis. Pooled

odds ratios were calculated by the Mantel-Haenszel method. For risk of bias assessment, the QUIPS tool was used.

Results: In total 11397 articles were analysed of which 37 were eligible for data extraction. Data from more than 3 million patients with AP were analysed. CLD was a risk factor for increased mortality with an odds ratio (OR) of 2.53, 95% confidence interval (CI) (1.31 to 4.88) p= 0.01. Furthermore, renal, cardiac, and respiratory failure were more common in the CLD group with OR 2.52 p= 0.016, 2.22 p=0.005, and 2.47 p= 0.087, respectively. The presence of CLD also increased 2.5 times the odds of local complications such as acute necrotic and acute fluid collection. Infection rate results did not reach mathematical and clinical significance (OR 1.49, CI (0.2 to 11.07), I2 100%).

Conclusion: Acute pancreatitis patients with underlying chronic liver disease are at higher risk of both increased mortality and overall complications. Inconclusive results concerning infections rate could be ascribed to the lack of primary data. AP patients with CLD need more attention. (The last two authors equally contributed).

P-04-41

Time dependency and risk factors of splanchnic vein thrombosis development in the early phase of acute pancreatitis: a systematic review and meta-analysis

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Abstract

Background: Splanchnic vein thrombosis (SVT) is a local complication of acute pancreatitis (AP). Our main objective was to understand the time course and risk factors of SVT in the early phase of AP.

Methods: A systematic search was conducted on 27 October 2022, in four medical databases (Embase, PubMed, Scopus, Cochrane). Inclusion criteria were appropriate imaging (CT, MRI, US) in adult patients with AP and reliable reporting of imaging timing. Exclusion criteria were co-occurrence or recent history of malignant disease and recent surgical interventions. Pooled proportion of patients affected by SVT were calculated with 95%-Confidence Intervals (CI), and subgroup analyses were performed for diagnosis timing and disease characteristics. The Joanna Briggs Institute Critical Appraisal tool was used to assess the risk of bias, and the GRADEpro tool for the level of evidence. The PROSPERO registration number for the protocol is CRD42022367578.

Results: Data from 15 eligible studies and 1,979 patients were pooled; the proportion of patients with SVT in the early phase of AP (within 11 days after symptom onset or 5 days after admission) was 0.16 (CI 0.08-0.29). Occurrence was lowest 0-3 days after symptom onset at 0.05 (CI 0.00-0.45), while it increased almost five-fold to 0.23 (CI 0.02-0.79) between 3-11 days. Disease factors influencing SVT occurrence were severity (mild: 0.14 (CI 0.04-0.39), moderate: 0.23 (CI 0.09-0.47), severe: 0.31 (CI 0.15-0.54), p=0.21), aetiology (alcoholic 0.31 (CI 0.13-0.58), biliary 0.12 (CI 0.04-0.3), p=0.03), and pancreatic necrosis (absent 0.11 (CI 0.05-0.25), <30% necrosis 0.25 (CI 0.11-0.47), >30% necrosis 0.5 (CI 0.29-0.72), p= 0.01).

Conclusion: One in six patients develops SVT in the early phase of AP. A severe disease course, alcoholic aetiology, and pancreatic necrosis increase the risk of SVT. In addition, this risk seems to increase with the duration of AP; therefore, looking for and diagnosing SVT with imaging is important in the management of AP.

P-04-42

Risk factors for diabetes mellitus after acute pancreatitis: a systematic review and meta-analysis

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Abstract

Background: Within five years of having acute pancreatitis (AP), three in five people develop prediabetes (PD) or diabetes mellitus (DM). However, information on risk factors is limited. We aimed to identify risk factors for developing PD or DM following AP.

Methods: We systematically searched three databases up to 2021.11.18 extracting direct, within-study comparisons of risk factors on the rate of new-onset PD, DM or PD/DM in AP patients. Meta-analysis was performed using the random-effects model to calculate pooled odds ratios (OR) with 95% confidence intervals (CI).

Results: Of the 45 studies identified, 36 were included in the meta-analysis covering 71,367 participants. The odds of developing DM was significantly higher after severe AP (OR: 2.65; CI: 1.23-5.71) than non-severe, alcoholic AP (OR: 1.95; CI: 1.03-3.67) compared to other aetiologies and if pseudocysts developed (OR: 2.50; CI: 1.00-6.28) versus their absence. The odds of developing PD/DM was significantly higher after severe AP (OR: 3.16; CI: 1.13-8.83) than non-severe, severe and moderate AP (OR: 4.66; CI: 2.24-9.68) versus mild and presence of necrosis (OR: 5.53; CI: 1.59-19.21) versus its absence. Compared to other aetiologies there was a tendency for PD/DM development in hypertriglyceridaemic AP (OR: 3.27; CI: 0.84-12.67) and significantly lower odds of developing DM (OR: 0.61; CI: 0.44-0.85) and PD/DM (OR: 0.72; CI: 0.55-0.94) with idiopathic and biliary aetiology, respectively.

Conclusion: Severe and moderately severe AP, local complications, alcoholic and hypertriglyceridaemic aetiologies may be linked to a higher odds of developing PD or DM.

P-04-43

SARS-CoV-2 infection of the pancreas is dependent on host factor PLAC8

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Abstract

Although COVID-19 initially caused great concern about respiratory symptoms, most patients manifest gastrointestinal symptoms and mounting evidence shows that both the endocrine and exocrine pancreas are productively infected by SARS-CoV-2. However, prevalence and severity of pancreatic COVID-19 infection as well as its pathophysiology, are still under debate.

In pancreatic tissue from COVID-19 postmortem examinations, we found an important SARS-CoV-2 viral infiltration in both endo and exocrine compartments. We studied plasma from a retrospective cohort comprising 120 patients distributed in 3 severity-stratified groups according to the WHO ordinal scale. We found that the circulating levels of pancreatic damage biomarker PNLIP stratified patients according to COVID-19 severity and correlated with inflammatory biomarkers typically used in the clinic highlighting a relevant COVID-19-related pancreatic pathogenesis.

In a previous CRISPR-Cas9 screening we identified PLAC8 as an essential host factor required for SARS-CoV-2 lung infection. Since PLAC8 has been described in pancreatic tumourigenesis, here we investigated the role of this protein in COVID19-linked pancreatic pathophysiology.

Analysis of pancreatic autopsy tissue from COVID-19 patients showed that PLAC8 exhibited a significantly higher expression in COVID-19 patients than in uninfected controls ($p<0.05$) and co-localized with SARS-CoV-2-N in islets and acini.

To study the direct role of PLAC8 in SARS-CoV-2 infection, we generated PLAC8 knock-out by 2 sgRNA CRISPR/Cas9 in a panel of human pancreatic cancer cell lines. We performed functional infection studies by infecting the KO cells with a Spike-typed pseudovirus model comprising Wuhan-1, BA1 and BA4/5 variants of concern. We found that PLAC8 loss-of-function abolished infection of all SARS-CoV-2 variants. Importantly, these effects were completely rescued by ectopically expressing CRISPR-resistant GFP-fused versions of the protein on the KO cell lines.

We further confirmed the effect of PLAC8 loss-of-function using full SARS-CoV-2 infectious virus inoculum from Wuhan-1 and BA.1 strains. Consistently with our results, PLAC8 KO caused a striking reduction in the number of infected cells 24 h p.i. in both KO cell lines tested, compared with control cells. When we evaluated the replicative capacity by analysing infectious viral titres in the respective supernatants, the results showed that productive viral replication in was almost impaired by loss-of-function of PLAC8.

P-04-44

Can serum gasdermin D level predict severity of acute pancreatitis?

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Abstract

Background: Acute pancreatitis (AP) is a clinical picture characterised by uncontrolled enzymatic activity in the acinar cells of the exocrine pancreas resulting in inflammation and tissue damage. Disease prognosis varies greatly between patients and several scoring modalities are used to predict the outcome.

Gasdermin family is a protein family consisting of molecules partaking in physiological pathways such as cell differentiation, coagulation, inflammation and cell death. A specific subtype of gasdermin, gasdermin D (GSDMD), is a pore forming protein in the caspase system; resulting in inflammation and cell death. GSDMD levels are shown to go up in various disorders associated with inflammation such as non-alcoholic steatohepatitis and inflammatory bowel disease. In this study we planned to compare GSDMD levels of AP patients with healthy controls to identify a potential candidate molecule to predict the severity of AP.

Methods: Fifty-three patients diagnosed with AP and a control group consisting of 49 healthy adults were enrolled in the study. Serum GSDMD levels of patients were studied with Human Gasdermin ELISA kits (SunRed Biotechnology) and the results were given as ng/ml. AP patients were classified by Atlanta classification, Ranson score, BISAP, CTSI and Modified Glasgow-Imrie score. Intensive care unit (ICU) admission and mortality rates were also recorded and compared with serum GSDMD levels.

Results: The median GSDMD level was 3.73 ng/ml (2.97-5.2) in the control group and 4.01 ng/ml (3.49-4.64) in the AP group but this difference was not statistically significant. GSDMD levels were compared with all the aforementioned scoring system results of patients, as well as ICU admission and mortality rates. No statistically significant relationship was found with any of the parameters taken into account in the study, in contradiction to some studies in the literature.

Conclusion: GSDMD, as well as the whole gasdermin family, is a novel and promising target as both a biochemical marker and a potential therapeutic target. Future studies with higher numbers of study populations should reveal more about the role of this protein family in various inflammation-driven disorders.

P-04-45

The role of magnesium in acute pancreatitis & pancreatic injury: a systematic review

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Abstract

Background: As natural calcium-antagonist, magnesium (Mg) seems to counteract calcium (Ca) signalling pathways involved in the intracellular protease activation leading to acute pancreatitis. We systematically reviewed the current literature to investigate the role of Mg in the pathogenesis of acute pancreatitis and its possible use in detecting, predicting, and preventing acute pancreatitis.

Methods: A systematic search was performed in PubMed/Scopus/Web of Science to identify in vivo and in vitro

studies reporting data on Mg in acute pancreatitis.

Results: Twelve studies were included. Due to their heterogeneity, we conducted a review without intent of inference. Mg deficiency in pancreatic acinar cells seems to be frequently associated with serum hypocalcaemia and acute pancreatitis. Mg seems to contrast intracellular Ca accumulation, which induces the premature enzyme activation and acute pancreatitis. Several in vitro and in vivo experiments, included a randomised controlled trial, showed beneficial effects of Mg supplementation in counteracting Ca signalling pathways and subsequent pathological events.

Conclusion: Mg is a natural antagonist of Ca signalling pathways and, when deficient, predisposes to acute pancreatitis. Mg supplementation may be useful to prevent acute pancreatitis in many contexts, such as post-ERCP or after pancreatic surgery.

P-04-46

Visceral arterial pseudoaneurysms in acute necrotizing pancreatitis - a single-centre retrospective study

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Abstract

Background: Visceral artery pseudoaneurysm (VAP) is a rare complication of acute necrotizing pancreatitis (ANP) and pancreatic surgery associated with a lethal prognosis. Our aim was to determine risk factors in patients with ANP complicated by VAP.

Methods: A retrospective analysis of data evaluated patients with acute necrotizing pancreatitis treated at the Department of General Surgery No. 1 in the period from 2018 to 2022.

Results: The data of 107 patients were studied and a group of 6 patients (5.6%) with the course complicated by VAP was identified. In 4 (66.6%) cases with pancreatic necrosis of the pancreatic body and tail >50%, there was a pseudoaneurysm of the splenic artery and in 2 (33.3%) cases with pancreatic necrosis of the pancreatic head and body >50% - a pseudoaneurysm of the gastroduodenal artery. 2 cases with pseudoaneurysm of the splenic artery were treated endovascularly. One case (16.6%) of splenic artery pseudoaneurysm was fatal - the patient was readmitted one week after treatment of an episode of acute pancreatitis. Other cases required surgical intervention due to rupture and active bleeding into the abdominal cavity or cyst cavity, Grade C according to the ICGPS classification [3].

The average time from admission to diagnosis was X=36.3±3.83 days.

In 73 (68.2%) cases of ANP, the percentage of pancreatic necrosis was more than 50% (6 points on the CTSI Balthazar scale). Among 6 patients, 3 (50%) underwent drainage of acute necrotic collections, and 2 (33.3%) patients had Grade B pancreatic fistula – Disconnected pancreatic duct syndrome (DPDS).

Conclusion: Vigilance in this category of patients is critical for the early diagnosis and treatment. Possible found risk factors in this study were: pancreatic necrosis >50%, the presence of the DPDS – pancreatic fistula, the duration of the disease >32,47days, contamination of the pancreatic and parapancreatic necrosis. Further studies with a larger group of patients are needed to obtain statistically significant results.

P-04-47

The impact of a multidisciplinary team evaluation on the diagnosis and management of acute and chronic pancreatitis in a tertiary referral centre

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Abstract

Background: Multidisciplinary team meetings (MTM) have been adopted widely to ensure that oncological patients receive an optimal diagnosis, staging and treatment, especially in tertiary referral centres. The relevance of MTM on acute and chronic pancreatitis is unexplored. The aim of this study is to describe the experience of a tertiary referral centre MTM for pancreatic diseases in the management of patients with acute and chronic pancreatitis (AP/CP).

Methods: A prospectively maintained database of patients with AP/CP discussed in MTM from 10/2020 to 01/2023 was queried and patients analysed according with the subsequent clinical problems: aetiology of AP (EAP), treatment of AP complications (TAP), aetiology of chronic pancreatitis (ECP) and treatment of chronic pancreatitis complications (TCP).

Results: Globally 143 patients were included for a total of 201 discussions. 94 were AP and 49 CP (median/IQR age 55/43-68 years; males 58.3%). According with the established clinical questions:

- EAP (67 patients): the hypothesized aetiology before MTM discussion was in most cases autoimmune (64%) or idiopathic (18%). Imaging revision alone at the MTM changed the suspicious aetiology in 28%. After performing further investigations suggested by the MTM the final diagnosis was changed in additional 39% (3 overlooked cancers diagnosed).

- TAP (27 patients): mostly referred for pseudocysts (37%), management of complications in anatomical variants (17%), walled-off necrosis (13%). The problem was solved in 100% of cases, mostly by surgical (33%) or endoscopic (48%) treatments.

- ECP (14 patients): MTM changed the initial suspicion in 50% of cases, with previously unexplored genetic aetiology in 64% of cases. 50% of initially idiopathic CP cases had a definite aetiology.

- TCP (35 patients): mostly referred for appearance of focal lesion in CP (22%), pancreatic duct obstruction/stenosis (28%) or abdominal pain (28%) with resolution of the problem in 98% of cases by surgical (53%) or endoscopic (17%) treatments. Three malignant lesions were diagnosed.

Conclusion: Our observational study shows that a MTM conducted in tertiary referral centre for pancreatic diseases

allows to correctly establish aetiology and treat complications in AP and CP. A high rate of previously overlooked malignancies were diagnosed and genetic defects identified.

P-04-48

External pancreatic fistula as a risk factor for erosive complications in patients with infected walled-off necrosis

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Abstract

Background: One of the dangerous complications of acute pancreatitis (AP) is extraluminal bleeding, occurring because of pancreas necrosis (PN) and caused by vascular wall erosion of the peripancreatic artery.

Methods: A retrospective case-control study of 160 patients who underwent surgical interventions. Inclusion criteria: patients with infected AP who needed intervention. The median period of pancreatic necrosis infection was 12.5 (10 - 15) days of the disease. All patients underwent interventional treatment methods aimed at foci elimination of pancreatic infection (PI), including sonographically controlled percutaneous drainage interventions as the final method of walled-off necrosis treatment used in 15 (9.4%) patients, necrosectomy in 145 (90.6%).

Results: External pancreatic fistula (EPF) was diagnosed from 8th to 38th day of the disease, the appearance (QI - QIII) was 29(24 - 31) days. 76(47.5%) patients had EPF. The average time interval between disease onset and fistula diagnosis was 20.6±1.4 days. EEB (erosive extraluminal bleeding) developed in 4 out of 9 patients on average of 53.5±13.2 days. EEB was observed after discharge from the hospital in 5 out of 9 on average 524±22.4 days after AP onset, complicated the disease in 9 patients (5.6%). The course was complicated by EEB in 8 patients with EPF, EEB was observed in 1 patient without EPF.

A statistically significant difference in the development of EEB frequency was found in patients with EPF in comparison with no EPF ($p = 0.026$, $\chi 2$ criterion). The absolute risk (AR) of EEB development in patients with an existing EPF was 10.5% (95% CI4.6 – 18.5%), without - 1.2% (95% CI0.2 – 4.7%). Statistical differences ($p = 0.02$) in the two groups indicate a 9.3% (95% CI2.1 - 18.3%) increase in the AR of EEB occurrence in patients with EPF. The conducted analysis confirmed that EPF in patients with AP can lead to the development of EEB (HR8.8 (95% CI1.2 - 69.1, $p = 0.02$)).

Conclusion: The conducted study allows to regard as a risk factor for the EEB development the EPF presence in patients with ANP. The EEB risk, in case the disease course complicated by EPF, increases 9 times compared to patients with no EPF.

P-04-49

Admission risk factors and predictors of moderate or severe paediatric acute pancreatitis: a systematic review and meta-analysis

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Abstract

Background: Paediatric acute pancreatitis (PAP) has an increasing incidence and is now estimated to be almost as common as in adults. 20-30% of PAP patients will have a moderate or severe disease course (M/SPAP), characterised by organ failure, local or systemic complications. There is still no consensus regarding on-admission severity prediction in these patients. Our aim was to conduct a systematic review and meta-analysis of available predictive score systems and parameters, and differences between on-admission parameters in mild and M/SPAP.

Methods: We conducted a systematic search on the 14th February, 2022 in MEDLINE, Embase and CENTRAL. We performed random-effects meta-analysis of on-admission differences between mild and M/SPAP in laboratory parameters, aetiology, demographic factors, etc. calculating risk ratios (RR) or mean differences with 95% confidence intervals (CI) and created forest plots. For the meta-analysis of predictive score systems, we generated hierarchical summary receiver operating characteristic curves using a bivariate model. Chi-squared tests were performed and I2 values calculated to assess statistical heterogeneity.

Results: Forty-five studies – mostly retrospective cohorts – were eligible for inclusion. Among predictive score systems examined by at least 5 studies, the modified Glasgow scale had the highest specificity (91.5% for values ≥3), and the Paediatric Acute Pancreatitis Severity score the highest sensitivity (63.1% for values ≥3). The performance of other proposed score systems and values were summarised. Traumatic (RR: 1.70 95% CI: 1.09-2.67) and drug-induced (RR: 1.33 95% CI: 0.98-1.87) aetiologies were associated with a higher rate of M/SPAP, while anatomical (RR: 0.6195% CI: 0.38-0.96) and biliary (RR: 0.72 95% CI: 0.53-0.99) PAP tended to be less severe.

Conclusion: Many predictive score systems were proposed to assess the possibility of M/SPAP. While the most common ones exhibit good specificity, all have subpar sensitivity. Our systematic review provides a rigorous overview of predictive options assessed thus far, that can serve as a basis for future improvement of scores via the addition of parameters with a better observed sensitivity: e.g. lipase exceeding 7-times the upper threshold, haemoglobin, etc. The addition of etiological factors is another possibility, as they can herald a more severe disease course.

P-04-50

Drug associated acute pancreatitis: a systematic review of clinical and preclinical evidence

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Abstract

Background: To identify and classify drugs associated with acute pancreatitis (AP) through comprehensive analysis of all clinical and preclinical data.

Methods: Ovid Medline, Web of Science, EMBASE, and the Cochrane Library were searched using an a priori search strategy from database inception to May 2021 for all relevant studies of drug associated acute pancreatitis (DAAP). Case reports, prospective clinical trials reporting AP as adverse events, epidemiological studies on DAAP, and experimental studies of drug-induced pancreatic toxicity were included for data synthesis. Two reviewers independently

conducted study inclusion. All data, not just case reports as in previous studies, were used to develop a classification system for the implicated drugs.

Results: In total, 15,892 studies underwent title and abstract screening, of which 3455 studies underwent full text assessment. Of these, 712 case report studies (832 cases), 339 prospective clinical trials, 311 epidemiological studies, and 80 experimental studies were included for data synthesis and analysis. Using all data sources, 436 drugs showed a positive association with AP. Case reports identified 90 drugs with positive rechallenge data, of which 55 were Class Ia, and 45 Class Ib drugs. Clinical trial data revealed anti-cancer drugs, monoclonal antibodies, antivirals, and immunosuppressants to be associated with significantly increased relative risks of DAAP. Preclinical data showed 35 drugs exhibited direct pancreatic toxicity causing histological damage. Novel classification categories were developed for drugs identified in clinical trials, epidemiological studies, and experimental data. The classification system scored each drug in each of the four study types to generate total scores. Among the 436 drugs implicated in DAAP, 31 drugs scored strong likelihood, 118 drugs scored moderate likelihood, and 287 scored weak likelihood by the classification system. Azathioprine, L-asparaginase, didanosine, valproate, and methylprednisolone were the top 5 drugs revealing the strongest likelihood of DAAP.

Conclusion: This comprehensive systematic review has used all major data sources, not just case reports, to evaluate evidence of many drugs implicated in DAAP. A novel classification system is proposed that incorporates all these data sources and has potential to be applied to other types of drug associated organ injury.

P-04-51

Pancreatitis-induced duodenal wall enlargement and gallbladder perforation. A disguised association?

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Abstract

Background: Acute cholecystitis may progress to gangrenous disease and to gallbladder perforation, which may be triggered by infection or increased intraluminal pressure. Fail to notice acalculous cholecystitis in the setting of severe pancreatitis may result in serious deterioration of patient clinical condition if perforation occurs.

Methods: We describe the clinical features of patients with pancreatitis-induced duodenal stenosis due to chronic pancreatitis or to severe acute groove pancreatitis that developed unexpected gallbladder perforation from 2018 to 2022.

Results: Five patients (3 female/2 male; 38-75 years-old) fulfilled inclusion criteria. Three patients were heavy smokers and two had relevant ethanol consumption. Two patients had diabetes mellitus. None of the patients carried gallstones on imaging (US and/or MRI) at hospital admission. Four patients had clinical and morphological features consistent with acute pancreatitis complicated by groove pancreatitis, and the other patient showed increased duodenal wall thickness and duodenal stenosis. Three of these patients had experienced previous bouts of acute groove pancreatitis. Duodenal-pancreatic disease usually emerged way before gallbladder perforation. In three patients severe acute pancreatitis onset preceded perforation for more than 25 days. Patient critical conditions and limited bile duct dilation masked gallbladder involvement despite its progressive increment in diameter (9.7 +/- 0.6 cm) before disruption. Liver biochemistry was markedly altered in four patients. Blood cultures yielded E. Coli or Enterococcus sp in two patients. Patients were treated with supportive measures, antibiotics and invasive treatment: biliary stent-

ing (1), percutaneous cholecystostomy (1) or surgery (3). Morphological evaluation of resected gallbladders showed acute acalculous cholecystitis with wall necrosis. No patient died at the present episodes

Conclusion: Acalculous cholecystitis may develop during the course of severe pancreatitis with duodenal wall enlargement, and may progress unnoticed towards perforation in critically ill patients. Infection and increased luminal pressure may be contributing factors. Groove pancreatitis may be considered a predisposing condition for acalculous cholecystitis and gallbladder perforation.

P-04-52

Impact of gut decontamination by rifaximin in patients with predicted severe acute pancreatitis: a pilot study

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Abstract

Background: Gut decontamination could have some benefits in preventing infectious complications in acute pancreatitis (AP). The majority (~80%) of cases with Acute Pancreatitis follow a mild, self-limited, and an uncomplicated course. About 20% cases develop necrosis of the pancreatic and/or peri-pancreatic tissue (necrotizing pancreatitis). Most patients hospitalised to KIMS belong to this category. Most common route for infection of pancreatic necrosis is translocation of intestinal flora due to intestinal barrier failure, which occurs during 2-3 weeks. Infection of pancreatic necrosis is associated with high mortality of 30-39%. We studied the effect of rifaximin in preventing infection of pancreatic necrosis and mortality in patients of predicted severe acute pancreatitis.

Methods: Study design: Randomised control open label study

Place of Study: Department of Medical Gastroenterology, KIMS, Bhubaneshwar

Duration of study: 2 years

Sample size: 50 cases in each arm of study trial

Results: A significant difference was observed between median durations of hospitalization between the groups rifaximin vs placebo treatment .However, there was no statistically significant difference between the R1 and R0 group in terms of mortality rate.

Conclusion: The results indicate that rifaximin seems to be a promising novel therapeutic option in severe acute pancreatitis.

P-04-53

Bacterial infections during acute pancreatitis occur due to amphipathic liponecrosis

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Abstract

Background: The current studies were done to understand the mechanisms by which infections develop during sterile illnesses like acute pancreatitis (AP). Normally, transient bacteraemia commonly develops during dental ex-

tractions and endoscopic procedures like oesophageal dilations. However, this bacteraemia is promptly cleared. Therefore, bacterial translocation alone may not be sufficient to cause infections during AP. This suggests that the role of impaired bacterial clearance be examined during development of infections in AP.

Methods: We analysed admission blood samples of AP patients and compared them to normal controls. AP patients were characterised as being infected based on isolated organisms, diagnosed sepsis, or requirement of antibiotics for a suspicion of infection. Sample of rodents with caerulein, IL12+IL18 AP or those administered different non-esterified fatty acids (NEFA) were also analysed. The parameters included circulating albumin unbound-NEFA concentrations, the microbiome, and inflammatory cell injury. Uptake of unbound-NEFA into macrophages was studied using a novel fluorescent NEFA, along with studies on phagocytosis and mitochondrial function. The interactions of NEFA and membrane phospholipids (e.g., phosphatidylcholine; PC) were studied on isothermal titration calorimetry (ITC)

Results: Infected AP patients had higher serum unsaturated NEFA, unbound-NEFA including linoleic acid (LA) and oleic acid (OA), bacterial 16S DNA, increased annexin V positive myeloid (CD14) and CD3+ cells and mitochondrial DNA than non-infected ones. AP in general reduced alpha-diversity, altered beta-diversity, and enriched *Pseudomonadales*. Changes in infected AP were also noted in rodents with unbound unsaturated-NEFA. Unbound-LA interacted progressively stronger with PC, cardiolipin and albumin than with aqueous media on ITC. Unbound-NEFA uptake into cells enriched them in mitochondria, which depolarized, and induced voltage dependent anion channel oligomerisation, while reducing ATP, and impairing phagocytosis. In-vivo unbound-LA, OA increased bacteria in the circulation and pancreas, and impaired phagocytosis, resulting in infection. LA, OA showed greater effects than the hydrophobic palmitic acid.

Conclusion: Excessive release of NEFA in AP can increase unsaturated albumin unbound-NEFA. Their cellular uptake via membrane phospholipids can cause immune cell amphipathic liponecrosis. This can impair phagocytosis and bacterial clearance, which can result in a sterile to septic transition. This can cause infection during sterile inflammation like AP.

P-05-01

Extra-pancreatic manifestations in pancreatitis - an international survey report

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Abstract

Background: Many local and systemic manifestations have been reported in association with pancreatitis, anecdotally. However, prevalence data and systematic collection is lacking on the symptoms and diagnoses patients with pancreatitis experience that are extra pancreatic in origin. The aim of this study is to determine the prevalence of symptoms and diagnoses reported by a cohort of patients with pancreatitis.

Methods: Cross-sectional study approved by the Institutional review board and administered through a REDCap survey from April to May 2022. Survey was administered through the social media platform of a non-profit organization "Mission Cure" dedicated to the care of individuals with pancreatitis.

Results: We had 225 respondents: mostly adults, 69% females, 89% Caucasians with 74% residing in the USA. 42% of paediatric cohort and 50% of adults reported exocrine pancreatic insufficiency while 8% of paediatric cohort and 26% of adults reported DM. Type 3c DM was present in all paediatric cases and 45% of adult DM cases.

Nearly 45% of the adult respondents reported night-time sweating but this was reported in about 13% of children (p=0.002). Other symptoms frequently reported by respondents included brittle nails in 32% of the cohort (33% of adults, 25% of children), brittle hair (32% of cohort; 33% adults, 21% children), hair loss (29% of cohort; 31% adults, 13% children) and dry eyes (35% of total cohort; 37% of adults, 17% children). Although, many respondents had dry eyes; diagnosis of Sjögren's syndrome was rare in 3.1% of the cohort; all adults. Iron deficiency anaemia was frequently reported in 25% of adult respondents and 18% of children. Hypothyroidism was reported in 9.3% of the cohort, Raynaud's syndrome in 4% and celiac disease in 3.1%.

Conclusion: Patients with pancreatitis frequently report symptoms not known to be associated with pancreatitis. Studies investigating mechanisms for these associated symptoms should be explored.

P-05-02

Clinical evaluation of dynamic interfacial tensiometry in patients with chronic pancreatitis (CP)

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Abstract

Background: The human organism contains interfaces with enormous surfaces. Their physicochemical and biochemical processes are important for the vital functions of the organism. The interfacial properties reflect peculiarities of age, sex, health, and disease. Human biologic liquids contain low- and high-molecular surfactants, which are absorbed at liquid interfaces. The dynamic and equilibrium properties of any liquid interface are determined by the composition of the respective interfacial layers. Interfacial tension, dilatational viscosity, and elasticity depend on the interfacial composition. The components in liquid bulk phases should be measured by these properties. Surfactants (pancreatic enzymes, proteins, lipids, carbohydrates, electrolytes, etc.) in biological liquids like blood, urine, and pancreatic secretion change significantly in patients with CP. These changes affect the physicochemical properties of the biological liquids and can be detected using interfacial tensiometry and rheometry. The blood levels of substances with surfactant properties are changed in CP. We aimed to evaluate the diagnostic significance of the dynamic interphase tensiometry of blood in CP.

Methods: We examined 65 patients with CP and 68 healthy individuals. Before and after treatment, biochemical and immunological tests on the blood were done, as well as interphase tensiometry. The dynamic surface tension of blood serum was studied by the computer tensiometer MRT-2 Lauda (Germany). ST1 (t=0.01s), ST2 (t=1s), ST3 (balance ST, $t \rightarrow \infty$), and the angle of curved line inclination (ACLI) of the tensiogram were registered.

Results: ST1 in CP patients increased to 71.7±0.6 mN/m (70.0±0.4 mN/m in healthy), while ST3 decreased to 56.1±1.1 mN/m (60.0±0.4 mN/m in healthy). ST1 and ST2 levels in CP patients were affected by blood lipase activity (r=+0.58 and r=+0.60, respectively), while ACLI was affected by blood amylase activity (r=-0.66), IgG levels (r=+0.56), and circulating immune complexes (r=+0.58). ST1 and ST3 became normal in cases of improvement after CP exacerbations. Argumentative outcomes were observed in different sex groups of CP patients: women had higher ST2 and ST3 levels and lower ACLI levels than men.

Conclusion: Dynamic interphase tensiometry can be used for the integral estimation of biochemical and immunological changes in CP patients and for the control of treatment efficiency.

P-05-03

Rate and rehabilitation options in patients with post-gastric resection chronic pancreatitis

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Abstract

Background: Post-gastric resection chronic pancreatitis (PGRCP) is one of the pathogenetic types of chronic pancreatitis. PGRCP pathogenesis is studied insufficiently. Thus, we studied the excretory pancreatic function in patients after gastric resection to analyse the options of antihomotoxic therapy in the rehabilitation of patients.

Methods: We examined 52 patients who underwent gastric resection due to complicated gastric or duodenal ulcers in 1–12 years prior to our study. Forty of them had Billroth's operation II, and twelve had Billroth's operation I. Faecal elastase-1 levels were assessed. After discharge from the hospital, those patients were administered a combination of antihomotoxic preparations, such as Nux vomica-Homaccord, Mucosa compositum, and Momordica compositum (Heel, Germany), for one month (in addition to enzyme replacement therapy).

Results: After Billroth II, excretory pancreatic function decreased in 32 patients (80%). Faecal elastase-1 levels were normal in 8 patients (20%) and decreased (not less than 150 mcg/g) in 24 patients (60%); this meant mild pancreatic insufficiency. Five patients (12.5%) had levels of faecal elastase-1 between 100 and 150 mcg/g. This meant that they had moderate pancreatic insufficiency. Three (7.5%) patients who had gastric resection more than 8 years before our study were found to have moderate to severe disorder of pancreatic function. Most of them had chronic pancreatitis before the operation.

After Billroth I, excretory pancreatic function was decreased in 9 patients (75%). Faecal elastase-1 levels were normal in 3 patients (25.0%). Mild pancreatic insufficiency was found in 7 patients (58.4%), while moderate and severe insufficiency — in 1 and 1 patient, respectively (8.3% and 8.3%).

Antihomotoxic therapy was effective for rehabilitation in PGRCP. It helped reduce the clinical manifestations of the disease and the "deviation" of enzymes into the blood, improved the excretory pancreatic function and the mental health of the patients.

Conclusion: Reduction of excretory pancreatic function occurs in patients after gastric resection, predominantly of mild or rarely moderate to severe grade of pancreatic insufficiency. It is reasonable to include antihomotoxic drugs in complex therapy for rehabilitation.

P-05-04

A clinical case of severe drug-induced pancreatic and hepatic steatosis

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Abstract

Background: We present a case of pancreatic steatosis during long-term therapy with corticosteroids and the intake of gemcitabine and rosiglitazone. We could not find anything in the available literature about how paracetamol and metamizole might cause pancreatic and hepatic steatosis to start. We present a clinical case of pancreatic and

hepatic steatosis caused by long-term use of the analgesic Pentalgin.

Methods: A 56-year-old patient, L., came for an outpatient appointment. For about 10 years, she has been taking 2–3 Pentalgin tablets daily because of headaches. Pentalgin is a combination drug that contains 300 mg of paracetamol, 300 mg of metamizole sodium, 50 mg of caffeine, 10 mg of phenobarbital, and 8 mg of codeine phosphate. It should be mentioned that the patient is a radio engineer who has worked for many years at the Chernobyl nuclear power plant.

Results: The patient complained of severe general weakness, dizziness, and swelling of the legs and feet. These complaints first appeared about a year ago and gradually increased.

Objective examination revealed severe pallor of the skin and mucous membranes, small haemorrhages on the mucous membranes, and swelling of the legs and feet. The palpated liver was sharply enlarged (the lower edge in the small pelvis), dense, and painless. Laboratory study: severe anaemia, an increase in GGTP of 68 times with normal transaminases. Faecal elastase — 56 mcg/g. Severe hyperproteinaemia and hypoalbuminemia. A significant increase in blood urea and creatinine. Neurologist: encephalopathy of toxic origin. MRI: diffuse hepatic and pancreatic steatosis.

Diagnosis: drug-induced hepatic and pancreatic steatosis. Chronic toxic hepatitis. Severe exocrine pancreatic insufficiency. Toxic nephropathy, chronic kidney disease, stage IV. Toxic encephalopathy.

Pentalgin was withdrawn. A 50,000 FIP mini-microspheric enzyme preparation was given three times a day at main meals and 25,000 FIP at intermediate meals (therapy contributed to the disappearance of oedema and an increase in total protein and blood albumin); hepatotropic therapy. Treatment was administered by a nephrologist and a neurologist.

Conclusion: Prolonged use of paracetamol and metamizole can cause pancreatic and liver steatosis and toxic nephropathy.

P-05-05

Morphological and functional changes in the small intestinal mucosa in chronic pancreatitis

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Abstract

Background: Due to the progressing exocrine pancreatic insufficiency, intestinal dysbiosis and, further, secondary enteritis, occur in patients with chronic pancreatitis (CP). Inflammation of the small intestinal mucosa causes maldigestion and malabsorption. Atrophy of the small intestinal mucosa is a reason for the reduced efficacy of enzyme replacement therapy. We aimed to study morphological changes and enzymatic indices of small intestinal digestive function in patients with CP.

Methods: We examined 45 patients with CP. An aspiration biopsy of the mucous membrane of the first part of the small intestine was carried out. Then, amylolytic (by Smith-Roe method) and lipolytic (by Ugolev-Nurks method) enzymatic activity, the activity of lactase (by Linevsky method), saccharase (by Ugolev-Iezuitova method), maltase (by Linevsky method), glycine-L-leucine dipeptide (by Ugolev-Timofeeva method), monoglyceride lipase (by Ugolev-Chernyakhovskaya method), and alkaline phosphatase (by Fomina-Mikhlin method) were examined in the homogenate of mucosa samples. An absorptive function of the small intestine was evaluated by the D-xylose test. A

bacteriological culture of the jejunal contents was performed.

Results: Histological examination of the jejunal mucosa revealed villi epithelial dystrophy with marked leucopedesis, chronic jejunitis with varying degrees of atrophy, and significant inflammation.

According to the D-xylose test results, the small intestine's absorptive function was low.

Amylolytic and lipolytic activities of the membrane were elevated, and a reduced production of monoglyceride lipase was detected. An increased production of saccharase, a reduced level of glycine-L-leucine dipeptide in mucous membranes, and a rise in alkaline phosphatase contents were revealed. As a result of unusual microorganisms in the small intestine, bacterial proliferation was found in 66.7% of cases.

Conclusion: Secondary disorders of small intestine's enzymatic production occur (compensatory increase or decrease due to mucosal atrophy) in CP patients along with a reduction of intestinal mucosa absorptive function. The disorders observed in the small intestine should be taken into account in the management plan for patients with CP.

P-05-06

Glycaemic control and influencing factors among patients with post-chronic pancreatitis diabetes mellitus

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Abstract

Background: Glycaemic control is a top priority in all types of diabetes. Longer periods of exposure to hyperglycaemia are associated with increased microvascular events and increased mortality risk. Post-chronic pancreatitis diabetes mellitus (PPDM-C) is one of the less commonly evaluated complications of chronic pancreatitis (CP). The factors that influence glycaemic control in PPDM-C patients remain unclear. Hence, we aimed to identify these factors to guide the management of PPDM-C.

Methods: We conducted a retrospective study in PPDM-C patients admitted to our centre between January 2018 and September 2021, with the glycated haemoglobin A1c (HbA1c) evaluated upon admission. Poor glycaemic control was defined as an HbA1c level of >7%. Univariate and multivariate logistic regression analyses were performed to identify the influencing factors.

Results: Of the 224 PPDM-C patients, 61.2% had poor glycaemic control. On univariate analysis, the interval from the onset of CP to the development of diabetes and provision of interventional treatment, drinking, smoking, acute pancreatitis (AP) attack history, and oral hypoglycaemic agent (OHA) use were associated with glycaemic control. On multivariate analysis, smoking (0–20 pack-years, odds ratio [OR]: 4.11, 95% confidence interval [CI]: 1.58–10.67; >20 pack-years, OR: 9.55, 95% CI: 3.13–29.19) and AP attack history (OR: 2.25, 95% CI: 1.15–4.42) were independently associated with poor glycaemic control. OHA use (OR: 0.26, 95% CI: 0.12–0.59) was an independent protective factor.

Conclusion: Smoking and AP attack history were independent risk factors for poor glycaemic control in PPDM-C patients, and the detrimental effects of smoking were dose dependent. OHA use reduced the risk of poor glycaemic

control. Therefore, smoking cessation is very important for PPDM-C patients, and those with AP attack history may require early detection and timely diabetes treatment. Our results lay a theoretical foundation for future blood glucose management in PPDM-C patients.

P-05-07

The Indian translation of the comprehensive pain assessment tool short form for chronic pancreatitis (COMPAT-SF)

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Abstract

Background: The COMPAT-SF is a validated questionnaire for assessing pancreatic pain. However, until now, it has only been available in English and Danish. This study has translated the questionnaire into three Indian languages, Hindi, Telugu, and Bengali, to enable non-English speaking patients to complete the questionnaire. As there is a lack of validated pain assessment tools for pancreatic pain, constructing the COMPAT-SF into several languages is essential.

Methods: The COMPAT-SF was translated into Hindi, Telugu, and Bengali and back-translated to English by bilingual translators. Analysis showed >85% concordance between the original English version and the back-translated forms from the regional languages.

Eighteen bilingual chronic pancreatitis patients answered the COMPAT-SF questionnaire in Hindi and English, with 14 days in between. Differences were evaluated using intraclass correlation coefficients and Bland-Altman plots.

Fifteen chronic pancreatitis patients answered the Telugu questionnaire, and 30 answered the Bengali questionnaire. Answers from all three Indian languages were compared with answers from 92 English-speaking chronic pancreatitis patients. Confirmatory Factor Analysis was performed to ensure the overall validity of the translated questionnaires.

Results: Bland-Altman plots generally showed acceptable limits of agreements in all sub-scores (limits of agreement average at -18 to 18 with a mean difference of -0.091). In addition, the intraclass correlation coefficients were generally substantial or better (intraclass correlation coefficient of 0.83 or higher). The comparison of answers revealed expected cultural differences, but they were overall comparable. Confirmatory factor analysis showed an acceptable model fit on all indices.

Conclusion: Comparing the Hindi and the original versions of the COMPAT-SF revealed high comparability. The Telugu and Bengali versions show an acceptable fit in confirmatory factor analysis. The Indian versions of the COMPAT-SF are therefore deemed valid and reliable.

P-05-08

One episode of acute pancreatitis is just the beginning: the incidence of recurrent acute and chronic pancreatitis: a systematic review and meta-analysis

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Abstract

Background: Acute pancreatitis (AP) has a high incidence, and patients can develop recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP) after AP. We aimed to estimate the pooled incidence rates (IR), cumulative incidences, and RAP and CP proportions after AP.

Methods: Our protocol was registered on PROSPERO (CRD42021283252). The systematic search was conducted in three (Medline, Embase, Cochrane) databases on October 25th, 2022. Articles reporting the proportion of RAP or CP in patients after the first and multiple episodes of AP were eligible. IRs were calculated from articles reporting the mean follow-up time. The random effects model was used to calculate the pooled IR with 95% confidence intervals (CI). The I^2 value assessed heterogeneity. The risk of bias assessment was conducted with the Joanna Briggs Institute Critical Appraisal Tool.

Results: We included 106 articles in the quantitative synthesis and 26 in the IRs calculations. Our results showed that the incidence rate of RAP in adult patients after the first episode of AP was 5.5 per 100 person-years (CI: 4.1 to 7.3; I^2=93%), while in children, it was 3.7 per 100 person-years (CI: 2.8 to 5.0; I^2=0%). We also found that the IR of CP after the first episode of AP was 1.4 per 100 person-years (CI: 0.9 to 2; I^2=75%), while after RAP, it increased to 4.3 per 100 person-years (CI: 3.1 to 6.0, I^2=76%). The risk of bias was low in the majority of the included studies.

Conclusion: Our results showed that RAP affects many patients with AP. Compared to patients with the first AP episode, RAP leads to a threefold higher incidence rate for developing CP.

P-05-09

Age aspect of the immune status of patients with chronic pancreatitis

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Abstract

Background: Among the negative consequences of constant stressful exposure in patients with chronic pancreatitis (CP), immune deficiency develops, which may differ in different age periods. Thus, we studied and analysed the state of the immune system (IS) of patients with CP in the age aspect.

Methods: We studied the IS parameters of 161 patients with CP, with an average age of (58.17±2.46) years, which

were divided depending on the biological age into three groups: up to 45 years (54 patients), 46-65 years (76 examined), older than 65 years (31 patients). The control group consisted of 25 practically healthy individuals. The following parameters of IS were studied: the number of the total population of T-lymphocytes (CD3), B-cells (CD72), and subpopulations of T-helpers / inducers (CD4) and T-suppressors / killers (CD8), natural killers (CD16), which determined in a cytotoxic test using monoclonal antibodies of classes CD3, CD4, CD8, CD16, CD72 by enzyme immunoassay by the level of expression of membrane antigens.

Results & Conclusion: Revealed a decrease in CD3, CD4, CD8, CD16 and CD72 in young patients by 44.8; 36.1; 24.4; 32.2 and 18.4%, respectively ($p<0.001$); in middle age - by 54.6; 37.2; 29.9; 41.4 and 25.6%, respectively ($p<0.001$); in patients older than 65 years, probable T-lymphocytopenia was determined according to the indicated indicators by 66.4; 47.8; 37.7; 70.8; 41.5% ($p<0.001$) compared to the control group. With an increase in the age of CP patients, nonspecific activation of humoral immunity was observed due to an increase in IgG, IgA, IgM in young CP patients by 6.7; 13.3; 30.1% ($p<0.001$); by 9.6; 25.1; 30.1% in middle age ($p<0.001$) and by 16.9; 30.9; 41.4% over 65 years ($p<0.001$), respectively, compared with healthy individuals. The revealed tendencies for a decrease in complement activity by 56.6% in young patients by 54.8% on average and by 78.2% in the elderly ($p<0.001$) and an increase in the CIC in the contingent were confirmed and deepened with aging of patients by 58.9; 75.8 and 69.1%, respectively ($p<0.001$).

P-05-10

Evaluation of disease recurrence and evolution into chronic pancreatitis in 492 patients after a first episode of acute pancreatitis

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Abstract

Background: Acute pancreatitis (AP) may relapse and progress to chronic pancreatitis (CP). Risk factors for progression are many and not all clearly identified. Furthermore, it is unclear how many patients progress directly to CP or through a recurrence of pancreatitis. The aim of the study was to determine percentage of patients with recurrent and CP after a first attack of AP.

Methods: Patients with AP observed in our centre in the period 2013-2020 have been included. Exclusion criteria were a diagnosis of CP at first episode of AP, interval from first episode of AP and observation in Verona >1 year, and follow-up <1 year.

Results: We studied 492 patients (310 males and 192 females, estimated age 47.8±18.2 years, mean follow-up 4.6±2.7 years). Frequency of relapse was 44.7% and of diagnosis of CP 10.4%. Risk factors for relapse were gene mutations, anatomic abnormalities, oedema at first episode of AP, whereas a diagnosis of autoimmune pancreatitis and biliary aetiology were protective. Risk factors for CP were male sex, alcohol, cigarette smoking, recurrent pancreatitis, paraduodenal pancreatitis and outcomes of pancreatic necrosis.

Conclusion: Recurrence of pancreatitis and diagnosis of CP are frequently observed after a first episode of AP. CP may be diagnosed even in the absence of disease relapse, but disease relapse increases the probability of a diagnosis of CP during follow-up.

P-05-11

Differences in experimental pain sensitivity between African American and non-African American individuals

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Abstract

Background: Pancreatic Quantitative Sensory Testing (P-QST) is a neurosensory evaluation increasingly used to help characterize pancreatic pain. Because differences in experimental pain sensitivity have been reported across racial groups, this phenomenon is important to investigate prior to the wider distribution of the P-QST technique. Therefore, we aimed to assess pain sensitivity in African American (AA) individuals compared to a non-AA population.

Methods: This was a cross-sectional, multi-centre study of adults (≥18 years) with no pancreatic disease and no abdominal pain. Recruitment efforts focused on obtaining equal numbers of males and females and equal age distributions. All subjects underwent P-QST testing according to previously published techniques, including threshold measurements of pressure detection (PDT), pressure tolerance (PTT), conditioned pain modulation (CPM, reflective of intactness of descending pain control), and temporal summation (reflective of presence of central sensitization). Demographics and P-QST parameters were compared in AA and non-AA subjects.

Results: A total of 267 subjects (female n = 138, 52%) were included: 157 (59%) AA and 110 (41%) non-AA subjects. Both cohorts were well balanced with respect to age and gender distribution. The mean age was 48.0 (range 18-84) years. Indices of pressure stimulation (PDT/PTT sums, ratios) were comparable between the two subgroups. Subjects in the AA-cohort showed significant hyperalgesia to the cold-pressor test compared to the non-AA cohort. In the AA cohort, 52% of the subjects disengaged in the cold pressor test vs. 30% in the non-AA cohort (P=0.01). The risk of cold pressor test disengagement was increased in the AA-cohort vs. the non-AA cohort in time to-event analysis (hazard ratio 1.93, 95% confidence interval [1.28 to 2.89]; P=0.002) No significant differences were seen in CPM response (AA cohort median 18.4% vs. 19.2% in the non-AA cohort (P=0.82)) or for repetitive pin-prick stimulation (temporal summation).

Conclusion: P-QST measurements in AA patients were largely similar to those in non-AA patients, however significant differences were seen in the cold pressor test between groups which is similar to findings in prior studies. Further studies are needed to understand how experimental pain sensitivity differs between racial groups, and inform future modifications in normative values.

P-05-13

Psychological interventions improve mental health in inflammatory digestive system diseases: a systematic review and meta-analysis

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Abstract

Background: The rapid increase in inflammatory gastrointestinal disease cases poses a severe social and economic problem. These diseases not only worsen physical health but also have a significant impact on mental health. Our study aims to assess the effects of different psychological interventions on inflammatory digestive system diseases.

Methods: We registered the protocol of our meta-analysis in the international PROSPERO database (CRD42021282965). On October 12, 2021, we systematically searched the MEDLINE (PubMed), Cochrane Library (Central), and Embase databases. During data collection, we only included randomised controlled trials reporting the effects of different psychological interventions on the following inflammatory digestive system diseases: pancreatitis, hepatitis, inflammatory bowel diseases, microscopic and ischemic colitis, reflux disease, gastric ulcer, liver cirrhosis, celiac disease. Mental health-related clinical endpoints (depression, anxiety, overall-, physical- and mental quality of life, and perceived stress) were analysed. Standardised mean differences (SMD) were calculated using a random effects model and 95% confidence intervals (CI) to measure effect size.

Results: Of the 13,212 articles on the topic, 63 met our inclusion criteria. We analysed the data of 5,188 patients. Based on our results, psychological interventions reduced depression (SMD=-0.62; CI: -0.94; -0.30) and anxiety (SMD=-0.77; CI: -1.17; -0.36). Furthermore, the intervention also improved overall (SMD=0.30; CI: 0.09; 0.51) and physical (SMD=0.45; CI: 0.05; 0.85) quality of life. However, we did not find a statistically significant difference in the change in mental quality of life (SMD=0.80; CI: -0.41; 2.00) or perceived stress (SMD=-0.64; CI: -1.72; 0.44).

Conclusion: Our results highlight that psychological interventions improve mental health-related outcomes in patients with inflammatory digestive system diseases. It would be essential to introduce their regular use in everyday clinical practice.

P-05-15

Impact of acute pancreatitis on progression to chronic pancreatitis: results from the PaN-Eus registry

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Abstract

Background: Acute pancreatitis (AP), recurrent AP (RAP) and chronic pancreatitis (CP) are thought to be different stages of the same continuing inflammatory disease. We described the prevalence, associations and outcomes in patients with prior episodes of AP (PAP) who develop CP.

Methods: 447 patients were prospectively enrolled in the Basque-Navarrese registry of CP (PaN-EUS) across nine centres. We compared patients with PAP to those without previous history of AP (NPAP).

Results: We identified 290/447 (64.9%) patients with PAP, of which 181/447 (40.5%) had RAP. Patients with PAP

were mostly males (80.3% vs 69.4%) and younger (59.8 vs 64.9 years) (p<0.05). Furthermore, the mean age at CP diagnosis was lower for PAP patients (52.1 vs 57.9 years; p<0.05). Despite having previous AP episodes, severe pancreatitis or RAP was only considered the aetiology of CP in PAP group in 15.2%, with the primary cause being toxic-metabolic (72.4%). Additionally, active smoking was more prevalent in PAP group (61.3% vs 49.6%; p<0.05). Alcohol consumption was more frequent in the past in PAP (83.1% vs 72.6%) but they are currently fewer active drinkers compared to NPAP (43.6% vs 53.5%) (p<0.05). No significant differences were found regarding morphological CP features, finding parenchymal calcifications in 70.7% vs 77.7%, and moderate-severe ductal lesions in 72.6% vs 72.8%. PAP patients referred more frequently abdominal pain in the last year (28.9% vs 18.1%; p<0.05). More interventional endoscopic (32.3% vs 12.2%) and surgical (13.3% vs 4.5%) procedures were done in the PAP group (p<0.05). In terms of comorbidities, no differences were found in the prevalence of diabetes mellitus (DM) (51.0% vs 49.7%) and exocrine pancreatic insufficiency (EPI) (70.6% vs 68.8%). Moreover, nutritional parameters were comparable between groups. Finally, self-perceived quality of life (QoL) was similar between both groups, as measured using the visual analogue scale and health index (derived from Eq5D5L questionnaire).

Conclusion: PAP patients who progress to CP are men, younger, more active smokers and less active alcohol users, compared to NPAP. They suffer more frequently from abdominal pain and required more interventional procedures. However, PAP is not related to CP comorbidities such as DM, EPI, malnutrition or worse QoL.

P-05-16

Overweight and obesity are frequent in patients with chronic pancreatitis. Results from de Basque-Navarrese registry of patients with chronic pancreatitis

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Abstract

Background: Chronic pancreatitis (CP) is characterised by abdominal pain and loss of pancreatic parenchyma, leading frequently to exocrine and/or endocrine insufficiency. Maldigestion, malabsorption and malnutrition are consequences of these events. Low Body Mass Index (BMI) would be expectable in this setting. We aimed to explore the BMI distribution in a cohort of patients with CP and to assess which factors affected this distribution.

Methods: The Basque-Navarrese registry of CP (PaN-Eus) is a prospective multicentre registry that uses the AEG-RedCap platform. It includes patients from nine centres in northern Spain. The WHO BMI classification was used to establish different groups.

Results: In total, 447 patients were included. Mean age was 61.6 (± 10.8), 76.5% males. Median time from CP diagnosis was 67 months (0-456). The most frequent aetiology was toxic-metabolic (74.5%). Mean BMI was 25.6 (± 4.4). Fourteen patients (3.1%) were underweight; 180 (40.3%) had normal weight; 179 (40%) overweight and the remaining 74 patients (16.6%) had obesity (of which 62, 9 and 3 were class I, II and III, respectively). Pancreatic calcifications were present in 73.2%, and 72.7% had moderate or marked ductal lesions. Diabetes mellitus (DM) and Exocrine Pancreatic Insufficiency (EPI) had been diagnosed in 50.6% and 69.6% respectively. 86.1% of patients with EPI were on enzyme replacement treatment. BMI levels were similar regardless of sex, the presence of pancreatic calcifications, DM diagnosis, previous tobacco or alcohol use, and active alcohol use. However, BMI was lower in active smokers (24.7 vs 26.4; p<0.01), in patients with moderate or severe ductal lesions (25.2 vs 26.6; p<0.01) and in patients diagnosed with EPI (25.3 vs. 26.3; p=0.01). BMI values were not related to age (rs 0.09), nor to the dura-

tion of CP (rs 0.05).

Conclusion: Most of our patients with CP were overweight or obese. A lower BMI was only related to active tobacco use, to the presence of moderate or severe ductal pancreatic lesions, and to previous diagnose of EPI.

P-05-17

Spinal excitability in patients with painful chronic pancreatitis

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Abstract

Background: Abdominal pain is common in patients with chronic pancreatitis (CP), but management is challenging – possibly due to altered pain processing within the central nervous system rendering conventional treatments ineffective. We hypothesized that many patients with painful CP have generalized hyperalgesia correlating with central neuronal hyperexcitability.

Methods: Seventeen CP patients with pain and 20 matched healthy controls underwent experimental pain testing, including repeated pain stimuli (temporal summation), pressure algometry performed in dermatomes sharing spinal innervation with the pancreatic gland (pancreatic areas) and remote dermatomes (control areas), a cold pressor test and a conditioned pain modulation paradigm. To probe central neuronal excitability, the nociceptive withdrawal reflex was elicited by electrical stimulation of the plantar skin, and electromyography was obtained from the ipsilateral anterior tibial muscle together with somatosensory evoked brain potentials.

Results: Compared to healthy controls, patients with painful CP had generalized hyperalgesia as evidenced by 45% lower pressure pain detection thresholds ($P<0.05$) and decreased cold pressor endurance time (120 vs. 180 seconds, $P<0.001$). In patients, reflex thresholds were lower (14 vs. 23 mA, $P=0.02$), and electromyographic responses were increased (16.4 vs. 9.7, $P=0.04$) during the withdrawal reflex, reflecting predominantly spinal hyperexcitability. Evoked brain potentials did not differ between groups. A positive correlation was found between reflex thresholds and cold pressor endurance time ($\rho=0.71, P=0.004$).

Conclusion. We demonstrated somatic hyperalgesia in patients with painful CP associated with spinal hyperexcitability. This highlights that management should be directed at central mechanisms using, e.g.,gabapentinoids or serotonin-noradrenaline reuptake inhibitors.

P-05-18

Chronic pancreatitis patients often have undiagnosed osteoporosis and sarcopenia

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Abstract

Background: Chronic pancreatitis (CP) may lead to diabetes and pancreatic exocrine insufficiency (PEI). PEI may lead to maldigestion and malnutrition, which may cause fat-soluble vitamin deficiency, sarcopenia and abnormal bone density. We aim to find out how osteoporosis, sarcopenia and vitamin deficiency is found and treated in CP

patients.

Methods: A 4–5-year follow-up was implemented on CP patients. We recorded disease duration, BMI, smoking, alcohol consumption and medication. The serum values for A, D and E vitamins, albumin, creatinine, haemoglobin, calcium and magnesium and faecal elastse-1 was determined. Bone density measurement was taken from the proximal femur and lumbar spine. CT/MRI scans were used to measure for psoas muscle area.

Results: A total of 33 patients (median age 62 [39-81] years, 61% male) were included. None of these patients had earlier diagnosis of osteopathy, and none of them had known vitamin deficiency or were sarcopenic. Nineteen patients (57%) had pancreatic exocrine insufficiency and of these seven patients (37%) had no pancreatic enzyme replacement therapy (PERT) and one (5%) had inadequate enzyme therapy. During the study, osteoporosis was diagnosed in 20% and sarcopenia in 48% of patients. PEI and inadequate PERT was associated with low E vitamin levels (75% vs. 0%, p=0.012), higher risk of osteoporosis (43% vs. 5.6%, p=0.013) and sarcopenia (80% vs. 36%, p=0.044)

Conclusion: This study demonstrates that chronic pancreatitis is associated with osteoporosis, sarcopenia and vitamin deficiency. If untreated, pancreatic exocrine insufficiency is associated with increased risk of these outcomes. This highlights the importance of identifying and treating PEI in CP patients.

P-05-19

The impact of pancreatic fibrosis at fibronectin and hyaluronic acid plasma levels: preliminary study results

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Abstract

Background: To clarify connections between pancreatic fibrosis grade and biomarkers (fibronectin and hyaluronic acid) plasma levels.

Methods: This study was conducted within the healthcare research project “Assessment of pancreatic fibrosis as a prognostic factor for its diseases course” funded by Autonomous non-profit organization “Moscow Centre for Innovative Technologies in Healthcare” administered by the Moscow Healthcare Department.

We measured fibronectin (FN) and hyaluronic acid (HA) plasma levels from 73 patient who underwent surgery from April to December 2022 due to benign and malignant pancreatic tumours as well as advanced chronic pancreatitis (CP), mean age 56.8±14 (25-84). Plasma levels of FN (pFN) and HA (pHA) were measured by an enzyme-linked immunosorbent assay (ELISA). Morphological signs of CP as well as pancreatic fibrosis grade were assessed by experienced pathologists according to Klöppel & Maillet’s scoring system for the evaluation of the extent of fibrosis in CP.

Results: We received significant intergroup differences between mean values of pFN level in groups divided by peri- and intralobular fibrosis grade (p=0.026 and p=0.008, respectively). PFN mean level was lower in patients with pancreatic ducts containing protein plugs (79.5±53.8µg/mL) than without (96.3±45.7µg/mL), p=0.023. PHA mean level was higher in patients with pancreatic ducts containing protein plugs (119±160.8ng/mL) than without (65.2±94ng/mL), p=0.03. Also, we saw higher levels of pHA in cases with prominent and enlarged peripheral nerves (160.7±196.3ng/mL), than in cases with normal peripheral nerves in pancreatic tissue (65.1±89.5ng/mL), p=0.034.

Conclusion: Morphological signs of CP and pancreatic fibrosis like pancreatic ducts obstruction by protein plugs and prominent enlarged peripheral nerves in pancreatic tissue as well as pancreatic peri- and intralobular fibrosis grade affect pFN and pHA levels. It could be useful for noninvasive pancreatic fibrosis diagnosis and even for patients selection for advanced diagnostics.

P-05-21

Paraduodenal pancreatitis: preliminary data from an Italian multicentre registry

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Abstract

Background: Paraduodenal pancreatitis(PP) is a form of chronic pancreatitis affecting an area defined "groove", between the head of the pancreas, the duodenum and the main biliary tract. Pathogenesis and natural history is still unclear and the treatment include both medical therapy and surgery. We performed a multicentre retrospective study to explore the burden of the disease, and its evolution towards exocrine pancreatic insufficiency(EPI) considering also neoplastic evolution.

Methods: We collected data from both academic and non-academic Italian centres. All patients with diagnosis of PP were included in the registry. Data were extracted at the time of diagnosis and during follow-up. Univariate and multivariate analysis were performed to explore the relations between variables and outcomes of interest.

Results: We collected 208 patients (87.5% male) from 16 centres. Mean age at diagnosis was 51(± 11) years and mean time from clinical presentation to diagnosis was 18(±29) months. 88.4% had history of alcohol abuse and 89% of smoking. 36 patients (17.9%) had diabetes at diagnosis, while 80 patients (41.5%) had chronic pancreatitis. Clinical presentation included abdominal pain (89.1%), jaundice(18.5%), nausea(47.1%) and vomiting(32.6%). Initial laboratory tests showed a mean increase of bilirubin of 1.62(±1.7) times upper limit of normal (ULN), Amylase 2.9(±2.5)

times ULN, Lipase 3.2(±3.1) times ULN. 6(3%) patients developed pancreatic cancer after a mean time of 10.3(±10.8) months from PP diagnosis. 49 patients (23.6%) had EPI at diagnosis, while further 49 patients developed it during follow up. Among patients with EPI at diagnosis, 19(38.8%) recovered with no more signs of EPI at the last follow up. Preliminary analyses showed that EPI at diagnosis was associated to EPI at the last follow-up (OR 2.6, p=0.012). Mean time to develop EPI was 17.1(±23.5) months. Conservative treatment was chosen in 54.3%, surgery in 17.3% and endoscopic therapy in 16.35% cases. Over a median follow-up of 36 (range, 1-168) months, mortality was 4.8%.

Conclusion: Paraduodenal pancreatitis is an uncommon disease, mainly diagnosed in male patients with history of alcohol and smoking. Moreover, conservative strategy was the treatment of choice in our cohort of patients.

P-05-22

Surgery in chronic pancreatitis after implementation of multidisciplinary team assessment - a single centre prospective study from Oslo

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Abstract

Background: Surgery is one of several treatment options for pain syndrome in chronic pancreatitis (CP). Even though numerous publications report promising results, surgery in CP has got little attention among Scandinavian surgeons. Due to the complexity of CP, multidisciplinary team (MDT) discussion might benefit these patients. This study reports the results of surgery for CP after introduction of dedicated CP-MDT meetings.

Methods: This is a prospective single-centre study on short- and long-term outcome in surgically treated CP patients at Oslo university hospital (OUH). Surgical candidates were discussed and selected in dedicated CP-MDT-meetings. All patients were prospectively included in the study and followed at the out-patient clinic. Primary endpoint was daily use of Oral Morphine Equivalents (OMEQ) comparing postoperative use with preoperative. Secondary endpoint was surgical outcome.

Results: From February 2016 to December 2022, 80 CP patients were operated due to pain syndrome. 64 (80%) consumed opioids daily preoperatively with a median consumption of 42 mg OMEQ (range 2.5-420). A tailored surgical treatment including either decompression, resection or combined surgical techniques were applied, including total pancreatectomy and islet auto transplantation (TP-IAT) in 16. Postoperative complications (Clavien-Dindo>3a) occurred in eight patients (10%). There was no postoperative 90-days mortality. Follow-up rate was 94% (n=75). Patients with malignancy (n=2) were excluded from the long-term follow-up data. The remaining 73 patients had a median follow-up time of 20 months (3-77 months). 64 of 72 patients (89%) reported complete (n=55) or partial (n=9) pain relief after the operation.

Conclusion: Surgery in CP was performed with low morbidity and no mortality. The majority of patients achieved complete or partial response on pain syndrome. Tailoring of CP treatment in MDT-meetings seems beneficial, both regarding treatment options and surgical strategy.

P-06-01

Autoimmune pancreatitis and micronutrients: a pioneer study

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Abstract

Background: Nutritional deficiencies, including fat-soluble vitamins, water-soluble vitamins and minerals have been studied in the setting many autoimmune diseases, including those involving the digestive system. However, despite the well-known pancreatic involvement in IgG4-related diseases, nutritional deficiencies in autoimmune pancreatitis (AIP) have not been examined so far. The aim of the present study was to determine the prevalence of micronutrient deficiencies in patients with AIP as well as to investigate their relationship with relapse.

Methods: We retrospectively analysed medical records of patients followed up for AIP at our Pancreas Outpatient Clinic between January 2001 and March 2022. Demographic and clinical data were collected. The primary outcome was the prevalence of micronutrient deficiencies during AIP follow-up. The secondary outcome was the prevalence of AIP relapse, with exposure defined as micronutrient deficiency occurring at any time during follow-up. Micronutrient variables were solely described categorically as deficient or normal, according to the reference values at the time of each test.

Results: One hundred patients were included in the final analysis. The male-to-female ratio was 2.5:1; median age at diagnosis was 57 years (range 19-85). Median follow-up was 53 months, and during this time, 38% of patients suffered from at least one micronutrient deficiency. The most prevalent micronutrient deficiencies were vitamin D (16.1%) and zinc (25.5%). There were no statistically significant differences in prevalence of micronutrient deficiency stratified by AIP subtype. Relapse was observed in 37% of the AIP patients. Initial analysis showed that AIP relapse was associated with any micronutrient deficiency as well as zinc and vitamin D deficiency, but after stratifying for AIP type 1 and adjusting for PEI and elevated IgG4 levels, the association ceased to be statistically significant.

Conclusion: Zinc and vitamin D deficiencies may be common in patients with AIP, indicating that these micronutrients might play a role in the natural course of AIP. Importantly, any micronutrient deficiency may be prevalent even in the light of treated PEI, which emphasizes importance of micronutrients as an additional tool in the workup and follow-up of AIP patients.

P-06-02

Incidence of autoimmune pancreatitis detected after pancreatic resection performed for suspected malignancy: a scoping review

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Abstract

Background: Autoimmune pancreatitis (AIP) can be difficult to diagnose as it frequently presents symptoms similar

to those of pancreatic cancer. Pancreatic resection is considered to be a curative treatment for pancreatic ductal adenocarcinoma (PDAC). This scoping review aims to study the incidence of AIP in patients underwent pancreatic resection for clinical manifestation of cancer.

Methods: A comprehensive search was conducted in 3 databases PubMed, Embase, and the Cochrane Library, using the following terms: autoimmune pancreatitis, pancreatic resection and supplemented by manual checks of reference lists in all retrieved articles.

Results: Ten articles were included in the final analysis. 8,917 pancreatic resections were performed for the clinical suspicion of pancreatic cancer. AIP accounted for 140 cases (1.6%). Type 1 AIP accounted for the majority of cases, representing 94% (132 cases), while type 2 AIP accounted for the remaining 6% (8 cases) after further classification. AIP accounted for almost 26% of all benign diseases undergoing unnecessary surgery and was over-represented in males with 70% of cases compared to 30% in females. The mean age for AIP patients was 59 years. Serum CA 19-9 levels were elevated in 23 out of 47 (49%) AIP patients, where higher levels were detected more frequently in patients with type 1 AIP (51%, 22 out of 43) than in those with type 2 AIP (25%, 1 out of 4). The sensitivity of IgG4 levels in type 1 AIP was low (43%, 21/49 patients).

Conclusion: Even with modern diagnostic methods, distinguishing between AIP and PDAC can still be challenging, which can result in unnecessary surgical procedures in some cases. Serum CA 19-9 and IgG4 levels are not useful in distinguishing between AIP and PDAC. Work must be done to improve diagnostic methods and avoid unnecessary complicated surgery.

P-06-03

Clinical outcomes of patients with type 2 autoimmune pancreatitis in a large single-centre cohort with long-term follow-up

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Abstract

Background: Type 2 is a less frequent and known form compared to type 1 autoimmune pancreatitis (AIP). Despite considered as a benign form, only few studies with a short follow-up have been published on type 2 AIP.

Methods: Patients with definitive or probable diagnosis of type 2 AIP by International Consensus Diagnostic Criteria (ICDC) present in our prospectively maintained database since 1995 were identified. All patients were contacted and clinically evaluated during the year 2022. Uncontactable patients and patients refusing clinical evaluation were considered as lost at follow-up. Clinical, radiological, serological, and pathological reports were evaluated.

Results: Eighty-eight patient out of 420 AIP patients present in the database (21%) were diagnosed as type 2 AIP (55 males, 33 females, mean age at clinical onset 33.5±13.5 years, range 16-71). According to the ICDC, 21 patients (23.8%) had a definitive and 67 a probable diagnosis of type 2 AIP. Mean follow-up time was 9.2±7.1 years (range 1-27 years). No differences were observed comparing patients with definitive and probable type 2 AIP diagnosis. Concomitant IBD was reported in 77 patients (87.5%), mostly diagnosed before or at the same time of type 2 AIP. Nine patients were drop out (10.2%). Survival curve evaluated a probability of relapse of 27% at 5 years and 29% at 10 years. Risk of endocrine or severe exocrine insufficiency were relatively low, 5% and 25% respectively. Four extra-pancreatic malignancies (5%) were diagnosed (1 renal, 1 breast, 1 rectum and 1 prostate cancer), none pancreatic. 1 patient died for car accident.

Conclusion: Patients affected by type 2 AIP have a benign long-term clinical outcome. Mortality rate was low, as well as extra-pancreatic and pancreatic malignancies.

P-06-04

A positive cytokine/chemokine feedback loop establishes plasmacytoid dendritic cell-driven autoimmune pancreatitis in IgG4-related disease

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Abstract

Background: The pathogenesis of the murine model of autoimmune pancreatitis associated with IgG4-related disease (AIP/IgG4-RD) by administration of polyinosinic-polycytidylic acid, is incompletely understood. While murine and human AIP/IgG4-RD is driven by pancreatic plasmacytoid dendritic cells (pDCs) producing IFN-a, the origin of these cells and their relation to effector T cells is unknown.

Methods & Results: Here we show that murine AIP/IgG4-RD is initiated by TLR3-bearing conventional DCs in the uninflamed pancreas whose activation by polyinosinic-polycytidylic acid causes IFN-a, C-X-C motif chemokine ligand 9 (CXCL9), and CXCL10 secretion and this, in turn, induces migration of C-X-C motif chemokine receptor 3 (CXCR3)+ T cells. These CXCR3+ T cells, via their secretion of C-C motif chemokine ligand 25 (CCL25), then facilitate migration of pDCs bearing C-C chemokine receptor 9 into the pancreas to create a feedback loop anchored by the now dominant pDC production of IFN-a and the induced CXCR3+ T cells that amplify pDC migration. Remarkably, the interaction between CXCR3+ T cells and pDCs exists at the functional levels since the interaction enhances the production of CCL25 and IFN-a by the CXCR3+ T cells and pDCs, respectively.

Conclusion: Evidence presented here that a similar disease mechanism is present in human AIP/IgG4-RD creates new avenues of disease treatment.

P-06-05

AiPPEAR: a multicentre study on AutoImmune Pancreatitis, Pancreatic and Extrapancreatic cAnceR

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Abstract

Background: Autoimmune pancreatitis (AIP) is a rare form of chronic pancreatitis (CP), with frequent relapses. Japanese studies and one German study have proposed that AIP patients have a higher incidence of malignancy

compared to the normal population, however, data is scarce.

Our primary aim is to determine the occurrence of any first invasive cancer in AIP patients. The secondary aim is to determine the characteristics of AIP patients with distinct pancreatic and/or extrapancreatic cancers.

Methods: This study is an international, multicentre, retrospective, collaborative cohort study of European AIP patients within the Pancreas2000 framework. Patients diagnosed with AIP after 2005 will be eligible for the study. Patients younger than 18 years at last contact and those with follow-up of less than 12 months will be excluded. Primary outcome is defined as the standardised incidence rate of a first invasive cancer occurring after diagnosis of AIP compared to age-grouped and gender-matched controls of the general population. Cancer incidence in the general population will be determined using the scientific publication "Cancer Incidence in Five Continents, Volume XI". Individual cancers will be classified according to the ICD-10 or any previous version. For pancreatic cancer, we will conduct a sensitivity analysis, where AIP patients with cancer in the first 12 or 24 months after diagnosis, will be excluded. Secondary outcomes are defined as AIP features associated with incidence of cancer. Demographic, clinical, radiological and treatment characteristics will be collected retrospectively in a REDCap database.

Conclusion: It remains unresolved whether AIP patients are at increased risk of pancreatic or extrapancreatic cancer. With this study, valuable insights regarding this knowledge gap will be obtained.

P-06-06

Validation of MRI-morphologic radiological diagnostic criteria in a retrospective cohort of autoimmune pancreatitis (AIP) patients

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Abstract

Background: Autoimmune pancreatitis (AIP) is a rare disease that can be diagnosed, according to the International Consensus Diagnostic Criteria (ICDC). Contrast-enhanced MRI with MRCP has largely replaced other imaging techniques and ERCP for the assessment of ductal morphology in AIP. Aim of the study is to review and optimize the MR-morphologic diagnostic criteria for AIP in terms of specificity and sensitivity in the diagnosis and differential diagnosis of the pancreaticobiliary system.

Methods: Hundred-fifty-six (n=156) high-quality MRIs were retrospectively analysed: AIP n=56 diagnosed according to ICDC, chronic pancreatitis (CP) n=25, pancreatic cancer (PDAC) n=25, primary sclerosing cholangitis (PSC) n=25, non-HPB subjects n=25. The MRI reading was conducted in a blinded fashion, using defined criteria (pancreatic parenchyma, halocapsule, pancreatic duct, icicle sign, atypical findings, extrapancreatic findings) by at least two radiological experts. The statistical analysis was performed by means of Proportion test, Chi-square test or Fisher's exact test, One-way ANOVA and Cohen's Kappa Statistic of the level of agreement.

Results: The level of agreement was moderate to substantial agreement (κ 0.23-0.85). A proportion test (AIP versus controls -PDAC vs PC vs PSC vs non-HPB subjects-) showed that the restricted diffusion (Reader 1: Sens 47.83%,Spec 89.29%,NPV 75.76%,accuracy 74.51%; Reader 2: Sens 56.86%,Spec 73.26%,NPV 74.12%,accuracy 72.30%), sausage-like enlargement (Reader 1: Sens 30.91%,Spec 98.98%,NPV 71.85%,accuracy 74.51%; Reader 2: Sens 26.79%, Spec 98.00%, NPV 70.50%, accuracy 72.43%), hyper-enhancement of ductal wall (Reader 1: Sens 14.29%, Spec 96.67%, NPV 67.44%, accuracy 71.90%; Reader 2: Sens 8.51%, Spec 95.45%, NPV 66.14%, accuracy 74.10%), the

icicle sign (Reader 1: Sens 10.91%, Spec 100%, NPV 66.67%, accuracy 65.30%; Reader 2: Sens 37.50%, Spec 91.00%, NPV 72.22%, accuracy 71.79%) and the delayed enhancement in the venous phase (Reader 1: Sens 8.70%, Spec 83.15%, NPV 63.79%, accuracy 74.10%; Reader 2: Sens 32.61%, Spec 79.31%, NPV 69.00%, accuracy 75.19%) show a good accuracy distinguishing AIP from controls.

Conclusion: Our study showed that the sausage-like enlargement, restricted diffusion, delayed enhancement in the venous phase, the icicle sign and hyper-enhancement of ductal wall show a good accuracy distinguishing AIP from controls. Otherwise, the other radiological parameters were not statistically significant.

P-07-01

Natural compound library screening identifies corynoline for the treatment of pancreatic fibrosis and chronic pancreatitis

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Abstract

Background: Chronic pancreatitis (CP) is a progressive pancreatic fibrosis and chronic inflammatory syndrome with no effective treatment. Traditional Chinese medicine (TCM) has been applied in China for thousand years, and its curative effect is remarkable. However, its application is limited due to its unclear composition and mechanism. TCM monomer is the active ingredient in Chinese herbal medicine. Compared with Chinese herbal formula, monomers have clear structure and are important source of new drug development. Therefore, it is of great value to develop drugs for CP from TCM monomers.

Methods: Antifibrotic drug candidates were identified by functional screening of 1771 TCM monomers in human pancreatic stellate cells (HPSC), subsequent validation, and mechanistic in vitro and in vivo studies. We used TGF-β1 to stimulate HPSC, thereby establishing an in vitro model of pancreatic fibrosis. In vivo, we injected caerulein into mice by intraperitoneally for 4 consecutive weeks to establish a mouse model of CP. To identify potential targets of natural compounds, we employed limited proteolysis with mass spectrometry (LiP-SMap) to identify cellular proteins that could directly bind natural compounds.

Results: High-throughput natural compound library screening identified a TCM monomer named corynoline with antifibrotic effect and low toxicity in HPSC. Subsequently, we verified the antifibrotic effect of corynoline in mouse model of CP. Using LiP-SMap, we identified PSMA2 which was the component of the 20S core proteasome complex as the target of corynoline.

Conclusion: We identified the TCM monomer corynoline as drug candidate for therapeutic applications in pancreatic fibrosis and CP.

P-07-02

Development of new molecules with potential pharmacological activity for the treatment of acute pancreatitis based on an esteric coupling reactions between trehalose (disaccharide) and non-steroidal anti-inflammatory drugs

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Abstract

Background: Acute pancreatitis (AP) is one of the most common diseases in gastroenterology. Nevertheless, neither the aetiology nor the pathophysiology of AP are fully understood and causal treatment options are not available. Recently we demonstrated that Heparanase (Hpa) is adversely involved in the pathogenesis of AP and inhibition of this enzyme ameliorates the manifestation of the disease. Moreover, a pioneer study demonstrated that Aspirin has inhibitory effect on Hpa. Additional compound which possesses mild pancreato-protective effect against AP, is trehalose, a common disaccharide. Therefore, we hypothesize that combination of Aspirin and trehalose may exert pancreato-protective effect more than each drug alone. Recently, we have synthesized new chemicals, termed Aspirlose, Diclose and Indose which are the products of the chemical coupling between trehalose with one of the following NSAIDs: Aspirin, Diclofenac and Indomethacin, respectively. Our aim was to develop a new compound for the treatment of AP which combines trehalose with NSAIDs that will be administered either pre to AP development in subject predispose to the disease or aftermath. We demonstrated that either Aspirin or trehalose alone are effective in ameliorating experimental AP, while a combination of both compounds ameliorated more effectively the disease development.

Methods: AP induced by caerulein in Heparanase-overexpressing transgenic mice (Hpa-Tg) and their wild-type (WT) BALB/c mice, with or without either Aspirin, trehalose, Diclofenac, Indomethacin, Aspirlose, Diclose or Indose. The animals sacrificed 24h following the disease induction and the severity of AP was evaluated by the serum pancreatic enzymes amylase and lipase, histological alterations and inflammation parameters.

Results: Caerulein-induced AP in WT mice resulted with significant rises of amylase and lipase along disruption of pancreatic tissue as well as enhancement of inflammatory pathways. All these deleterious responses were more profound in Hpa-Tg animals. Pre-treatment with either Aspirin, trehalose, Diclofenac, or Indomethacin reduced inflammatory response along remarkable reduction in amylase and lipase in both mice groups. Noteworthy, Pre-administration of either Aspirlose, Diclose or Indose ameliorated AP more efficiently than each drug alone.

Conclusion: Combination of trehalose with NSAIDs is more effective in mitigating AP than each drug alone and may uses as a novel therapy for this common orphan disease.

P-07-03

Loss of the intracellular transport protein CLN8 increases autophagy and ER-phagy in acute experimental pancreatitis

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Abstract

Background: The initiation of acute pancreatitis (AP) depends on the activation of trypsinogen by cathepsin B (CTSB), a lysosomal hydrolase. The export of CTSB from the ER into the Golgi-network is controlled by the ceroid-lipofuscinosis neuronal protein 8 (CLN8). In this project, we are interested, whether a depletion of this protein impairs

lysosomal enzyme transport and alters severity of acute pancreatitis.

Methods: Pancreatic acinar cells were isolated by collagenase digestion from CLN8 knockout mice and corresponding control mice. Afterwards, they were stimulated by supramaximal concentrations of cholecystokinin (CCK). By sucrose gradient centrifugation, subcellular fractions of pancreas homogenates were prepared, followed by measurements of enzymatic activities of CTSB and cathepsin L (CTSL). Electron microscopic imaging of pancreatic acinar cells of CLN8 knockout and control mice was performed. Acute pancreatitis was induced by serial intraperitoneal caerulein injections in CLN8 knockout mice and wild-type controls. Disease severity was determined by serum amylase and lipase activity, activities of CTSB, CTSL, and trypsin in pancreas homogenates and histological damage.

Results: In isolated and supramaximal stimulated pancreatic acinar cells of CLN8 deficient mice we observed lower intracellular trypsin, CTSB, and CTSL activities, indicating a milder disease severity during the early phase of acute pancreatitis. Loss of CLN8 did not lead to an alteration of lysosomal enzyme expression and subcellular distribution. In the caerulein model of acute pancreatitis, there was a transient decrease in severity of acute pancreatitis, measured by serum amylase and lipase as well as CTSB, CTSL, and trypsin activities in pancreas homogenates at 1h. These differences were counterbalanced at later time points. Interestingly, an increase of ER-stress, autophagy and ER-phagy was observed in CLN8 knockout mice. In electron microscopic images of the pancreas we detected misshaped mitochondria accompanied by an increased number of autophagosomes.

Conclusion: Deficiency of CLN8 leads to a milder onset of acute pancreatitis but ultimately results in similar disease severity at later time points, which might be explained by an increase of ER-phagy and ER-stress in the absence of CLN8. The subcellular distribution of lysosomal enzymes seems to be independent of CLN8.

P-07-04

Sensors of apoptotic cells receptor tyrosine kinases AXL and MERTK modulate pancreatic tissue repair and remodelling

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Abstract

Background: Studies suggest that sensors of apoptotic cells-the receptor tyrosine kinases AXL and MERTK, cooperated with IL-4 or IL-13 mediate macrophage reparative reprogramming and facilitate tissue repair. This study was designed to investigate the role and underlying mechanisms of AXL and MERTK in pancreatic tissue repair and remodelling following a severe attack of acute pancreatitis (AP).

Methods: The changes of serum GAS6, PROS1, and soluble AXL in patients and mice with AP and AXL and MERTK in pancreatic macrophages were analysed. AP model was induced by two-day caerulein hyperstimulation (100 µg/kg, 10 hourly injections per day) in wild-type (WT), global (Axl-/-Mertk-/-), myeloid-specific (AxlLysMΔMertkLysMΔ), or resident macrophage-specific (AxlCsf1rΔMertkCsf1rΔ) deficient mice. Pancreatic tissue injury and repair responses were evaluated at 2, 4, 6, 8, 14, 21 days after severe AP induction. Bulk and CD45+ single-cell RNA sequencing of the pancreas at Day 4 from WT and AxlLysMΔMertkLysMΔ mice were performed to investigate molecular signature of pancreatic tissue repair and immune microenvironment. The frequency of pancreatic innate immune cells and its subtypes were analysed by flow cytometry. The effect of adoptive M2 macrophage immunotherapy was assessed.

Results: Serum GAS6, PROS1, and soluble AXL in patients and mice and AXL and MERTK in pancreatic macrophages were changed dynamically during injury and repair phages of AP. Global and myeloid-specific, but not resident

macrophage-specific deletion of AXL and MERTK impaired pancreatic tissue repair after AP induction. Myeloid-specific deletion of AXL and MERTK delayed pancreatic acinar genes, but sustained pancreatic ductal genes with pancreatic embryonic developmental signals including Notch, Hedgehog and Wnt pathways. Genetic ablation of AXL and MERTK induced a unique pancreatic transcriptomic signature, featured by upregulated inflammatory signalling pathways and downregulated amino acid metabolism and pancreatic exocrine function. Furthermore, it also induced a unique pattern of pancreatic immune microenvironment, featured by accumulation of CXCR2+ neutrophils and interactions between myeloid populations. Adoptive M2 macrophage immunotherapy effectively restores the capacity of pancreatic repair.

Conclusion: AXL and MERTK in macrophages plays crucial role in mediating pancreatic repair after severe AP. Macrophage-associated immunotherapy may serve as a promising therapeutic strategy for pancreatic tissue repair during severe AP.

P-07-06

Tenascin C deficiency impairs epithelial regeneration after caerulein-induced acute pancreatitis

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Abstract

Background: Tenascin C (TNC) is an extracellular matrix protein, expressed during tissue injury and one of the key stromal factors contributing to progression of different types of tumours, including pancreatic cancer. However, its role in pancreatic inflammation and regeneration is still not well defined. In this study, we investigated the effects of TNC on the development of acute pancreatitis and in post-disease pancreatic regeneration using a genetically engineered mouse model.

Methods: The caerulein-induced acute pancreatitis model was applied in TNC knockout (KO) and C57BL/6J wild-type (WT) mice. Pancreatic tissues were harvested at different time points (3, 12, 24, 48 hours, 7 and 21 days). The severity of the disease was scored on Hematoxylin-Eosin stained sections according to the amount of oedema, interstitial/parenchymal inflammation and acinar-ductal metaplasia (ADM). Immunohistochemistry was performed for assessment of proliferation (Ki67), ADM (amylase and CK19/Sox9), pancreatic stellate cell activation (alpha-smooth muscle actin) and for the expression of integrin ß6, which is a known TNC-receptor. Stained slides were evaluated semi-quantitatively or fully automatically using Aperio ImageScope. Statistical analyses were performed using GraphPad Prism.

Results: The severity of the disease was similar in WT and KO groups and regeneration was completed by 7 days. However, the TNC-KO group displayed a slightly delayed regeneration compared to the control group, with lower Ki67-proliferation rate at 3 and 12 hours in the whole parenchyma and delayed increase of Sox9 expression. TNC-KO mice revealed the highest ADM score at 24h compared to all other groups. The expression of integrin ß6 was increased in the whole parenchyma at 3 and 12 hours in both genotypes, but higher levels where found in TNC-KO mice at 12 hours. The expression levels of alpha-SMA and integrin ß6 were higher in ADM areas compared to the whole parenchyma without differences between TNC-KO and WT mice.

Conclusion: TNC deficiency slightly impairs pancreatic regeneration after caerulein-induced acute pancreatitis, underscoring the relevance of an intact stromal scaffold for maintenance or restoration of tissue integrity.

P-07-07

The anti-coagulant dabigatran inhibits trypsin and has therapeutic activity in trypsin-dependent pancreatitis

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Abstract

Background: Pancreatitis, the inflammatory disorder of the pancreas, has no specific therapy. Genetic, biochemical, and animal model studies revealed that trypsin plays a central role in the onset and progression of pancreatitis. Our aim was to perform biochemical, pharmacokinetic, and preclinical mouse experiments to offer proof of concept that the oral anticoagulant, dabigatran etexilate can inhibit pancreatic trypsins in man and mice, and shows therapeutic efficacy in trypsin-dependent pancreatitis.

Methods: Enzyme kinetic parameters of native and recombinant human and recombinant mouse trypsin isoforms were measured in the presence and absence of dabigatran, and inhibitory constants (K_i) were determined. We measured dabigatran plasma concentrations in mice after oral administration of dabigatran etexilate. We tested the efficacy of dabigatran etexilate in the *T7K24R* mouse model of trypsin-dependent pancreatitis.

Results: We found that dabigatran competitively inhibited all human and mouse trypsin isoforms (K_i range 10–79 nM) and dabigatran plasma concentrations in mice given oral dabigatran etexilate well exceeded the K_i of trypsin inhibition. In *T7K24R* trypsinogen mutant mice, a single oral gavage of dabigatran etexilate was effective against caerulein-induced progressive pancreatitis, with a high degree of histological normalization.

Conclusion: Our observations indicate that dabigatran is a potent trypsin inhibitor and dabigatran etexilate shows therapeutic activity against trypsin-dependent pancreatitis.

P-07-08

Inflammatory epigenetic priming of pancreatic acinar cells promotes tissue regeneration after renewed inflammation

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Abstract

Background: Pancreatitis is an important risk factor for the development of pancreatic ductal adenocarcinoma (PDAC). During the course of pancreatitis, the organ is able to activate regenerative mechanisms accompanied by a transient dedifferentiation of acinar cells. This results in acinar-to-ductal metaplasia (ADMs), which is controlled by epigenetic mechanism. Subsequently, ADMs differentiate into acinar cells to restore tissue integrity. In this project, we aim to investigate whether inflammation-induced acinar cell regeneration leads to permanent changes of histone modifications at regulatory gene regions that affect renewed inflammation-driven regeneration processes.

Methods: Wild-type mice were treated with caerulein to induce pancreatitis or treated with NaCl as a control, recovered for 28 days until another caerulein-pancreatitis was induced to analyse acinar cells regeneration steps over

time. Cell stress, ADM formation and immune cell infiltration were detected at different time points after second caerulein-administration by immunohistochemistry (IHC) or immunofluorescence (IF) staining. ADM formation capacity of recovered acinar cells (28 days) was measured by 3D-collagen-culture. Transcriptomic profiles and epigenetic changes of recovered acinar cells (28 days) were analysed by RNA-Seq and qPCR and by ChIP (H3K27ac)-qPCR, respectively.

Results: Our data demonstrated that mice with a previous event of inflammation showed reduced pancreatic oedema at one hour after a second episode of caerulein-pancreatitis. However, the mice did not exhibited differences in immune cell infiltration. Five days after the second episode of caerulein-pancreatitis, the mice had a lower number of ADMs still present in the pancreas, suggesting more rapid tissue recovery. Consistent with these data, we demonstrated that acinar cells recovered from pancreatitis have an increased ability to undergo ADM formation in 3D-collagen-culture, indicating an enhanced regenerative potential. Although the acinar cells recovered from pancreatitis showed no change in the expression of the acinar differentiation gene Rbpjl, we detected enriched H3K27ac level on the Rbpjl gene promoter.

Conclusion: Our results suggest that regenerated acinar cells that have already recovered from pancreatitis accumulate activating histone modification H3K27ac at acinar cell differentiation genes, such as Rbpjl, to accelerate tissue regeneration when confronted with a subsequent inflammatory event.

P-07-09

Protective effects of the insulin-mimetic, SPROTONE, on cellular models of acute pancreatitis

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Abstract

Background: There is a strong link between diabetes and severity of acute pancreatitis (AP). Our previous studies have shown that insulin directly protects acinar cells during cellular and in vivo models of AP in diabetic mice (Ins2Akita) and pancreatic acinar cell-specific insulin receptor knock out mice (PACIRKO). This is due to insulin-induced Akt-mediated phosphorylation of 6-phosphofructo-2-kinase fructose-2,6-biphosphatase (PFKFB2) which drives glycolysis and maintains cellular ATP, thereby preventing cytotoxic Ca2+ overload and necrosis. Insulin infusion might seem like a simple therapeutic solution for AP but is very precarious in critically ill patients due challenges of blood glucose control and the risk of severe ketoacidosis. Therefore, agents that mimic the downstream effects of insulin in pancreatic acinar cells without these deleterious systemic effects, may be an alternative therapeutic strategy for the treatment of AP. Our aim was to test the putative protective effects of the plant-derived nutraceutical SPROTONE, which exhibits anti-diabetic and insulin-mimetic properties, on cellular models of AP.

Methods: Sprotone is formulated from sprouted cereals (70 %, wheat, ragi), pulses (26 % horse/green gram) and oil seeds (4 % fenugreek/flax seed). Ethanol extracts of Sprotone were tested on acutely isolated pancreatic acinar cells treated with the bona-fide pancreatitis-inducing agent, palmitoleic acid (POA, 30-100 µM) and several readouts of acinar injury were assessed. Cytotoxic Ca2+ overload was assessed by fura-2 imaging, magnesium green and luciferase-based luminescence assessed ATP depletion. Relative glycolytic vs mitochondrial metabolism was assessed using NADH autofluorescence. Western blotting for phospho-Akt and phospho-PFKFB2 assessed the downstream mechanism of insulin and Sprotone.

Results: Sprotone, at concentrations that exhibited no toxic effects on resting Ca2+ (0.03 %), attenuated the POA-induced ATP depletion and Ca2+ overload. This was also due to a shift from mitochondrial metabolism towards glycol-

ysis. Sprotone (0.03%) induced Akt and PFKFB2 phosphorylation.

Conclusion: These data suggest that Sprotone mimics the downstream protective effects of insulin on pancreatic acinar cells. If these effects can be translated to in vivo models of acute pancreatitis, Sprotone could represent a safe and alternative treatment for AP.

P-07-10

Genetic and functional analysis of chymotrypsin-like protease (CTRL) in chronic pancreatitis

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Abstract

Background: Genetic predispositions play a crucial role in the pathogenesis of early-onset chronic pancreatitis (CP). So far, several genes have been identified as risk factors, most of which encode digestive enzymes. However, there are many idiopathic CP cases with no identified underlying cause. Chymotrypsins are a family of serine proteases that can cleave trypsinogen and lead to its degradation. Given that the chymotrypsins *CTRC*, *CTRB1*, and *CTRB2* have been associated with CP, we genetically and functionally investigated chymotrypsin-like protease (CTRL) as a potential risk factor.

Methods: We screened 1,059 CP patients and 2,099 controls for *CTRL* mutations by whole-exome sequencing. To analyse secretion and proteolytic activity, we performed Western blots and activity assays. To investigate the potential impact of the mutations on endoplasmic reticulum (ER) stress, we measured BiP mRNA expression using qPCR Taqman assays and performed XPB1 splice PCR.

Results: Functionality was unchanged in 7/17 CTRL mutations examined. Five mutations showed normal secretion but reduced (p.G20S, p.G56S, p.G61S) or abolished (p.G37E, p.S208F) activity. Another five mutations (p.C201Y, p.G215R, p.L218Rfs33, p.C220G and p.G230S) were not secreted and already showed reduced or no activity intracellularly. However, intracellular retention did not lead to ER stress.

Conclusion: We identified several *CTRL* variants, some of which showed potent effects on protease function and secretion. However, we observed these effects with mutations found in both patients and controls. *CTRL* loss-of-function mutations were not significantly enriched in patients, so *CTRL* is unlikely to be a risk factor for CP.

P-07-11

Depletion of α-SMA+ myofibroblast aggravates pancreatitis in mice

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Abstract

Background: Pancreatitis is a sterile inflammation with an often pronounced systemic inflammatory response. During pancreatitis, pancreatic stellate cells (PSCs) become activated and acquire myofibroblast like features that over express α-smooth muscle actin (aSMA) followed by excess synthesis of extracellular matrix proteins, which contributes to the development of pancreatic fibrosis. Moreover, activated PSCs acquire immunomodulatory features during acute (AP) and chronic pancreatitis (CP). In our present study, we study the role aSMA positive myofibroblasts for pancreatitis.

Methods: Transgenic mice expressing herpes simplex virus thymidine kinase gene driven by mouse ACTA2 promoter region were used to deplete proliferating PSCs through ganciclovir treatment. We studied the effect of aSMA+ myofibroblasts ablation in a severe model of pancreatitis (duct ligation (pDL)) in aSMA-tk mice after, 12h, 24h and 48h (acute phase) and 14 and 28 days (chronic phase). Serum lipase, faecal elastase, blood glucose and lung MPO levels were measured to assess pancreatitis severity and function. For histological assessment, we performed haematoxylin and eosin, picrosirius red fast green and immunohistochemistry stainings. Von Frey filament (VFF) and open field tests were used to assess pain in mice.

Results: After pDL, we observed a significant reduction in the aSMA+ cell population in pancreatic tissue (∼56% after 28 days, p=.01) in aSMA-tk mice. Subsequently, we noticed a significant reduction in pancreatic fibrosis in aSMA-tk mice ($p<0.5$). Local pancreatic damage, exocrine insufficiency as well endocrine insufficiency was not changed after aSMA cell depletion. However, there we observed extensive lung injury in AP in aSMA-tk animals associated with an excess mortality and increased pain sensitivity shown by open field and VFF tests at day 14 (p=0.01) and 28 (p=0.0001). Moreover, aSMA-depleted mice with CP experienced significant weight loss.

Conclusion: Our study confirms a significant contribution of aSMA+ myofibroblasts on the course of acute and chronic pancreatitis. Depleting them may lead to reduction of fibrosis but at cost of severe lung damage in AP, pain and weight loss in CP. The pathomechanism behind these phenomena and alterations in myofibroblast-inflammatory crosstalk are addressed in our ongoing studies.

P-07-12

Dimethyl trisulphide alleviates the severity of experimental acute pancreatitis through acinar cytoprotection

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Abstract

Background: Acute pancreatitis (AP) is a potentially life-threatening disease without specific treatment. During AP, endogenous hydrogen sulphide (H_2S) production is increased by certain enzymes and is related to AP severity. Interestingly, exogenous slow H_2S-releasing organosulfur agents (e.g. diallyl disulphide and GYY4137) exert anti-inflammatory effects. Dimethyl trisulphide (DMTS) also belongs to the organosulfur molecule family; it shows biological activity and decreases carrageenan-induced paw inflammation, but its effect on AP is unknown. Our aims were to investigate the in vivo and in vitro effects of DMTS in experimental AP.

Methods: AP was induced in FVB/n mice or Wistar rats by intraperitoneal injection(s) of caerulein, ethanol-palmitoleic acid, or L-ornithine-HCl. DMTS treatments were administered subcutaneously simultaneously with AP induction. Disease severity was determined by evaluating pancreatic histological scoring, pancreatic water content and myeloperoxidase activity. Pancreatic heat shock protein 72 (HSP72) expression, sulphide and protein persulfphidation were measured. Tetrazolium salt (MTT) and propidium iodide were utilised to assess cellular viability on primary acinar cells. Intracellular concentrations of reactive oxygen species (ROS) and Ca^{2+} were determined by microfluorimetry.

Results: DMTS treatment significantly alleviated the severity of all three AP models. It decreased the pancreatic infiltration of leukocytes and cellular damage. DMTS also reduced the pancreatic myeloperoxidase activity. During AP, DMTS upregulated the HSP72 expression and elevated serum sulphide and protein persulfphidation. However, pancreatic sulphide levels were unaltered by AP induction or DMTS treatment. DMTS showed cytoprotection against hydrogen peroxide (H_2O_2) and AP-inducing agents (chenodeoxycholate, L-arginine-HCl) in isolated acini. DMTS reduced ROS levels when acinar cells were treated with H_2O_2 or menadione and modulated physiological, but not pathophysiological Ca^{2+} signalling.

Conclusion: Our results suggest that DMTS is a sulphide donor which has anti-inflammatory and antioxidant effects. The beneficial effects of DMTS in AP could be caused by upregulation of HSP72 expression, by its antioxidant properties, by being a H_2S donor molecule, and/or by reducing leukocyte infiltration. Overall, organosulfur compounds are worth further investigation in this potentially lethal disease.

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P-07-13

Determining the role of Serpin E1/PAI-1 in the development and progression of chronic pancreatitis

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Abstract

Background: Chronic pancreatitis (CP) is a multifactorial, fibroinflammatory disease in which chronic inflammation leads to irreversible structural and functional damage to the pancreas. The incidence of the disease is steadily increasing, but no specific therapy is currently available, making the identification of new therapeutic targets a priority. A major morphological feature of chronic inflammation is fibrotic transformation of the tissue, in which the TGF-β pathway plays a prominent role. One component of this signalling process is plasminogen activator inhibitor-1

(PAI-1), which role is known in the regulation of fibrosis during chronic inflammation in other tissues, but its precise role in the pancreas is unknown.

We aimed to define the role of PAI-1 in the development of chronic pancreatitis and to investigate the effect of its inhibition on disease progression.

Methods: In this study chronic pancreatitis was induced in FVB/N mice with 8X50 µg/kg bw i.p. caerulein injection, given every hour, every 3 days for a total of 5 times. PAI-1 activity was inhibited with a specific inhibitor – TM5275 – which was administered orally at a dose of 10 mg/kg bw for 6 days after the 3rd caerulein treatment. To assess the extent of inflammation and fibrosis hematoxylin-eosin and Crossman's trichrome staining were performed, and biochemical assays were used to determine amylase activity and hydroxyproline concentration. PAI-1 expression in the pancreas was examined by RT-qPCR and immunofluorescence staining.

Results: After induction of chronic pancreatitis, the body weight of the animals and pancreatic weight/body weight ratio considerably decreased. Histopathology showed significant pancreatic atrophy and fibrosis, biochemical assay showed increased hydroxyproline concentration and decreased amylase activity while expression of SERPINE1 (the gene encoding PAI-1) and PAI-1 was significantly higher. The rate of body weight and pancreatic weight loss were reduced, pancreatic atrophy, fibrosis and hydroxyproline concentrations were significantly decreased in the TM5275-treated group, no change was detected in amylase activity.

Conclusion: Our results suggest that PAI-1 expression is increased in chronic pancreatitis and that its inhibitions can reduce fibrosis. These data suggest that inhibition of PAI-1 could potentially be a new therapeutic target for the treatment of chronic pancreatitis.

P-07-14

The pancreatic proteases as new analgesic targets in acute and chronic pancreatitis

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Abstract

Background: Acute (AP) and chronic pancreatitis (CP) are characterised by early protease activation with subsequent inflammation, tissue damage and therapy-resistant pain. These mechanisms are triggered by a perineural inflammatory response via proteinase-activated receptors. It is yet not known which protease subclasses specifically mediate pain in AP and CP.

Methods: We performed a quantification of all major protease classes (serine-, cysteine-, aspartate- and metalloproteases) in the pancreas of male C57Bl6/J mice with caerulein-induced AP and CP. For the purpose analgesic therapy, we implanted osmotic pumps filled with specific inhibitors of these protease classes for continuous s.c. application. The abdominal pain reaction was examined via standardised mechanosensitivity, using "von Frey" test (scale from 0 to 20). After sacrificing the pancreatic tissue was pathomorphological analysed. To detect neuronal activity, posterior horn cells of pancreas-innervating spinal cord segments between Th9-12 were immunohistochemically stained for cFos.

Results: We found that intrapancreatic protease levels in AP or CP were markedly altered compared to healthy controls. In detail, the expression of cysteine protease cathepsin S was three times higher in AP and CP than in normal pancreas. Furthermore, there was an increase in the intrapancreatic amounts of ADAM9, MMP2, MMP3 and MMP9. Selective inhibition of these proteases led to a significantly lower pain level. In CP, when compared to placebo mice (Von-Frey-Score 11,2 ± 1,08), treatment with SB3CT (inhibitor of MMP2 and MMP9) decreased pain

to 9,13 ± 1,05, APC366 (inhibits mast cell tryptase) to 8,33 ± 1,55, SB366791 (TRPV1 antagonist) to 8,67 ± 1,37, and LY3000328 (inhibitor of cathepsin S) to 3,25 ± 0,43. To verify the mechanism, $MMP9^{-/-}$ mice were included, which showed almost complete absence of pain. In our histopathological analyses, there was much less tissue damage in animals treated with the selective inhibitors. The pancreata had a significantly lower degree of fibrosis. Additionally, in CP, there was a clear reduction of cFos activity in posterior horn cells (Th9-12).

Conclusion: Selective protease inhibition ameliorates the severity of pain, tissue damage and neuronal activity in acute and chronic pancreatitis. Thus, protease inhibition may lead to a significant improvement of analgesic therapy in the clinical management of acute and chronic pancreatitis.

P-07-15

Anti-inflammatory effects of Xuebijing injection on acute pancreatitis: network pharmacology identification and experimental validation

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Abstract

Background: Xuebijing injection (XBJ) contains traditional Chinese Medicine extracts for intravenous administration that has been widely used for the treatment of acute pancreatitis (AP) in China. However, the underlying mechanisms of XBJ for AP are still unclear.

Methods: In this study, we aimed to reveal the underlying mechanisms of XBJ in AP through network pharmacology and experimental validation. First, we constructed a network of XBJ-AP and identified active ingredients and potential targets of XBJ for AP. Then, we performed functional enrichment analysis and protein-protein interaction analysis to explore the biological functions and pathways of XBJ targets in AP. Next, we selected key targets for further validation by molecular docking and experimental assays. Three different doses of XBJ (2.5, 5 and 10 mg/kg) were superimposed on severe AP model induced by caerulein (50 μg/kg/h × 7) & lipopolysaccharide (10 mg/kg) to evaluate the efficacy of XBJ *in vivo*.

Results & Conclusion: We identified 8 active ingredients and 61 potential targets of XBJ for AP through network of XBJ-AP. XBJ targets were mainly involved in inflammatory response and immune response. The results of molecular docking showed that 8 active ingredients had high binding affinity with key targets (IL-1β and IL-6). The results of experimental assays showed that XBJ (10 ml/kg) treatment significantly alleviated the pancreas histopathological damage and reduced the serum levels of amylase, lipase, IL-1β, and IL-6 in AP mice.

P-07-16

Targeting N-methyl-D-aspartate (NMDA) receptor 1A reduces pain in chronic pancreatitis mouse models

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Abstract

Background: Severe neuropathic pain is a prevalent symptom of Chronic Pancreatitis (CP), affecting approximately 90% of patients and presenting a significant clinical challenge. Despite all efforts, a viable opioid-based therapy option for abdominal pain in CP remains elusive, resulting in poor prognosis and reduced quality of life of the patients. Recent studies have suggested a relationship between CP pain and neurobiology and neuropathophysiology. Recently, our group demonstrated that nNOS antagonist NPLA was effective in reducing severe abdominal pain in a caerulein-induced CP mice model. In addition, the activation of N-methyl-D-aspartate (NMDA) receptors has been known to be associated with neuropathic pain. Therefore, we focused on elucidating and targeting the glutamate-mediated vicious cycle of NMDA receptors to relieve pain in CP.

Methods: Quantitative Polymerase Chain Reaction (Q-PCR), Western-Blot, and Immunohistochemistry (IHC) techniques were performed to detect the expression and immunoreactivity of NMDAR1A in CP and normal pancreatic tissues of both humans and mice. For the IHC studies, at least three different tissues were obtained from different patients, and the QuPath program was utilised to analyse the tissues. In vivo studies were conducted using a caerulein-induced CP mouse model and NMDAR1A antagonist (TCN-201) treatment was administered to four groups of mice (Sham, analgesic alone, TCN-201 alone, analgesic+TCN-201, n=7/group, 28 mice in total), and abdominal pain scores were recorded via the Von-Frey test.

Results: qPCR and WB analyses of human/mouse CP and NP tissues indicated NMDAR1 is overexpressed at both gene and protein levels. The IHC results supported this finding, as NMDAR1A immunoreactivity was significantly increased in CP patients compared to normal pancreas tissues, particularly in the nerves within the tissue. Furthermore, the pain scores of CP patients were used to classify them, and the NMDAR1A immunoreactivity was found to be correlated with the severity of pain, suggesting that NMDAR1A may play a role in neuropathic pain in CP patients. Besides, NMDAR1A antagonist treatment led to a significant reduction in pain sensation of CP-induced mice.

Conclusion: These findings suggest that NMDA receptors and related intracellular downstream effectors may be a valuable target for investigating and reducing neuropathic pain in CP.

P-07-17

The microbiome in pancreatic disease: a technical audit

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Abstract

Background: Accurate microbiome analysis depends on meticulous sampling, analysis, and data-processing. We therefore audited published papers on microbiomes in pancreatic disease against current best standards.

Methods: Audit criteria were set by discussion between the authors. 13 criteria covered: generic scientific methodology; sample acquisition and processing; sequencing; data processing, manipulation and storage. The search: (((Pancreas) OR (Pancreatitis) OR (Pancreas AND Cancer)) AND (Microbiome OR Microbiota)) was run on PubMed, EMBASE and Web of Science to date end 2021. Results collated on a Mendeley database were screened by JH and DF. Selected studies were assessed for compliance with each criterion by JH, DF and AL using Raayan software. Data were entered into an Excel database for further analysis.

Results: Of 2566 reports identified 2334 were rejected on initial abstract screening. Detailed screening rejected a further 153, leaving 79.

Study design: cross sectional 84%, longitudinal 16%; prospective 53%. Sample controls 92%. Sample collection team specified 3%.

Sampling site: faeces 49%, pancreas 30%, oral 15%, bile 10%, blood 10%, duodenum 5%. NB some sampled multiple sites.

Sample storage temp: ambient 9%, -20C 4%, -80C 73%, -150C 2%. Immediate processing 11%, other 1%.

DNA extraction: validated kit 84%, bespoke 4%, not stated 12%. Bead beating documented, 66%.

Analytical controls stated: 38%. Sequencing depth stated: 42%. Diversity indices: Shannon index 63%. Data sharing: 42%.

Conclusion: We found good basic methodology but most studies were cross-sectional, which is questionable as microbiomes are dynamic. The use of faeces in half the studies is understandable, but it may be acting as proxy for other sites. The lack of important technical details probably reflects investigators and reviewers being new to the field. Technical factors such as sequencing-depth and the use of the Shannon Index which may limit identification of lower-abundance species should be available to the reader. Data-sharing availability of 42% is similar to or better than elsewhere. We conclude that many reports appear technically deficient, suggesting that investigators and reviewers require education in these technologies. Agreed guidelines for the conduct and reporting of microbiome analysis would be beneficial to all.

P-07-18

Transcriptomic profiling reveals molecular and inflammatory gene signatures of acute pancreatitis in cyclophilin D knockout and wild-type murine blood

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Abstract

Background: Acute pancreatitis (AP) is an inflammatory disease with severity mediated by the circulation. Cyclophilin D modulates opening of the mitochondrial permeability transition pore that has a key role in the progression of AP. Biological insights into the stepwise development and progression of AP are imperative to develop tailored approaches for diagnosis and optimal clinical management of AP.

Methods: Acute pancreatitis was induced in wild type (WT) and cyclophilin D knockout (Ppif-/-) C57BL/6 mice by intraperitoneal caerulein (CER-AP) or ethanol and palmitoleic acid (FAEE-AP) or ductal injection of taurolithocholic acid 3-sulfate (TLCS-AP), while controls received equivalent saline or no injections. Blood was sampled at 12 hours and mRNA content analysed using Agilent two-colour microarray. Transcripts of blood from AP patients and healthy

controls in the GEO database (GSE194331) were used for comparison by the least absolute shrinkage and selection operator (LASSO).

Results: Comparison of gene expression between all three models and controls identified 99 upregulated mRNAs in WT, whereas the same comparison in Ppif-/- identified 158 upregulated and 38 downregulated mRNAs, and 84 of the upregulated genes were common to WT and Ppif-/-; comparison between WT and Ppif-/- controls identified 45 upregulated and 32 downregulated mRNAs strongly enriched in nitric oxide metabolism in Ppif-/-. Pathway analysis identified multiple upregulated inflammatory responses in both WT and Ppif-/- typified by positive regulation of leukocyte activation, with suppression of inflammatory inhibition. LASSO confirmed differential expression of 41 genes in both murine and human datasets and was used to define a novel inflammatory gene expression signature comprised of five genes.

Conclusion: Transcriptomic profiling revealed the molecular and inflammatory landscape of AP from mouse models, identified differential expression common to murine and human AP, and defined an inflammatory gene signature applicable to both. These data identify potential biomarkers and targetable inflammatory processes.

P-08-02

Prognostic value of longitudinal body composition analysis using deep learning-based segmentation in pancreatic cancer

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Abstract

Background: Sarcopenia has been reported to be related to pancreatic cancer prognosis. However, a comprehensive analysis of body compositions and their longitudinal changes is lacking. Therefore, this study analysed the association between body composition changes and survival in patients with metastatic pancreatic cancer.

Methods: In this retrospective cohort study, we reviewed 456 patients with metastatic pancreatic cancer who received palliative chemotherapy in Seoul National University Hospital in Korea. Using deep learning-based, fully automated segmentation of initial computed tomography (CT), areas of muscle, subcutaneous fat, and visceral fat were extracted at the level of the L3 vertebra. Skeletal muscle index (SMI), visceral adipose tissue index (VATI), subcutaneous adipose tissue index (SATI), and mean muscle attenuation (MA) were calculated. The effects of initial and longitudinal changes of body compositions on survival were analysed.

Results: Higher MA at initial CT was significantly associated with better OS in both males and females (hazard ratio [HR], 0.706; 95% CI, 0.538–0.925 for males, and HR, 0.656; 95% CI, 0.475–0.906 for females), whereas higher SATI (HR, 0.568; 95% CI, 0.388–0.830) was significantly associated with better OS in female patients only. In longitudinal analysis, SMI, VATI, and SATI significantly decreased between initial and 2-month CT, whereas mean MA significantly decreased between 2-month and 6-month CT. In stratified cox regression analysis of longitudinal changes, decrease of SATI in male patients was associated with poor OS (HR, 0.513; 95% CI, 0.354–0.745).

Conclusion: Initial and longitudinal changes of body composition derived from deep learning-based segmentation can be utilised to predict survival of metastatic pancreatic cancer.

P-08-03

Acute pancreatitis secondary to migration and impaction of the intragastric balloon

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Abstract

Background: The intragastric balloon (IGB) is a minimally invasive endoscopic treatment for obesity, with effective and safe outcomes and an overall complication rate of only 2.8%. While serious complications are rare, it is crucial to recognize them for proper patient management. Our objective is to highlight a severe and rare complication that resolves with prompt device removal.

Methods: We present the case of a patient with an intragastric balloon who experienced digestive intolerance and abdominal pain, associated with analytical alterations (amylase 2.800 U/l (28-100 U/l), lipase 274 U/l (12-60 U/l), PCR 32.8 mg/l (< 5 mg/l). Abdominal Computed Tomography with intravenous administration of contrast revealed migration of the balloon, occupying the first and second duodenal portions, compressing them, and also affecting the Vater ampulla. Additionally, there is an increase in the density of periduodenal and peripancreatic fat and a small amount of loco-regional free fluid. These findings are consistent with pancreatic inflammation and duodenal inflammatory/ischemic reaction due to the impaction of the intragastric balloon in the duodenum.

Results: An endoscopy was performed with sedation by an anaesthesiologist, and the balloon was removed without incident. The patient evolved favourably, being discharged in 48 hours.

Conclusion: Although it is infrequent, few cases of pancreatitis secondary to IGB have been reported and two causal mechanisms have been described. In the first one, more common, pancreatitis is caused by direct compression of the pancreatic parenchyma by the balloon. In the second one, indirect, pancreatitis is a consequence of the migration of the device to the duodenum. The risk of migration is described with a frequency of 1.4%, although it increases after 6 months of use, and is associated with loss of device volume. The onset of abdominal pain and digestive intolerance in patients with an intragastric balloon should be treated as an emergency because it might be secondary to a serious underlying complication, such as pancreatitis, which may require device removal. Imaging studies allow assessment of such complications, being the most appropriate imaging technique a contrast-enhanced abdominal CT scan. Withdrawal is usually required and performed endoscopically.

P-08-04

Exceptional annular pancreas divisum

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Abstract

Background: *Annular pancreas divisum* (APD) is a rare congenital variant of pancreatic anatomy that may cause symptoms of recurrent pancreatitis and gastric outlet obstruction. Pancreas divisum (PD) is the most common congenital anomaly of pancreatic ducts. It is present in 0.5-11% of the general population. Annular pancreas (AP) has a much lower incidence (3/20,000 autopsies). The coexistence of both anomalies (APD) is unusual, with limited cases documented in the literature. We describe an exceptional form of annular pancreas divisum diagnosed by ERCP.

Methods: A 14-year-old woman with *Congenital Cerebellar Ataxia* presented recurrent episodes of pain in the upper abdomen radiating to the back, as well as postprandial nausea and vomiting. Laboratory tests showed amylase and lipase levels increase. Abdominal ultrasonography and CT were inconclusive. ERCP was performed.

Results: Cannulation of the major papilla showed a normal bile duct and a short-arborized pancreatic duct (ventral

pancreas). Cannulation of the minor papilla revealed a normal dorsal pancreatic duct as well as a branch that completely crossed the duodenum and ended at the contralateral wall (on the right lateral duodenal side), with duodenal compression and accumulation of contrast agent. These ERCP findings suggested an *Annular Pancreas Divisum* (APD). Unfortunately, the evolution could not be documented as the patient did not attend subsequent check-ups.

Conclusion: A*nnular pancreas divisum* (APD) is a rare congenital anomaly in which both failures (pancreatic migration and fusion) coexist during the fourth week of intrauterine life. Our patient was an exceptional case since the annular duct (AP) drained into the Santorini duct and was associated with pancreas divisum (PD). The AP can give symptoms in children or young adults (abdominal pain, nausea, and vomiting) on the degree of obstruction. Treatment in these cases should be surgical (duodenal bypass). The diagnosis was performed by ERCP with a successful injection of major and minor papilla.

P-08-05

A deep learning based approach to assess tumour characteristics in patients with pancreatic ductal adenocarcinoma

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Abstract

Background: Pancreatic cancer is a devastating disease with a dismal prognosis, currently on track to become the second most lethal cancer by 2030. This can be attributed to the current lack of available biomarkers, a resilience to current treatments and most importantly, because of the pernicious characteristics of this disease. In this project, we explored the possibilities of artificial intelligence regarding medical imaging analysis and how this can be used to detect pancreatic cancer on portal venous phase CT-images.

Methods: We furthered the development of an older hybrid model consisting of both convolutional layers and a transformer encoder. We used imaging data (n=600) originating from three publicly available datasets (MSD, CPTAC-PDA & NIH Pancreas CT) in order to train and test our model. Prior to training, all patients radiologically assessed as IPMN/PanNETs/unequivocal/missing labels were excluded. Final number of patients (n=354) were split into training, validation & testing as (165, 29, 160).

Results: Our model reached a sensitivity of 95% and specificity of 90% for pancreatic cancer (95% CI 0.87-0.96, p=0.3865 & p=<2e-16 for Acc > NIR). It also displayed an average foreground dice score of 0.784 for normal pancreatic tissue and 0.644 for pancreatic cancer.

Conclusion: Hybrid-based AI models continue to demonstrate potential in relation to detection and volumetric assessment of pancreatic cancer.

P-08-06

CT radiomics analysis in the differential diagnosis between pancreatic cancer and chronic pancreatitis

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Abstract

Background: Radiomics is a method that extracts many features from radiographic medical images using data-characterisation algorithms. The goal of this study was to determine whether CT-based machine learning of radiomics features could help to differentiate between pancreatic cancer (PC) and chronic pancreatitis (CP).

Methods: The CT images of 31 PC and 22 CP were retrospectively analysed in the three-dimensional regions of interest in the arterial phase (AP) and venous phase (VP) and segmented by 3D Slicer software. 121 radiomics features were extracted and a random forest was used to distinguish PC from CP. A multivariable logistic regression model was established based on the selected radiomics features. The radiomics score was calculated, and the nomogram was established. The discrimination of each model was analysed by the receiver operating characteristic curve (ROC).

Results: Using machine learning, significant differences were observed in the distribution of gender (P = 0.03), carbohydrate antigen 19-9 (P < 0.01), and carcinoembryonic antigen (P < 0.01) in patients with PC and chronic pancreatitis. The area under the ROC curve (AUC) value of AP multivariate regression model, VP multivariate regression model, AP combined with VP features model (Radiomics) was 0.907, 0.931, and 0.937, respectively. The sensitivity and specificity of the Radiomics model were 0.94 and 0.92, respectively.

Conclusion: Radiomics features help non-invasive differentiate PC from CP with an overall accuracy of 93.1%. The Radiomics model could be a potential tool to distinguish pancreatic cancer from chronic pancreatitis and aid in clinical decisions.

P-08-07

Endoscopic papillary large balloon dilation with wide sphincterotomy and brief balloon expansion is safe and leads rarely in recurrence in large common bile duct stones

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Abstract

Background: While endoscopic papillary large balloon dilation (EPLBD) is an recommended method for large common bile duct stone (CBD) removal, the published results are controversial regarding the dilation times and the extent of sphincterotomy used. Contrary to original EPLBD technique, the purpose of this study was to analyse practical outcomes of EPLBD with very brief papillary dilation time preceded by a standard size endoscopic sphincterotomy in an unselected population with large CBD stones.

Methods: The data was collected from a prospectively hospital-based registry containing details of all ERCP (endoscopic retrograde cholangio-pancreatography) procedures and any readmissions for complications in a teaching tertiary referral centre. The study population consisted of patients undergoing EPLBD procedure during a nine-year period from May 2011 to April 2020. Postoperative outcomes were compared to sex and age-matched control pa-

tients (3:1) with CBD stones undergoing other endoscopic interventions.

Results: During the study period a total of 4,338 patients underwent ERCP, of whom 1,847 patients (43%) had CBD stones. A total of 165 patients (median age 75 [23-97] years, 65% female) underwent EPLBD. The median follow-up time after ERCP was over four years, median 52 mo (range 2-110 mo). Technical success was achieved in all cases. Ten patients (6.1%) underwent subsequent scheduled new ERCP. Only two patients (1.2%) required later unplanned endoscopic treatment for CBD stones. Eleven patients (6.7%) developed post-ERCP complications, mostly mild. Compared to CBD stones treated without EPLBD, (n=495), the overall risk of post-ERCP complications was similar (6.7% vs. 7.5%, p=0.729).

Conclusion: Slightly modified EPLBD with very brief dilation time is an excellent technique in patients with large CBD stones, also when preceded by a standard or wide sphincterotomy. After EPLBD, the recurrence rate is extremely low in the long follow-up time, suggesting cost-effectiveness of EPLBD in achieving definite stone clearance. The risk of complications in EPLBD for large stones was low also in frail elderly and did not differ from controls treated for simple CBD stones.

P-08-08

Morphology of the papilla can predict a higher rate of post-ERCP adverse events - a systematic review and meta-analysis

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Abstract

Background: Endoscopic retrograde cholangiopancreatography (ERCP) is the most commonly used therapeutic procedure for pancreaticobiliary disorders. Although the incidence of adverse events is high, how to achieve safe and effective cannulation is still a question. Thus, we aimed to assess the influence of papilla morphology on ERCP outcomes and adverse events.

Methods: PROSPERO registration number: CRD42022360894. We systematically searched three medical databases from inception in October 2022. Studies detailing the cannulation process or the rate of adverse events in the context of papilla morphology were included. For the primary classification of the papilla, the Haraldsson system was used. A pooled event rate with a 95% confidence interval (CI) was used for the effect size measure. The risk of bias assessment was performed using the Joanna Briggs Institute Critical Appraisal tool for studies reporting prevalence.

Results: A total of 17 studies were eligible, and 14 of them were included in the quantitative synthesis. In the case of studies using the classification proposed by Haraldsson, certain morphological variants were associated with a higher tendency for difficult cannulation. The rate of difficult cannulation was the lowest in type I („regular") papilla (26%; CI: 18–37), followed by type III („protruding or pendulous") (35%; CI: 25–48) and type II („small") papilla (39%; CI: 28–52). The highest rate was observed in the case of type IV („creased or ridged") papilla (41%; CI: 28–55). For post-ERCP pancreatitis, the event rate was the highest in type II („small") papilla (11%; CI: 8–15), and the lowest in type I („regular") (6%; CI: 5–8) and III („creased or ridged") papilla (6%; CI: 4–8). There was no difference in the event rate for cannulation failure and post-ERCP bleeding between the different papilla types. Most studies carried a low risk of bias.

Conclusion: Compared to the regular papilla type, other types are associated with a higher rate of difficult cannulation. Type II („small") papilla is associated with a higher rate of post-ERCP pancreatitis.

P-08-10

A machine-learning based decision tool selecting patients with idiopathic acute pancreatitis for endosonography to exclude a biliary aetiology

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Abstract

Background: Aetiology of acute pancreatitis can be established in the majority of patients. However, in 25 % of cases it remains elusive. Biliary microlithiasis/sludge is detected in up to 75% of patients with idiopathic acute pancreatitis (IAP). As recurrent biliary pancreatitis can be prevented, the underlying aetiology of IAP should be established. The aim of this multicentre retrospective study was to develop a machine learning-aided non-invasive prediction tool to guide clinicians in the selection of idiopathic acute pancreatitis patients to be referred to endosonography to establish aetiology and allow treatment.

Methods: We retrospectively used routinely recorded clinical and laboratory parameters of 1340 consecutive patients with confirmed acute pancreatitis admitted to our tertiary care hospital between 2015 and 2020. Patients who did not receive endosonography as part of the diagnostic work-up and whose pancreatitis episode could be adequately explained by other causes than biliary sludge and microlithiasis were excluded. We trained supervised machine learning classifiers using H2O.ai automatically selecting the best suitable predictor model to predict microlithiasis/sludge. The predictor model was validated in two independent retrospective cohorts from two tertiary care centres (TU Munich & University Medical Centre Göttingen).

Results: Twenty-eight categorized patients' variables recorded at admission were identified to compute the predictor model with an accuracy of 0.84 [95% CI 0.791, 0.9185], positive predictive value of 0.84 and negative predictive value 0.80 in the identification cohort (218 patients). In the validation cohort, the robustness of the prediction model was confirmed with an accuracy of 0.76 [95% CI 0.673, 0.8347], positive predictive value of 0.76 and negative predictive value of 0.78 (117 patients).

Conclusion: We present a robust and validated machine learning-based predictor model consisting of routinely recorded lab work at admission that can predict biliary sludge and microlithiasis as cause of acute pancreatitis and select patients for EUS.

P-08-11

Influence of prevalence and localisation of necrotic lesions on the course of acute necrotizing pancreatitis

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Abstract

Background: Acute necrotizing pancreatitis (ANP) is a life-threating disease with many factors involved on it prognosis. The prevalence and localisation of the pancreatic and parapancreatic lesions play an important role in predicting complications and the course of the disease. Our purpose was to compare the clinical results of treatment of patients with ANP depending on the prevalence and localisation of necrotic lesions.

Methods: Results of treatment of 147 patients with ANP who were admitted to our clinic from 2017 to 2021 was analysed. Depending from CT data they were divided into 3 groups: isolated pancreatic necrosis (IPN), peripancreatic necrosis (PPN) and combined pancreatic necrosis (CPN). Complications, mortality rates, organ failure (OF) and necessary for open surgical interventions in each group were analysed.

Results: There were 44 patients (29.9%) cases of IPN, 22 (14.9%) – PPN, and 81 patients (55.1%) – of CPN. OF was diagnosed in 46.6%: persistent – in 23.8%, and multiple – in 29.3% of patients with CPN. In patients with IPN OF was found in 18.4% and in persons with PPN - in 31.3%. Open surgical interventions were required in 24.5% of patients with IPN, 25.2% with PPN and 48.3% with CPN. Mortality was presented only in CPN group and reached 17.3%.

Conclusion: Prevalence and localisation of necrotic lesions of the pancreas can predict the course of ANP.

P-08-12

Endoscopic ultrasonography in the diagnosis and treatment of paraduodenal pancreatitis

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Abstract

Background: Paraduodenal pancreatitis (PP) is a chronic inflammation of the pancreatic tissue, which is ectopised in the wall of the duodenum. The disease can be independent or accompanied by obstructive pancreatitis in the orthotopic gland. Endoscopic ultrasonography (EUS) greatly facilitates the diagnosis of PP. Treatment tactics are far from a solution and range from conservative treatment and endoscopic interventions to pancreatoduodenal resection. We wanted to assess the possibilities of EUS for the diagnosis and treatment of PP.

Methods: Results of treatment of 42 patients with PP from 2012 to 2021 were analysed. There were 38 men, 4 women. The average age of the patients was 32±2.35 years. All patients underwent a preoperative examination: laboratory tests, ultrasound, MRI and CT of the abdominal organs, endoscopy and EUS. Efficacy of visualization methods for PP diagnosis as well as complications after interventional treatment were studied..

Results: The most frequent clinical signs of PP complications were: abdominal pain, nausea, vomiting, melena, anaemia and weight loss. Stenosis of the lumen of the upper third of the descending part of the duodenum with frequent erosions formation was observed endoscopically in majority of patients. Among all evaluated methods, EUS was the most sensitive for PP diagnosis. Under EUS-guided interventions included: puncture of the cyst of the

wall of the duodenum in 26 patients, endoscopic cystoduodenostomy without stenting in 12 persons and endoscopic cystoduodenostomy with stenting in 4 cases. There were no complications of EUS-guided interventions. Above mentioned treatment was ineffective in 4 patients, to all of them pancreatoduodenal resection was applied.

Conclusion: EUS is the most sensitive method for diagnosis of PP. EUS-guided cystoduodenostomy is the most effective operation for PP treatment.

P-08-13

Endosonography in the diagnosis and treatment of acute peripancreatic fluid collections

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Abstract

Background: Acute peripancreatic fluid collections (APFC) is a frequent complication of acute pancreatitis. The majorities of the APFC are sterile and resolve spontaneously, but some of them could transfer to a pseudocyst. Choosing of appropriate treatment strategy in this situation has not been fully resolved yet. We aimed to study the efficacy of the endosonography (EUS) guided interventions for the treatment of patients with APFC.

Methods: The analysis of EUS treatment of 65 patients with APF during the period 2012-2021 was performed. First revealed postoperative organ failure, the duration of the intensive care after surgery, infectious and postoperative complications, postoperative mortality were calculated.

Results: There were next indications for EUS interventions: compression of the terminal part of the common bile duct with the mechanical jaundice - 18, compression of the duodenum with the gastrostasis, infection (suppuration) - 28. All patients underwent puncture of APFC with subsequent lavage of pathologic foci by an antiseptic. The obtained material was sent for biochemical and bacteriological analysis. Such EUS-guided interventions were the final method of treatment in 43 (66.2%) patients. Repeated procedures were performed in 22 (33.8%) cases and consisted of introduction of double-pigtail stent under EUS control. There were no necessary for any open surgery and no cases of organ failure and mortality.

Conclusion: EUS-guided mini invasive surgery is highly effective methods for treatment of complicated APFC.

P-08-14

PROTOCOL trial – PROTon pump inhibitors and stent OCclusion rate Of Lumen apposing metal stents

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Abstract

Background: A common complication of acute pancreatitis is the formation of necrosis in 5-10% of all patients, which leads to an increased overall mortality of 28% for infected necroses. Currently, lumen apposing metal stents (LAMS) are widely used to address necrotic masses. LAMS-occlusion is postulated to be a considerable complication. However, the prevalence, clinical impact and management of LAMS-occlusion-related complications remains uncertain. Moreover, the German guidelines for management of acute pancreatitis do not specify whether a concomitant proton pump inhibitor (PPI)-therapy should be discontinued or not. A recent study suggested a lower rate of LAMS-occlusions, but a higher number of required endoscopic necrosectomies upon concomitant PPI-therapy. Thus, current data are conflicting.

Methods: We aim to perform an expert survey and a multicentre retrospective cohort study to elucidate the clinical importance of LAMS-occlusion-related complications and the effect of PPI-discontinuation on occlusion. First, a survey will be sent to European centres with special expertise in pancreatology. Here, we aim to assess the number of LAMS applied annually, whether the experts consider occlusion a clinically relevant complication, and whether there are standard operating procedures for LAMS-occlusion and PPI-discontinuation. Second, we will perform a retrospective multicentre cohort study to assess patient data for PPI intake, frequency of LAMS-occlusion and other complications using a RedCap database. This study will be supported by the AG Pancreas (DGVS).

Results: We will present first results from the expert survey and the preliminary results of 80 LAMS applied to drain necroses upon acute pancreatitis from January 2017 until December 2021 at the University Hospital Göttingen. Seventy patients took PPI (87.5%). Fourteen LAMS were occluded and 13 of these were associated with PPI-intake resulting in an OR of 2.0. We therefore aim to include a total number of 639 patients into our retrospective study based on a power calculation of this preliminary dataset.

Conclusion: We aim to present preliminary results from the expert survey and retrospective cohort study. Furthermore, we want to invite further centres to participate.

P-08-15

EUS-guided gastroenterostomy versus enteral stenting for frailer patients with malignant gastric outlet obstruction: a matched prospective comparison

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Abstract

Background: Despite the advantages of EUS-guided Gastroenterostomy (EUS-GE) over enteral stenting (ES) for malignant Gastric Outlet Obstruction (mGOO) in retrospective series, ES is still advocated for patients with shorter life expectancy, whilst no prospective comparison is available.

Methods: All consecutive patients with mGOO treated between March-2021 and June-2022 in a tertiary, academic centre were allocated to EUS-GE versus ES after multidisciplinary discussion and included in a prospective registry

(PROTECT, NCT04813055) with monthly follow-up. Technical/Clinical Success, Adverse Events, Symptom's recurrence, and Survival were compared after 1:1 matching for primary disease, disease stage, ASA score and Charlson Comorbidity Index (CCI).

Results: During study period, 52 EUS-GE and 28 ES were performed (higher baseline ASA score [p=0.02] in the ES group). After matching, 22 patients per arm were analysed, with no baseline differences in age, sex, BMI, primary disease (pancreatic cancer=86%) and stage (metastatic=69%), CCI (8 [5-9]) and ASA score. Technical success was 100% in both arms (p=1). Patients treated with EUS-GE experienced higher clinical success (ability to eat at least a soft solid: 100% vs 73%, p=0.01) and shorter refeeding time (2[1-2] versus 3.5[2-7] days, p=0.002), with a trend to reduced adverse events (5% vs 14%, p=0.3). During a median FU of 75[42-103] and 45[18-143] days respectively, symptoms' recurrence was 5% vs 29% (p=0.04) without any difference in overall survival.

Conclusion: In this first, prospective, matched comparison including frailer patients with more advanced neoplasms, EUS-GE confirmed higher and faster clinical success than ES, with reduced dysfunction and without any increased invasiveness.

P-08-16

EUS-guided gastroenterostomy for management of malignant gastric outlet obstruction: a prospective series from the PROTECT registry

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Abstract

Background: In the setting of malignant Gastric Outlet Obstruction (GOO), retrospective studies have shown several advantages of EUS-guided gastroenterostomy (EUS-GE) compared to enteral stenting and surgical bypass. However, no prospective data is available to date.

Methods: All consecutive EUS-GE performed between March-2021 and June-2022 in a tertiary, academic centre were included in a Prospective Registry Of Therapeutic EndoscopiC ulTrasound (PROTECT, NCT04813055), with monthly follow-up. The primary aims were Clinical Success (possibility to eat at least soft solids), Adverse Events (AEs, according to ASGE Lexicon) and long-term Dysfunction, shown as frequencies (proportions) and medians (interquartile ranges).

Results: Fifty-one patients [male 56.9%; median age 64 (57.5-72), 74.5% with pancreatic cancer, 64.7% with metastatic disease] underwent EUS-GE during the study period, through the Wireless Simplified Technique (WEST), using an electrocautery-enhanced Lumen Apposing Metal Stent (20mm large in 96.1% of cases). Technical success was 98%. Clinical success was reached in 98% of the as-treated population after 2 (1-2) days. AEs were registered in 6 (11.8%) patients, 3 moderate, 1 severe and 2 fatal (exacerbations of pre-existing cholangitis). Median hospital stay was 6 (4-11) days. After a median follow-up of 73 (30-126) days, a recurrence of GOO was noted in 3/48 (6.3%). Median estimated Dysfunction-Free Survival at Kaplan-Meier analysis was 376 (95%CI 323-430) days.

Conclusion: In this first, prospective, single-centre experience, EUS-GE shows excellent efficacy in relieving malignant GOO, with an acceptable safety profile and long-term patency. These data suggest potential advantages of EUS-GE over both standard alternatives, to be confirmed in randomised comparisons.

P-08-17

Same-session endoscopic diagnosis and symptoms' palliation in pancreatobiliary malignancies: clinical impact of rapid-on-site evaluation

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Abstract

Background: Besides increasing adequacy, rapid-on-site evaluation (ROSE) during endoscopic ultrasound (EUS) or endoscopic retrograde cholangiopancreatography (ERCP) may have an impact on choices and timing of subsequent therapeutic procedures, yet unexplored.

Methods: We conducted a retrospective evaluation of a prospectively maintained database of a tertiary, academic centre with availability of ROSE and hybrid EUS-ERCP suites. All consecutive patients referred for pathological confirmation of suspected malignancy and Jaundice or gastric outlet obstruction (GOO) between Jan-2020 and Sep-2022 were included.

Results: Of 541 patients with underlying malignancy, 323 (59.7%) required same-session pathological confirmation (male: 54.5%; age 70 [62-77]; pancreatic cancer: 76.8%, cholangiocarcinoma 16.4%). ROSE adequacy was 98.9% for EUS and 50% for ERCP-guided sampling. Amongst 302 patients with Jaundice, ERCP cannulation was successful in 83.7%, but final drainage was completed in 97.4% thanks to 37 EUS-Choledochoduodenostomies and 5 EUS-Hepaticogastrostomies. Amongst 21 patients requiring GOO palliation, EUS-Gastroenterostomy was performed in 15 and duodenal stenting in 6. All 53 therapeutic EUS procedures occurred after adequate ROSE. Amongst ERCP-guided placement of stents, the use of plastic stents was significantly higher amongst patients with inadequate ROSE (10/11 [90.9%] versus 14/240 [5.8%], p<0.0001, OR=161 [19-1352]). Median hospital stay for diagnosis and palliation was 3 [2-7] days and median time to chemotherapy was 33 [24-47] days.

Conclusion: Nearly two-thirds of oncological candidates to endoscopic symptoms palliation requires contemporary pathological diagnosis. An adequate ROSE allows same-session state-of-the-art therapeutics standardly restricted to pathologically confirmed malignancies (e.g. uncovered SEMS or therapeutic EUS), potentially leading to shorter hospital stay and time to chemotherapy.

P-08-18

Endoscopic ultrasound-guided detective flow imaging (DFI) to evaluate pancreatic microvascularisation in patients with non-calcific chronic pancreatitis: a prospective, single-centre, observational study

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Abstract

Background: Diagnosis of non-calcific chronic pancreatitis (CP) remains a clinical challenge. Together with morphological changes, evaluation of pancreatic microvascularisation could be useful in these patients, since the pancreatic inflammatory process could alter it. The development of techniques allowing the evaluation of microvascularisation (Detective Flow Imaging, DFI) guided by endoscopic ultrasound (EUS) opens a new area of interest in this setting. EUS-DFI allows the evaluation of microvascularisation and low-velocity blood flow without the need of contrast agents. There are no data on the potential usefulness of this technique in the evaluation of CP. Aim of our study was to evaluate the findings of EUS-DFI in patients with clinically suspected CP.

Methods: A prospective, single-centre, observational study was designed. Patients undergoing EUS with advanced imaging for the evaluation of CP were included. Procedures were performed with a linear echoendoscope (Fujifilm 740UT) attached to the ultrasound system Arietta 850. EUS criteria of CP according to Rosemont classification were evaluated. EUS-DFI findings were classified into 4 grades (grade 0- absence of microvascularisation; grade 1- reticular pattern with minimal microvascularisation; grade 2- reticular pattern with moderate microvascularisation; grade 3- reticular pattern with marked microvascularisation. Correlation between EUS-DFI grades and the different groups of the Rosemont classification was analysed by chi-squared test.

Results: 56 patients were included (mean age 54 years, range 21-78, 23 males). 13 patients (23.2%) presented a normal pancreas at EUS, 10 (17.9%) indeterminate findings of CP, 31 (55.4%) suggestive changes of CP and 2 (3.6%) consistent with CP. A EUS-DFI grade 0 (n=13) was just seen in normal pancreas. A EUS-DFI grade 1 (n=11) was associated with indeterminate findings of CP in 82% of the cases. A grade 2 (n=26) was associated with suggestive findings of CP in 96% of the cases, whereas a grade 3 (n=6) was seen in patients with suggestive (n=4) and consistent (n=2) findings of CP ($p<0.001$).

Conclusion: The evaluation of pancreatic microvascularisation by EUS-DFI can be a useful tool for the evaluation of the inflammatory process in CP. Further studies are needed to evaluate the accuracy of this new technology for the diagnosis and activity evaluation of CP.

P-08-19

A long-term follow-up of patients with painless chronic pancreatitis after ESWL and endoscopic management

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Abstract

Background: Pain is one of the most common manifestation of chronic pancreatitis (CP). However, there existed another form of CP called painless CP, characterised as absence of pain and diagnosed mostly due to check-up. Research concerning clinical features of painless CP is limited and no studies describing long-erm outcomes of endoscopic treatment for painless CP patients have been reported. Thus, this study constructed a clinical cohort of patients with painless CP and analysed their baseline data, long-term outcome of endoscopic treatment to understand better the clinical characteristics of painless CP patients.

Methods: This cohort retrospectively enrolled patients with a diagnosis of painless CP admitted to our gastroenterology department receiving endoscopic treatment and /or extracorporeal shock wave lithotripsy (ESWL) between January 2008 and October 2020. Detailed demographic data and CP-related medical history information were statistically analysed. The last follow-up time was April 2022 and information (weight, improvement of digestive symptoms and pancreatic function, etc.) was recorded.

Results: A total of 209 painless CP patients were included, with median age at treatment of 54.0 (44.0–61.0) years old, including 132 (63.2%) males. The median follow-up time was 47 months, ranging from 20 to 166 months. The most common reason leading to diagnosis of CP was check-up (73.7%), followed by pancreatic insufficiency (18.1%). Diabetes mellitus (DM) and steatorrhea were present in 105 (50.2%) and 69 (33.0%) patients before endoscopic treatment, respectively. Patients with DM before endoscopic treatment had higher age of diagnosis (P=0.020) and treatment (P=0.025). Patients with steatorrhea before endoscopic treatment had lower BMI (P=0.02) and more patients had decreased weight (P=0.006) . Glycated haemoglobin was significantly decreased (P=0.002) while weight showed no difference after endoscopic treatment (P=0.244). Complete relief of steatorrhea was found in 25 of patients who report steatorrhea before endoscopic treatment. The univariate results showed that sex, smoking and drinking history were associated with complete relief of steatorrhea, and multivariate analysis suggested that male (OR=0.17; 95% CI, 0.34-0.88; P = 0.034) was an independent influencing factor.

Conclusion: Patients with painless CP had better glucose control and achieved relief of steatorrhea after endoscopic treatment especially in female patients.

P-08-20

Impact of biliary stent on endoscopic ultrasound fine needle biopsy (EUS-FNB) performance in pancreatic solid lesions diagnosis

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Abstract

Background: Data about the impact of biliary stents on the diagnostic yield of EUS-guided tissue acquisition (EUS-TA) for diagnosing pancreatic head lesions are scarce and controversial. With the introduction of the new needle for fine-needle biopsy the EUS diagnostic yield is increased. The aim of the study was to assess whether the presence of plastic or metal stents impairs the diagnostic performance of EUS-FNB.

Methods: Retrospective study on consecutive patients who underwent EUS-FNB between January 2018 to November 2022 for pancreatic solid lesion of the head/uncinate process. Data about sex, age, lesion site and size, type and calibre of needle used, number of passes, presence and type of biliary stent were collected. Continuous variables were compared using the Student t-test. Categorical variables were compared using the Fisher's exact test. A $p < 0.05$ was considered significant.

Results: We enrolled 265 patients (46% male, mean age 69±12). The mean size of lesion was 29±11 mm. In the 41.5%, 22 G Acquire needle was used. The median number of needle passes was 3 (range 1-3). 58 patients had biliary stents at time of the EUS-FNB and in 53.4% was metallic. Overall, the EUS-FNB was diagnostic in 88.3% lesions. There was no difference in term of lesion's size (30.1±8 vs 29.4±11 p 0.66), use of 22 G needle (26/58 vs 84/207 p 0.65) and number of passes (2±1 vs 2±1 p 0.88) between patients with or without biliary stent. The use of a 22 G needle was associated with a higher rate of diagnostic sample (103/234 vs 7/31 p 0.03). The rate of diagnostic biopsy in the group without stent was 78.6% while in the group with biliary stent was 21.4% (p 0.64). At the univariate and multivariate regression analysis the presence of biliary stent did not influence the EUS-FNB performance (OR 0.9 95%CI 0.3-2.4).

Conclusion: The presence of biliary stent does not influence the diagnostic performance of EUS-FNB in pancreatic solid lesion thanks to the introduction of FNB needle. The use of 22 G FNB needle seems to improve the diagnostic rate independently by the presence of the stent.

P-08-21

Outcomes predictors in endoscopic ultrasound-guided choledochoduodenostomy with lumen-apposing metal stent: a systematic review with meta-analysis

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Abstract

Background: EUS-guided choledochoduodenostomy (EUS-CDS) is a minimally invasive procedure used to treat malignant biliary obstruction (MBO) by the transduodenal placement of a lumen-apposing metal stent (LAMS) into the extrahepatic bile duct. In order to identify the factors that contribute to safe and effective EUS-CDS procedures using LAMS we performed a systematic review of the literature with meta-analysis.

Methods: The methodology of our analysis was based on PRISMA recommendations. Electronic databases (Medline, Scopus, EMBASE) were searched up to November 2022. Full articles including patients with distal malignant biliary obstruction who underwent EUS-CDS using LAMS after failed ERCP were eligible. Technical success, clinical success, and adverse events were pooled by means of a random model. Multivariate meta-regression and subgroup analysis were performed to assess the correlation between outcomes and different variables.

Results: Twelve studies with 845 patients were included in the meta-analysis. Pooled technical and clinical success rates were 96% (95%CI: 94%-98%; I2=52.29%) and 96% (95%CI: 95%-98%), respectively, with no significant association with baseline characteristics, such are sex, age, common bile duct (CBD) diameter and stent size. The pooled AE rate was 12% (95%CI: 8%-16%; I2=71.62%). The AE rate was significantly lower when using an 8x8mm stent as compared to a 6x8 mm LAMS (OR 0.59, 0.35-0.99; p=0.04), with no evidence of heterogeneity (I2=0%).

Conclusion: EUS-CDS with LAMS is confirmed to be a safe and effective option for relief of MBO. The selection of

appropriate stent size is crucial for achieving optimal outcomes.

P-08-22

The impact of pancreatic fibrosis at multidetector computed tomography results: preliminary study results

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Abstract

Background: To clarify connections between pancreatic fibrosis grade and results of multidetector computed tomography (MDCT).

Methods: This study was conducted within the healthcare research project “Assessment of pancreatic fibrosis as a prognostic factor for its diseases course” funded by Autonomous non-profit organization “Moscow Centre for Innovative Technologies in Healthcare” administered by the Moscow Healthcare Department.

We analysed results of contrast-enhanced 128-row MDCT from 43 patients who underwent surgery from April to December 2022 due to benign and malignant pancreatic tumours as well as advanced chronic pancreatitis (CP), mean age 56.8±14 (25-84). We calculated normalized contrast enhancement ratio during the pancreatic (PP) and venous phases (VP), as well as contrast enhancement ratio between VP and non-contrast MDCT Morphological signs of CP as well as pancreatic fibrosis grade were assessed by experienced pathologists according to Klöppel & Maillet’s scoring system for the evaluation of the extent of fibrosis in CP.

Results. We received significant intergroup differences between mean values of normalized contrast enhancement ratios during PV and pancreatic duct epithelium metaplasia (p=0.02) and within morphological signs of pancreatic inflammation (p=0.017). There were differences in mean values of normalized contrast enhancement ratios during PV in groups divided by perilobular fibrosis grade (p=0.04). Unenhanced pancreas density value significantly differed in patients with pancreatic inflammation signs (33.1±11HU) and pancreatic duct epithelium metaplasia (33.1±8.1 HU) than in patients without both phenomena (40.8±5.9HU and 41.2±9.5HU, respectively), with p=0.01 and p=0.001, respectively. We revealed significant intergroup differences in unenhanced pancreas density value depending on intralobular fibrosis grade. Enhancement ratio values were also significantly different in groups divided by perilobular fibrosis grade (p=0.024).

Conclusion. Morphological signs of CP and pancreatic fibrosis like pancreatic tissue inflammation and pancreatic duct epithelium metaplasia as well as pancreatic peri- and intralobular fibrosis grade affect MDCT pancreas enhancement characteristics. It could be useful for noninvasive pancreatic fibrosis diagnosis and prognosis.

P-08-23

Shear wave elastography for the diagnosis of non-calcific chronic pancreatitis: a prospective, single-centre, observational study

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Abstract

Background: Diagnosis of non-calcific chronic pancreatitis (CP) is a clinical challenge. EUS shows a high diagnostic sensitivity in this context, but specificity of mild EUS changes is limited. New advanced imaging techniques associated to EUS, such as strain elastography (SE), have proven to be useful in this context. Recently, the development of shear wave elastography (SWE) opens a new alternative for the evaluation of pancreatic fibrosis. Aim of our study was to evaluate the accuracy of SWE for the evaluation of patients with clinical suspicion of CP.

Methods: Prospective study of patients undergoing EUS. Procedures were performed with a linear echoendoscope (Fujifilm 740UT) attached to the ultrasound system Arietta 850. EUS criteria for CP from Rosemont classification were evaluated. A significant area corresponding to the pancreatic body was selected for SWE. Five SWE measurements were done and the mean wave velocity (Vs) and pressure (Kpas) were calculated. SE was performed at the same location, and the strain histogram (SH) and the strain ratio (SR) were quantified. Data are shown as mean (95%CI) and percentage, and were analysed by ANOVA and linear regression.

Results: 56 patients were included (mean age 54 years, range 21-78, 23 males). 13 patients (23.2%) presented a normal pancreas, 10 (17.9%) indeterminate findings for CP, 31 (55.4%) suggestive of CP and 2 (3.6%) consistent with CP. The Vs was 1.67 (1.33-2.01) in normal pancreas, 2.13 (1.70-2.57) in indeterminate for CP, 2.70 (2.52-2.89) in suggestive for CP and 3.19 (1.10-5.29) in consistent with CP ($p<0.0001$). Pressure (KPas) was 9.18 (4.99-13.37) in normal pancreas, 14.70 (8.40-21.01) in indeterminate for CP, 23.09 (19.95-26.24) in suggestive for CP and 31.55 (16.09-79.19) in consistent with CP ($p<0.0001$). Number of EUS criteria for CP correlated with Vs ($r=0.672$, $p<0.001$), and Kpas ($r=0.640$, $p<0.001$). SR correlated with Vs ($R=0.689$, $p<0.001$) and Kpas ($R=0.661$, $p<0.001$). SH correlated with Vs (0.713, $p<0.001$) and Kpas (0.661, $p<0.001$).

Conclusion: EUS-SWE (Vs and Kpas) allows evaluating the degree of pancreatic fibrosis in CP. EUS-SWE results correlate significantly with EUS-SE.

P-08-24

Strain elastography for the diagnosis of non-calcific chronic pancreatitis (CP). Strain ratio or strain histogram?

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Abstract

Background: Strain elastography (SE) allows quantifying the degree of pancreatic fibrosis in CP. Two methods of

measuring pancreatic fibrosis by SE, the strain ratio (SR) and the strain histogram (SH) are available. No study has compared so far these two methods for the diagnosis of CP. Aim of our study was to evaluate the diagnostic yield of SR and SH for non-calcific CP.

Methods: A prospective, comparative study of the diagnostic accuracy of SR and SH for CP was designed. Patients undergoing EUS for the evaluation of CP were included. Patients with calcifying CP were excluded. Procedures were performed with linear echoendoscopes (Pentax 34J10, 38J10, and Fujifilm 740UT) and the ultrasound system Arietta 850. Rosemont EUS criteria for CP were evaluated. An area of the pancreatic body (A) was selected for SR and SH measurement. A soft extrapancreatic area was additionally selected as reference area for SR (B), being the quotient B/A the SR result. Data are shown as percentages, mean (95%CI), and analysed by ANOVA and linear regression. The diagnostic accuracy of SR and SH were evaluated using the Rosemont classification as the reference method. STARD criteria for studies of diagnostic accuracy were followed.

Results: 141 patients were included (mean age 47 years, range 17-77, 62 males). 22 (15.6%) patients presented a normal pancreas, 65 (46.1%) indeterminate findings for CP and 54 (38.3%) suggestive for CP. SR was 1.99 (1.85-2.13), 3.18 (3.02-3.34), and 4.46 (4.16-4.75), and SH 146.63 (136.07-157.18), 101.09 (95.99-106.19), and 79.88 (75.18-84.58) in normal pancreas, indeterminate and suggestive of CP, respectively ($p<0.0001$). Number of EUS criteria correlated significantly with the degree of pancreatic fibrosis as evaluated by SR ($r=0.768$, $p<0.0001$) and SH ($r=0.752$, $p<0.0001$). A SR > 2.33 showed sensitivity of 94.2% and specificity of 95.2% for the diagnosis of CP, with an area under the ROC curve of 0.982. Similarly, a SH <115 showed sensitivity of 85.8% and specificity of 100%, with area under the ROC curve of 0.965.

Conclusion: The quantification of pancreatic fibrosis by SR and SH during pancreatic EUS-SE show a very high and similar diagnostic accuracy in patients with suspected CP.

P-08-25

Timing of lumen-apposing metal stents removal in pancreatic fluid collections: could we go beyond?

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Abstract

Background: Lumen-apposing metal stents (LAMS) are becoming the mainstay treatment for pancreatic fluid collections (PFC). A 4-weeks interval for LAMS removal has been suggested to avoid adverse events (AEs) such as buried stent and bleeding. However, recent evidence is changing this paradigm. Aim of the study is to evaluate the rate of AEs in patients with PFC undergoing LAMS removal < 4 weeks and > 4 weeks from placement.

Methods: Retrospective study on patients underwent EUS-guided drainage of PFC with LAMS at Therapeutic Endoscopy Department of Campus Bio-Medico Hospital of Rome. PFC and LAMS features were collected. AEs were defined as bleeding, LAMS obstruction and buried LAMS. Categorical variables were analysed by Fisher's exact test, and continuous variables were analysed by Student's t-test. $P < 0.05$ was considered significant.

Results: From May 2018 to January 2023 fifty-five patients with PFC were enrolled (60% (33/55) male; mean age 60±15). 19/55 (34.5%) were located in the head of the pancreas. The 52.7% were larger than 80 mm. A 15x10 mm LAMS was used in 38/55 (69.1%) of the procedures. In the majority of the procedures (50/55), gastric access was

used. In 11/55 LAMS was dilated in the same session. During follow-up 4 AEs occurred (2 bleeding and 2 stent obstruction) and half of them were before 4 weeks. The mean time of LAMS indwelling was 89 days. In 5 patients a LAMS migration was observed. The persistence of LAMS > 4 weeks was not associated with a higher risk of AEs. There was no difference in the rate of AEs in term of PFC size, LAMS dilation and access site. The use of LAMS with calibre > 15 mm was associated with a higher risk of AEs (3/4 vs 35/51 p 0.02). There was no difference in terms of AEs occurrence with the mean age (57±13 vs 59±15 p 0.8) and the mean time of LAMS removal (181±118 vs 82±100 p 0.06).

Conclusion: When needed, LAMS removal > 4 weeks appears to be as safe as LAMS removal within 4 weeks. However, further studies are needed to support these findings.

P-08-26

Deep learning-based algorithm for PDAC metastasis prediction on CT images

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Abstract

Background: Up to 52% of Pancreatic Ductal Adenocarcinoma (PDAC) patients are diagnosed with metastasis. Visual inspection of whole-body radiology image is currently the main method used by clinicians to determine the presence of metastasis. Predicting the presence of PDAC metastasis is crucial for stablishing a precision treatment. We aimed to build an artificial intelligence algorithm to predict presence of metastases in PDAC patients based on primary tumour CT image analysis.

Methods: Contrast-enhanced CT images from 111 PDAC patients from two hospitals in Spain contributing to the PanGenEU study were manually segmented and randomly grouped into training and validation set on cross-validation. For each patient, the cross-section slices and their corresponding masks with the top 4 largest tumour area were retrieved and the tumour region was extracted automatically. Subsequently, each image and its masks around tumour centre were rotated with a step 60° to generate the single patient ensembles. A powerful fusion deep learning model named PMPD (Pancreatic Tumour Metastasis Prediction via Deep learning) was developed to predict the presence of metastasis accurately. Presence/Absence of metastases were predicted by the proportion of extracted images classified as metastasis by the PMPD and the cutoff value was determined using the validation set. We further designed 3 basic deep learning models to comprehensively compare them with the PMPD.

Result: At the patient level, the PMPD model achieved a mean accuracy of 0.856 and a mean AUC of 0.851. When stratified by the different metastasis sites, the weight-average, micro-average, and macro-average were 0.919, 0.919, and 0.942, respectively. When grouping patients according to the metastasis sites, the AUC of local and distance metastasis was 0.860 and 0.851, and the accuracy was 0.909 and 0.885, respectively. For tumours smaller than 2cm in size, the PMPD model had an AUC of 0.855 and an accuracy of 0.889.

Conclusion: The proposed model may represent a powerful tool for identifying individuals with or without metastasis using only the tumour image from their CT-scan, which could aid in the clinical management of PDAC patients.

P-08-27

Dynamic contrast-enhanced ultrasound (D-CEUS) to predict biological behaviour in pancreatic cancer: monocentric study preliminary results

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Abstract

Background: Pancreatic cancer (PC) is one of the most lethal tumours worldwide, and in 2030 it will become the second leading cause of cancer related death. Computed tomography (CT) and magnetic resonance imaging (MRI) are the gold standards to stage the disease. Nevertheless, these imaging modalities are unable to provide real-time information on biological characteristics of tumours, such as vascularity, which is proportional to angiogenesis, growth rate, and necrosis. Dynamic contrast-enhanced ultrasound (D-CEUS) is able to evaluate microvascular perfusion in real time and provide quantitative parameters. We aimed to evaluate the role of D-CEUS in characterisation of PC.

Methods: 38 patients with suspected PC were prospectively enrolled between October 2022 and March 2023. All patients underwent endoscopic ultrasound guided biopsy for histological diagnosis and CT or MRI for staging. According to these modalities, patients were divided into three categories: resectable PC (R-PC), locally advanced PC (LA-PC), and metastatic PC (M-PC). D-CEUS was performed the same day of lesion biopsy, and time-intensity parameters were compared among tumour categories. The diagnostic performances of selected parameters were evaluated by receiver operating characteristic (ROC) analysis.

Results: PC was diagnosed in 36 (94.7%) patients and classified as R-PC, LA-PC and M-PC in 5 (13.9%), 13 (36.1%) and 18 (50%) patients, respectively. Among perfusion parameters, time to peak (TTP) showed a trend to increase in LA-PC patients (median 18.03 sec, interquartile range [IQR] 14) compared to R-PC group (median 12.9 sec, IQR 3.05) ($p = 0.05$) and it was significantly higher in LA-PC group compared to M-PC group (median 12.35 sec, IQR 4.08) ($p = 0.03$). A cut-off value of 11.6 sec showed a good accuracy to distinguish LA-PC from M-PC (area under the ROC curve = 0.74) with maximal specificity (100%) but low sensitivity (50%).

Conclusion: Quantitative perfusion parameters extracted from D-CEUS seem to be useful in distinguishing the invasiveness of PC. In particular, TTP, a parameter related to blood flow was higher in LA-PC compared to M-PC, suggesting different microvascular characteristics of the tumours. Further studies on larger population are needed to confirm these findings and explore the biological basis for this phenomenon.

P-08-28

Clinical outcomes of endoscopic ultrasonography-guided transmural drainage with lumen apposing metal stent for peripancreatic fluid collection

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Abstract

Background: Endoscopic ultrasonography-guided transmural drainage (EUS-TD) for peripancreatic fluid collection (PFC) can be performed quickly and minimally invasively with the use of a novel fistula-forming prosthetic material, lumen apposing metal stent (LAMS), which is now widely used. The purpose of this study was to clarify the current clinical outcomes of a LAMS.

Methods: We performed a retrospective study of patients who underwent EUS-TD with a LAMS for PFC between September 2019 and November 2022 at our hospital.

Results: Twenty-six patients were treated with a LAMS. The patient characteristics were as follows: male to female ratio, 16:10; median age, 66.5 years (20-89); PFC type: acute peripancreatic fluid collection (APFC) 2, acute necrotic collection (ANC) 7, pancreatic pseudocyst (PPC) 9, walled-off necrosis (WON) 4, and postoperative pancreatic fistula (POPF) 4.The procedure characteristics were as follows: transgastric route to transduodenal route ratio, 23:3; puncture sites: pancreatic head 9, pancreatic body 6, and pancreatic tail 11; median maximum diameter of PFC was 78.5 mm (42-200); median total procedure time was 19 minutes (9-37), and median time from puncture to LAMS placement was 3.5 minutes (2-5); technical success rate was 100% (26/26), and clinical success rate (cyst diameter reduction and improvement in clinical findings within 48 hours) was 84.6% (22/26). Patients without the 1st clinical success had their PFC treated by repeated direct endoscopic necrosectomy (DEN) or additional insertion of another LAMS in 4 patients. The complication rate was 11.5% (3/26), and all cases were bleeding. They healed by interventional radiology or endoscopic intervention. The inserted LAMS was removed in 20 cases, and not removed in 6 cases (impossible 4; death 2). No stent-related problems occurred in the unremoved cases.

Conclusion: EUS-TD by a LAMS is the first choice for PFC because it is a safe and quick procedure with high drainage effect. Patients who require long-term implantation of a LAMS should be carefully monitored for stent-related problems in the future.

P-08-29

Pancreatic steatosis: metabolic implications and correlation with ultrasound findings

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Abstract

Background: Pancreatic steatosis (PS) is often associated with metabolic disorders, such as insulin resistance, type 2 diabetes and obesity. PS is an increasing incidental finding, detected during abdominal ultrasound. Currently, the most reliable method to quantify pancreatic fat is magnetic resonance imaging (MRI). However, MRI is not cost-effective for diagnosis and follow-up of PS. Our study aims to validate an ultrasound-based diagnostic and staging

method for PS and to correlate the ultrasound degree of PS to early stages of metabolic disorders before diabetes occurrence.

Methods: A total of 26 non-diabetic patients with ultrasound PS were recruited (mean age 55.1 yrs), 16 women and 10 men. The average value of BMI was 29.33+/- 8.38 kg/m2. All subjects underwent a 2-h oral glucose tolerance test (75 g glucose) with measurements of glucose and insulin. We also estimated beta-cell function through Disposition Index and Insulinogenic Index and insulin sensitivity by Matsuda Index. Furthermore, patients underwent upper abdominal ultrasound with qualitative and semiquantitative evaluation of pancreatic and hepatic degree of adipose infiltration.

Results: PS was present in 26.9% of the patients as mild, 69.2% as moderate, 3.8% as severe. Hepatic steatosis was present in 61.5% of the patients. Among all patients, 69.2% exhibited normal glucose tolerance (NGT) while the remaining 30.7% had impaired glucose tolerance (IGT). Within the NGT group, 5.5% displayed severe PS, 72.3% moderate PS, 22.2% exhibited mild PS. Among the IGT group, 62.5% presented moderate steatosis, while 37.5%% mild steatosis. Our findings did not reveal any significant association between the degree of PS assessed by ultrasound and the metabolic parameters investigated. Lastly, as the metabolic values worsened, any correlation was found with pancreatic stiffness.

Conclusion: Pancreatic steatosis did not show correlation with metabolic parameters worsening in a group of patients with NGT and IGF. Therefore, likely the onset of metabolic impact of pancreatic steatosis occurs in advanced stages of the disease. Thus, prediabetic subjects require long-term follow-up to detect changes in PS with metabolic parameters worsening. Moreover, further studies in patients with diabetes are also necessary to understand if a higher degree of PS correlates with worse metabolic control.

P-08-30

Maintaining plastic stent after metal stent removal is associated with less recurrence of peripancreatic collections

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Abstract

Background: Peripancreatic collections (PC) represent potentially serious local complications of acute pancreatitis. Transmural endoscopic drainage using luminal apposition metal stent (LAMS) is crucial in the sequential approach. The risk of recurrence after removal of the LAMS remains an unaddressed concern. The replacement of LAMS with transmural plastic stent (PS) may potentially prevent this event.

Methods: Descriptive, retrospective and single-centre study, based on the prospective registry of all PC drained with LAMS in a tertiary hospital between 2016 and 2022. Our objective was to identify the factors related to recurrence of collections.

Results: A total of 63 patients with PC underwent EUS-guided drainage using a LAMS during the study period. The final cohort had a mean age of 59.53 +/- 14.31 years and 82% of patients were males. Aetiologies of acute pancreatitis were: gallstones 52.4%, alcohol induced 17.4%, post-ERCP 4.8%, others 25.4%. Main indication for endoscopic drainage was infected walled-off pancreatic necrosis (WON) in 39 patients (62%). The median size of collection was 83 mm (48-229 mm). Patients were followed-up for a mean of 15.68 months and time to LAMS removal was 35 days. 14 patients required also percutaneous drainage.

In more than half of the patients (35/63) PS was left after removal of LAMS. Recurrence of PC occurred in 14 patients, 2 with PS and 12 without. In the univariate analysis it was observed that recurrence is significantly lower in patients who maintain a PS (14% vs 85%, $p < 0.05$) and in patients who underwent dual modality drainage (both endoscopic and percutaneous) ($p < 0.05$). No complications of long-term indwelling transmural stents were observed. Patients with asymptomatic recurrence (9/14) were managed conservatively.

Conclusion: It is important to identify patients at high risk of recurrence of PC following removal of transmural stents. Maintaining a transmural plastic stent after LAMS removal prevented recurrence of PC in this cohort. The small sample size and retrospective nature are limitations of the current study. Further prospective trials are required to compare the effect of replacing LAMS with a PS versus no plastic stent on the incidence of recurrent PC.

P-08-31

Prognostic value of preoperative CT scan derived body composition measures in resected pancreatic cancer

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Abstract

Background: It is still unclear if preoperative body composition may affect prognosis of pancreatic cancer patients undergoing surgery. The aim of the present study is to assess the extent to which preoperative body composition impacts on postoperative complication severity and survival in patients undergoing pancreatoduodenectomy for cancer.

Methods: A retrospective cohort study was performed on consecutive patients who underwent pancreatoduodenectomy with preoperative CT scan imaging available. Body composition parameters including total abdominal muscle area (TAMA), visceral fat area (VFA), subcutaneous fat area (SFA) and liver steatosis were assessed. Sarcopenic obesity was defined as a high VFA/TAMA ratio (>3.2). Postoperative complication burden was evaluated with the comprehensive complication index (CCI).

Results: Overall, 371 patients were included in the study. At 90 days after surgery, 80 patients (22%) experienced major complications. The median CCI was 20.9 (IQR 0-30). At multivariate linear regression analysis, preoperative biliary drainage, ASA score ≥3, fistula risk score and sarcopenic obesity (37% increase; 95% CI 0.06-0.74; p=0.046) are correlated to increase CCI. Patients' characteristics associated to sarcopenic obesity were: older age, male gender, obesity and preoperative LS. At a median follow-up of 25 months (IQR 18-49), median disease-free survival (DFS) was 19 months (IQR 15-22). At cox-regression analysis, only pathological features were associated with DFS, while liver steatosis and other body composition measures did not show a prognostic role.

Conclusion: The combination of sarcopenia and visceral obesity was significantly associated with increased complication severity after pancreatoduodenectomy for cancer. Patients' body composition did not affect disease free survival after pancreatic cancer surgery.

P-08-33

Endoscopic papillectomy: a multicentre, retrospective, nationwide study after the standardisation of the technique

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Abstract

Background: In the last 20 years, endoscopic papillectomy (EP) has become the gold standard treatment for ampullary adenomas and early stage adenocarcinomas, thereby replacing surgical resection, which is burdened by higher rates of morbidity and mortality. However, the data supporting safety and efficacy of EP derive from multiple retrospective studies, that included procedures mostly performed before 2015, when first guidelines on endoscopic management of AN were available. This had an impact on large variability in patient selection criteria and endoscopic techniques, resulting in heterogenous outcomes. Therefore, the aim of our study is to provide data on efficacy and safety of this technique, by including consecutive patients treated after the standardization of this technique.

Methods: All patients who underwent EP at 19 Italian centres between January 2016 and December 2021 were included. Clinical success was defined by the complete endoscopic management of the neoplasm and any eventual recurrence found in the follow-up period. EP-related adverse events and recurrences were recorded.

Results: A total of 225 patients were included. The mean lesion's size was 20 mm (5–80 mm). En bloc resection was possible in 72.5% of cases, with an overall R0 resection rate of 50.7%. During a mean follow-up period of 23.2 months, recurrences were diagnosed in 17.2% of patients, 61.3% of which were successfully treated with an additional endoscopic treatment. Thus, clinical success was achieved in 76.7% of the cases. In multivariate analysis, R1 resection, lesion size and histological diagnosis were predictors for recurrence. Intra-procedural bleeding occurred during 12.4% of EP. Post-EP adverse events (AE) occurred in 39.5% of patients, including delayed bleeding (20.9%), pancreatitis (13.3%) and perforation (2.2%). Complications were mild or moderate in 88.9%, while the 11.1% were severe, according the ASGE Lexicon. No EP-related deaths were recorded.

Conclusion: The results of our study confirm the efficacy of endoscopic papillectomy in the treatment of ampulla of Vater neoplasms in the current clinical practice. Most of recurrences were successfully endoscopically managed. However, even if performed by expert endoscopists, EP is a procedure associated with not negligible risk of compli-

cations.

P-08-34

The use of a novel haemostatic peptide gel in the management of walled-off pancreatic necrosis (WOPN) drained using lumen apposing metal stents (LAMSs): a case series

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Abstract

Background: Bleeding is one of the most fearsome and frequent adverse event in case of EUS- guided drainage of WOPN using LAMSs and of direct endoscopic necrosectomy (DEN). When it occurs, its management is still controversial. In the last few years, a novel haemostatic peptide gel has been introduced, expanding the toolbox of the endoscopic haemostatic agents. The aim of this case series was to evaluate safety and efficacy of this new haemostatic agent in preventing and controlling bleeding of WOPN drained using LAMS.

Methods: This is a multicentre, retrospective pilot study from 3 high-volume centres in Italy, including all consecutive patients treated with the novel haemostatic peptide gel after LAMSs placement for the drainage of symptomatic WOPN, between 2019 and 2022.

Results: A total of 10 patients were included. All patients underwent at least one session of DEN. Technical success of the application of the haemostatic gel was achieved in 100% of patients. In 7 cases the haemostatic gel was placed for post-DEN bleeding prevention, with 1 patient that experienced bleeding after DEN. In 3 cases, on the other hand, the haemostatic gel was placed for active bleeding: 2 cases of oozing were successfully controlled with gel application; instead, a massive spurting from a retroperitoneal vessel required subsequent angiography. No re-bleeding occurred. No gel-related adverse events were reported.

Conclusion: This novel peptide gel could represent a promising haemostatic device both in preventing and managing active bleeding after EUS-guided drainage of WON. Further prospective studies are needed to confirm its efficacy.

P-08-35

Fully versus partially-covered self-expandable metal stents for palliation of distal malignant biliary obstruction: a meta-analysis.

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Abstract

Background: For distal malignant biliary obstruction (dMBO) self-expandable metal stents (SEMS) have shown improved patency over plastic stents. Whilst initial data suggest that Covered versus Uncovered SEMS increase Time to Recurrent Biliary Obstruction (TRBO), no data is available for Fully-Covered (FC) versus Partially-Covered (PC) design.

Methods: Pubmed, Scopus and Cochrane databases were screened from inception to January 2023 for all studies describing adult patients with dMBO, treated by endoscopic placement of FC or PC-SEMS and describing Adverse Events (AEs), Recurrences or TRBO for the specific stent subpopulation. A random-effects meta-analysis was performed following PRISMA checklist, reporting outcomes as pooled proportions or means [95% confidence interval (95%CI)]. Sub-analyses restricted to 1) prospective studies, 2) unresectable diseases, 3) pancreatic cancers were pre-planned. Heterogeneity and Publication bias were explored through I2 statistic and LFK index respectively. Standardised differences (d-values) were calculated between the two groups (CRD42023393965).

Results: From 1290 records, 62 studies (3327 patients with FC-SEMS and 2322 patients with PC-SEMS) were included.Comparison of FC versus PC-SEMS showed negligible differences (d-values<0.1) in the rate of total AEs (12% vs. 9.9%) and all specific adverse events, including cholecystitis (2.5% vs. 2.6%). In prospective studies, total recurrences were similar between FC-SEMS (21.5% [16.8-26.5], I2=72.5%) versus PC-SEMS (25.6% [20.6-30.9], I2=84.5%), despite small differences (0.117-d-values-0.215) in the rate of ingrowth (0.2% vs 2.8%) favouring FC-SEMS and migration (7% vs 4.3%) favouring PC-SEMS. These results were confirmed amongst unresectable diseases, with even a small difference in total recurrences (30.7% versus 25.9%) favouring PC-SEMS. In prospective studies, TRBO was estimated to be longer for PC-SEMS (369 [290-449] days, I2=71.9%) versus FC-SEMS (219 [165-273] days, I2=93.3%; d-value=0.129 [small difference]), with consistent results in unresectable diseases

Conclusion: FC-SEMS and PC-SEMS seem comparable in terms of AEs (including pancreatitis and cholecystitis) and recurrences, as migrations of FC-SEMS are compensated by ingrowths of PC-SEMS. Despite high heterogeneity and small standardised differences, PC-SEMS showed longer patency in prospective studies and amongst unresectable malignancies, potentially advising head-to-head comparison in this scenario.

P-08-36

Alternation of MRI and EUS in pancreatic cancer screening could increase detection of both pancreatic and extra-pancreatic findings

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Abstract

Background: Screening policies in pancreatic ductal adenocarcinoma (PDAC) are currently restricted to research programmes dedicated to high risk individuals (HRIs), which could be also at risk of other extra-pancreatic neoplasia for their genetic background. Our aim is to describe the pancreatic and extra-pancreatic findings during follow-up in HRIs recruited in two centres of the Italian Registry of Families at Risk of Pancreatic Cancer (IRFARPC).

Methods: IRFARPC surveillance criteria include: FPC kindreds, genetic chronic pancreatitis, Peutz-Jeghers syndrome, Familial atypical multiple mole melanoma (FAMMM), Lynch syndrome, mutation of BRCA1/2, ATM or PALB2 with at least 1 relative affected by PDAC. Screening modality included magnetic resonance (MRI) with contrast or endoscop-

ic ultrasound (EUS) performed yearly if no abnormalities requiring further diagnostic study are found. We included patients recruited at two centres recording age at screening start, risk category, screening modalities, screening rounds and any pancreatic and extra-pancreatic finding.

Results: Sixty-five patients were enrolled in the two centres. Mean age at surveillance start was 53,6 years; 43 (66.2%) were FPC, 7 (10.8%) BRCA1/2 mutated, 1 (1.5%) Lynch syndrome, 5 (7.7%) FAMMM, 1 (1.5%) PALB2 mutation, 1 (1.5%) ATM mutation, 1 (1.5%) Peutz-Jeghers syndrome, 6 (9.2%) genetic chronic pancreatitis. Pancreatic abnormalities at first round were found in 69.2% of patients, including cysts (21.5%), chronic pancreatitis (36.9%), solid lesions (3.1%) and Wirsung dilation (1.5%). Extra-pancreatic abnormalities were found in 47.7% of patients during first round, including benign lesions such as kidney and liver cysts (38.5%), liver and spleen angiomas (4.6%), liver FNH (1.5%), liver adenomas (1.5%), and those with malignant potential such as mammarian nodules (1.5%) and adrenal adenomas (1.5%). Patients with identification of extra-pancreatic findings had undergone in 70.9% of cases MRI and in 11.8% EUS ($p<0.0001$), while patients with pancreatic findings had undergone in 24.4% of cases MRI and in 75.5% EUS ($P<0.0001$).

Conclusion: Whether HRIs undergoing screening programs should undergo EUS or MRI is debated. EUS seems to detect more frequently pancreatic alterations, while MRI could be optimal for identification of extra-pancreatic findings. An alternation of the two imaging modalities could be optimal to improve detection of relevant findings.

P-08-37

Training in EUS: current state of training modalities from a worldwide survey

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Abstract

Background: Endoscopic Ultrasound (EUS) is an advanced procedure requiring a formal and specific training. Currently position papers by American and European societies for endoscopy (ASGE and ESGE) have been published on required training modalities, but data on the adoption of such standards lack. Our aim was to describe the current state of training in EUS around the world, investigate educational lacks and clarify expectations of trainees for their training period.

Methods: A survey was administered to Next-Generation EUS Pre-Course 2023 participants, all EUS trainees<40 years of age. This comprehended 66 questions evaluating 5 topics: trainees demographic data and basic competences, training centres characteristics, training modalities adopted, activities after the end of training period, trainees expectations and opinions. Survey responses were analysed using descriptive statistics.

Results: 114 EUS trainees replied from 5 continents (mostly from Europe); 59.9% males, 89.5% gastroenterologists (10.5% surgeons or internists). All trainees satisfied the basic requirements for endoscopic and ultrasonographic skills. 29.5% of trainees were trained in centres with EUS volumes<10/week. In the majority of cases training was performed adopting mostly or only linear probes (67.9%), 79.5% of training were in centres were same-session EUS-ERCP could be performed and 67.3% of trainees believed that the same person should be trained in both procedures. In contrast to books, videos or conferences, phantom models and in-vivo/ex-vivo models were very

rarely used during training, and also considered not very useful as learning opportunities. 61.1% of trainees aimed to achieve during training a complete autonomy in diagnostic EUS+FNA/FNB for all stations, plus at least an initial approach to therapeutic EUS. Most trainees affirmed that during training they expected more hands-on, therapeutic-EUS, FNA/FNB teaching on ultrasound machine and more focus on contrast/elastography skills.

Conclusion: EUS training around the world is variable and does not always respond to basic ASGE/ESGE suggestions. A higher volume of hands-on procedures with FNA/FNB should be guaranteed during training. It should be discussed whether a basic training period in EUS should include also an initial approach in therapeutic EUS, as expected by trainees.

P-08-38

Endoscopic ultrasound-guided drainage of pancreatic fluid collections with two different dedicated metal stents: a nationwide, multicentre, propensity score-matched comparison

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Abstract

Background: Management of peri-pancreatic fluid collections (PFCs) is often challenging. When indicated, Endoscopic ultrasound (EUS)-guided transluminal drainage is the first choice of treatment and the introduction of new dedicated stents represented a game changer. In particular Bi-Flanged Metal Stent (BFMS) and Lumen Apposing Metal Stent (LAMS), creating a stable fistula between the gastrointestinal wall and the target cavity, both reported high rates of technical and clinical success. The present study aimed to retrospectively evaluate the safety, technical and clinical success of the two different dedicated metal stents for EUS-guided drainage of PFC.

Methods: Data from a large multicentre series of patients with PFCs treated with Hot-Axios and Nagi stents were retrieved among 30 Italian centres during a 5-year period. Rate of adverse events (AEs), technical, clinical success and collection recurrence were taken into account as outcome measures. To overcome biases owing to the different distribution of covariates among the two groups, a 1-to-1 match was created using propensity score analysis.

Results: Out of 476 patients underwent EUS-guided drainage of PFC, 386 were treated with Hot-Axios and 90 with Nagi stent, with a median follow-up of 290 days (95% CI 244 to 361). Propensity score matching allocated 84 patients in each group. The two stents did not differ in terms of AEs rate (13% versus 15%, p=0.29). Overall, 11 AEs were observed in the Hot-Axios group, of which three (3.5%) mild, four (4.7%) moderate, three (3.5%) severe and one (1.1%) fatal, whereas 13 AEs were registered in the Nagi group, of which three (3.5%), five (5.9%), three (3.5%), and two (2.3%) mild, moderate, severe and fatal, respectively (p=0.63). Most common AE was bleeding (5.9% in both groups). Collection recurrence was observed in 4 cases after Hot-Axios (4.7%) and 3 cases (3.5%) after Nagi

stent (p=1.0). Technical and clinical success in the two groups were respectively 92% versus 95% (p=0.36) and 91% versus 94% (p=0.64).

Conclusion: Although literature is not univocal on which type of dedicated metal stent offers the best outcome for EUS-guided PFC drainage, our study demonstrates that Hot-Axios and Nagi stents have comparable safety profile with similar technical and clinical success rate.

P-08-39

Development and validation of the SDLD-score: a simplified tool to predict successful endoscopic papillectomy in ampullary lesions

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Abstract

Background: Endoscopic papillectomy (EP) is a standard treatment for most non-invasive ampullary lesions (AL) and early ampullary cancers but advanced lesions require surgery. However, management of AL can be challenging, depends on local expertise and may lead to over- or undertreatment. We developed a score to identify best eligible patients for endoscopic or surgical treatment.

Methods: 575 patients who underwent EP fulfilled the inclusion criteria without missing data. The cohort was split into a training set (416) and a validation set (159) by random. In the training set predictors for incomplete resection (R1) were analysed by logistic regression and incorporated to a score of four items. The score was validated in a separate independent cohort. Performance was estimated by the area-under-the-receiver-operating-characteristic-curve (AUROC).

Results: Size >30mm (odds ratio [OR] 4.3 (95%CI 1.8-10.3); p=0.001), high-grade dysplasia or invasive cancer (OR 7.1 (95%CI 3.9-13.0); p<0.001)), laterally spreading lesion (OR 3.4 (95%CI 1.4-8.5); p=0.009) and dilation of bile or pancreatic duct (OR 3.0 (95%CI 1.7-5.5); p<0.001) were identified as independent factors for incomplete resection (R1) and used to develop the SDLD score. AL not exceeding one item (0-1 points) had the highest R0-rate (training: 90.7%; validation: 89.5%). By fulfilling at least two criteria R1-rate was significantly increased (training: 55.7%; validation: 51.4%; p<0.001). The AUROC was 0.834 in the training cohort and 0.763 in the validation cohort.

Conclusion: The SDLD score accurately predicts incomplete resection in patients undergoing EP and may help to optimize the decision process for endoscopic or surgical resection of AL.

P-08-40

The clinical and procedure-related outcomes of endoscopic management of walled-off pancreatic necrosis

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Abstract

Background: The conventional treatment for necrotizing pancreatitis is surgical debridement, but this has a high morbidity and mortality rate. The use of endoscopic necrosectomy with repeated sessions of debridement and tube placement has increased in recent years. We aimed to present the experience of endoscopic drainage and necrosectomy in patients who developed walled-off pancreatic necrosis (WOPN).

Methods: The research included patients who underwent ERCP drainage for an infected WOPN or compression-related symptom between January 2015 and December 2021. Demographic, clinical, and procedure-related features and mortality were evaluated.

Results: A total of 53 patients with WOPN, consisting of 47 percent men (M/F: 25/28) with a median age of 52.4 (min-max: 24–79) years, were recruited for clinical and technical success. The median follow-up time was 68.4 (5–210) weeks. The most common cause in terms of aetiology is biliary pancreatitis (56.3%), followed by hypertriglyceridemia (11.3%), idiopathic pancreatitis (11.3%), and chronic pancreatitis (7.5%). WOPN localisation is most common in the body-tail part (56.3%), and a disconnected duct was observed in 11 patients in the cholangiogram.

The localisation of entry into the WOPN was determined as transgastric (n: 50) and transduedonal (n = 3). The total number of procedures performed on 53 patients was 244. Balloon dilatation was applied to the orifice in 43 patients. While direct and endoscopic necrosectomy was performed during the procedures, and dual modulation (simultaneous endoscopic drainage and percutaneous drainage) was used for 11 (20.7%) patients. While vascular compression and thrombosis complications were the most frequent side effects of WOPN, ascites owing to portal hypertension were noted in nine individuals. Fistulisation of the colon in four people was another critical complication. While the technical success rate was 96.2%, the clinical success rate was 90% in patients with technical success. A surgical necrosectomy was performed on 2 patients who were technically unsuccessful. The most common procedure-related complication was stent migration (n:17), followed by stent occlusion (n:7), bleeding (n:6), perforation (n:2), and pneumomediastinum (n:1). The mortality rate in the entire study population was 5.6%.

Conclusion: The success of well-managed endoscopic pancreatic necrosectomy is at least as good as surgery.

P-08-41

Safety of early versus late endoscopic or percutaneous interventions in infected necrotizing pancreatitis - a systematic review and meta-analysis

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Abstract

Background: IPN (infected pancreatic necrosis) treatment experienced a significant revolution in the past decades, yet the optimal time of intervention was not evaluated since the surgical era. We performed a systematic review and meta-analysis to compare early vs delayed endoscopic or percutaneous drainage in IPN.

Methods: A systematic search was performed on PubMed, Embase, Cochrane, Scopus, and Web of Science from inception until 31st March 2022, without restrictions. Eligible studies reported on differences in patients with IPN who underwent early drainage (<4 weeks) vs patients who had late intervention (>4 weeks). We included both randomised controlled trials (RCTs) and observational studies. Indication for drainage was IPN or persistent organ failure. The random-effects model estimated pooled odds ratios (OR) and mean differences (MD) with 95% confidence interval. Study protocol is registered on PROSPERO, CRD42022296711.

Results: Out of 10141 records screened, we included seven in the meta-analysis. Two studies are RCTs, and five are retrospective cohorts. Our analysis revealed no significant differences between the two groups for mortality rates [OR 0.95; 95%CI 0.52-1.72], for the incidences of new-onset organ failure [OR 0.91; 95%CI 0.26-3.13] bleeding [OR 0.85; 95%CI 0.46-1.58], and the need for open surgery [OR 1.13; 95%CI 0.17-7.62] while the length of hospital stay (LOH) [MD 4.33; 95%CI -2.96- 11,62] and number of days in intensive care unit (ICU) [MD 1.55; 95%CI -18.20- 21.29] tended to be longer in the early drainage.

Conclusion: Our results suggest that while early endoscopic and percutaneous intervention may not worsen the clinical outcomes they seem to be associated with prolonged LOH and ICU days.

P-09-07

Prediction of margin-free resection following neoadjuvant treatment for pancreatic ductal adenocarcinoma: a Bayesian model to predict R0 and R1 resection

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Abstract

Background: R0 resection is still the goal of surgical resection, however conventional staging is not reliable to determine response to neoadjuvant therapy. A preoperative predicting model could be helpful in a clinical setting, to identify patients with a higher chance to undergo R0 resection. We aimed to build a preoperative model to predict resection margin status after neoadjuvant treatment.

Methods: Patients undergoing curative-intent surgery for PDAC after any neoadjuvant treatment from 2010 to 2020 were retrospectively analysed from the database of Pancreatic Surgery of Pederzoli Hospital. A Bayesian Logistic regression model was estimated for predicting the R1 status. The Bayesian approach was chosen because it allowed to incorporate our data about R status predictors, with prior data extracted from the previous literature. Model performance was evaluated calculating the Area Under the Curve (AUC) on the average posterior probability of R1.

Results: Overall, 205 patients underwent curative-intent resection following neoadjuvant treatment. Median age was 64(56-70), 100(48.8%) were female and 126(66.3%) received either FOLFIRINOX or gemcitabine+nab-paclitaxel.

Radiotherapy was administered to 52(25.4%) patients. Pancreaticoduodenectomy was performed in 149(72.6%), distal in 49(23.6%) and total pancreatectomy 7(4.9%). R0 resection was achieved in 150(73.2%) of cases. In the final predictive model, age at surgery (OR 1.03 95%CI 1.01-1.06), location on pancreatic neck (OR 2.79 95%CI 1.12-7.20), arterial abutment/encasement (OR 5.69 95%CI 3.83-8.50), and preoperative tumour size (OR 1.0.8 95CI 1.03-1.13), were directly associated with R1 status. ASA score (1.70 95%CI 0.78), serum CA19-9 normalization (OR 0.86 95%CI 0.42-1.75) and venous abutment/encasement (OR 1.62 95%CI 0.78-3.45) were extracted from literature data. The model performance showed an AUC of 72%.

Conclusion: We provided a valid model to predict margin status after neoadjuvant treatment, which could help the clinicians to identify patients with higher chances for radical surgery. Since there are still no clear indications about the best patients to candidate to surgical resection following neoadjuvant treatment, the Bayesian approach's added value is to match our experience and to take into account previous knowledge in the field.

P-09-08

The choice of the most appropriate suture threads for pancreatic anastomoses on the basis of their mechanical characteristics

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Abstract

Background: The choice of the most appropriate suture threads for pancreatic anastomoses may play an important role to reduce the incidence of Post-Operative Pancreatic Fistula (POPF). Literature on this topic is still not conclusive. The aim of this study is to analyse the mechanical characteristics of suture materials to find the best suture threads for pancreatic anastomoses.

Methods: A single-axial electromagnetic actuation machine was used to obtain the stress-deformation relationship curves and in particular to measure the Ultimate Tensile Strength (UTS) and the Elastic Modulus at 0-3% deformation range (E0-3) of four different suture materials (Poliglecaprone 25, Polydioxanone, Polyglactin 910 and Polypropylene) at baseline and after incubation in saline solution, bile and pancreatic juice for 1, 3 and 7 days.

Results: At baseline Poliglecaprone 25 (UTS = 1721.1 MPa), Polydioxanone (UTS = 1726.3 MPa) and Polyglactin 910 (UTS = 1664.5 MPa) showed similar strength to the breaking point, Polyglactin 910 revealed to be the stiffer (E0-3 = 7663.9 MPa) and Poliglecaprone 25 the less rigid (E0-3 = 789.3 MPa). After 7 days of incubation, all suture materials presented statistically significant variations between the baseline and the wet conditions, regardless of the type of liquid analysed. Polydioxanone and Polypropylene showed stable values of UTS and E0-3 in all conditions, maintaining different levels of strength but similar Young's modulus. Polyglactin 910 presented significant UTS and E0-3 variations between different time intervals in any type of liquid analysed. Poliglecaprone 25 lost half of its strength in all biological liquids analysed but maintained low E0-3 values.

Conclusion: The analysis of suture threads at baseline and after incubation in bile and pancreatic juice revealed that Polydioxanone maintains stable UTS and E0-3 values in all conditions while Poliglecaprone 25 has the lowest E0-3, which could reduce the risk of lacerations of soft tissues. These results showed that Polydioxanone and Poliglecaprone 25 seem to be the best suture material to use for pancreatic anastomoses.

P-09-09

Correlation between inflammation, vascularization, adipocyte percentage and exocrine cell percentage at the resection margin and the postoperative pancreatic fistula rate after distal pancreatectomy – a pilot study

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Abstract

Background: A postoperative pancreatic fistula (POPF) is one of the most demanding complications after distal pancreatectomy and related to several risk factors. Our aim was to examine whether the extend of vascularization, the severity of general and macrophage-driven tissue inflammation, the adipocyte percentage or the exocrine cell percentage at the parenchymal resection margin can be considered as risk factors for developing a POPF.

Methods: In this pilot study we included 23 patients after distal pancreatectomy, 10 of whom developed a POPF and 13 of whom did not. The paraffin-embedded pancreatic resection margin was processed with immunostaining antibodies against CD45 (leukocytes), CD68 (macrophages), CD31 (vascularization) and panCK (acinar and ductal cells). With QuPath's positive pixel count feature (Software - Version 0.3), the slides were analysed. The results were related to the development of clinically relevant POPF according to the 2016 definition of the ISGPS. Using a T-test, the area of specifically stained cells and the area of adipocytes as a percentage of the total tissue area was compared between the two study groups for each staining.

Results: Regarding the CD45 stained tissues, the average area proportion of the POPF-Group (M=0,0026; SD=0,0021) and the no POPF-Group (M=0,0038; SD=0,004) did not show any significant differences (P=0,38). Tissues stained with CD68 antibody also showed no significant differences (P=0,57) between the POPF-Group (M=0,0007; SD=0,0004) and the no POPF-Group (M=0,0009; SD=0,0014). Furthermore the CD31 stained tissues showed no significant difference (P=0,65) between the POPF-Group (M=0,0152; SD=0,0201) and the no POPF-Group (M=0,0189; SD=0,0179). Considering the Adipocyte percentage, the two compared groups POPF (M=0,1112; SD=0,1059) and no POPF (M=0,1226; SD=0,1083) did not show any significant difference (P=0,8). And also in the tissues stained with PanCK we could not detect any significant differences (P=0,54) comparing the POPF-Group (M=0,5538; SD=0,22) and the no POPF-Group (M=0,4927; SD=0,2392).

Conclusion: Even though we could not show any significant influence of inflammation, vascularization, adipocyte percentage or exocrine cell percentage at the resection margin on the development of POPF after distal pancreatectomy, these factors should still not be completely neglected. Intending to understand their relevance more precisely, we are currently examining the tissues of additional patients.

P-09-11

Novel approach for locally advanced pancreatic cancer surgery: arterial resection and reconstruction first, RO-pancreatectomy and vein resection second. Experience of 107 arterial resections

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Abstract

Background: Modern results of neoadjuvant therapy have justified arterial resections for locally advanced (LA) PDAC. Restricted space, excess of "fixation points", significant duration of arterial and portal clamping are challenging conditions as for R0-pancreatectomy, so as for prevention of liver or intestinal ischemia in resections of mesenteric or hepatic arteries with PV/SMV. Novel approach "Arterial Resection and Reconstruction first, Ro-pancreatectomy and Vein Resection second" (ARR&(Ro+VR), can be a response on this challenge in majority of cases. With untouched venous inflow, arterial resection and reconstruction is safer before mobilization of the pancreas due to collaterals, which usually sacrificed during mobilization. Our aim was to assess safety and efficacy of PE+AR and ARR&(Ro+VR) method for LA-PDAC surgery.

Methods: Retrospective analysis of 107 arterial resections (AR), including 33 ARR&(Ro+VR), associated with 84 consecutive pancreatectomies(PE) (2009-2023yy).

Results: Mean OP time was 384±163min, mean blood loss - 351±196ml, rates of R0- and vein resections – 91.5 and 67%. Arteries resected were SMA(11), CA and hepatic(96) with branches, PD/DP/TP rate- 12%/53%/35%, morbidity 65%, Dindo-Clavien>3-24%, DGE – 29%/ Mortality- n5 (6.5%): bleeding(3),MI(1),sepsis(1)), gastric and liver ischemia–n5(6.8%) and 0, POPF B/C-n21(24.6%). For PDAC (n56) median OS- 28 months, median DFS-20 months, overall 5-year survival-28%, for patients with more than 6 chemotherapy courses–35%. In all cases IOUS and ICG angiography were obligatory technique for blood flow adequacy assessment. All the relapses, except four, were distant.

Conclusion: PE+AR can be a reasonable option for LA-PDAC patient selected by chemotherapy. ARR&(Ro+VR) approach can help to achieve R0-pancreatectomy and escape ischemic complications during arterio-venous resections.

P-09-12

How surgeon can proceed when vein reconstruction in locally advanced pancreatic cancer seems impossible

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Abstract

Background: Pancreatic cancer is considered locally advanced (LA-PDAC) if "SMV/PV are unreconstructible due to tumour involvement or occlusion". Vein reconstruction can be a critical point for LA-PDAC surgery, especially when all SMV tributaries involved. Our aim was to assess safety and efficacy of vein management during pancreatectomies for LA-PDAC with involvement of all SMV tributaries.

Methods: Retrospective analysis of 94 pancreatectomies for LA-PDAC with 107 arterial and 69 vein resections(2009-2022).

Results: Vein resection were performed in 74% of pancreatectomies: PD/DP/TP rate-20%/45%/35%. In 15 cases veins only were resected, in 47-arteries+veins, in 32–arteries only. PV-SMV reconstructions were done by direct anastomosis (n9), by patch (n9) and by graft interposition (n12). After resection of SMV with all the tributaries, reconstruction was completed by PV-one of the intestinal branches anastomosis (n21), IMV-SV anastomosis (n8) and without vein reconstruction (n10). Mean OP time-355±154min, mean blood loss-330±170ml, rate of R0-resections–91.4% morbidity 63%,Dindo-Clavien>3-23%,DGE – 25%,POPF B/C-26%. Overall mortality-5.3%, nil -after vein resections, 6.4% - artery+vein and 6.3% after arteries only resections. There were no difference in morbidity and mortality in groups of arterial, vein and combined resections, as well as in groups of different vein reconstructions. Specific complication of SMV resection without reconstruction was prolonged intestinal edema in 5 cases. For PDAC (n71) median OS ws 29 months, median DFS-20 months, overall 5-year survival-29%, after more than 6 chemotherapy courses–35%.

Conclusion: Pancreatectomies with vein resections in some cases can be CT-planned and successfully completed without vein reconstruction or by the anastomoses with SMV tributaries. Use of these techniques can reduce limitations for surgery of LA-PDAC.

P-09-13

Pancreatic ductal hypertension is the main multifactor of developing severe diverse clinical manifestations in patients with chronic pancreatitis

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Abstract

Background: In the development of chronic pancreatitis (CP), alcohol aetiology is dominant, while developing pancreatic hypertension is a classic component of the pathogenesis of this disease. Our aim was to show the effectiveness of timely elimination of pancreatic ductal hypertension based on organ-preserving surgery, which saves functional reserve of the pancreas.

Methods: Patients (87) with alcoholic aetiology CP with pancreatic ductal hypertension were operated on. All of them underwent a developed organ-preserving operation: full longitudinal pancreticopapilloduodenotomy with isolated pancreaticojejunoduodenoanastomosis (split-pancreas technique). There were no lethal outcomes. Patients of the main group (41/52.9%) were operated on according to strict selection criteria: the presence of pancreatic ductal hypertension (Wirsung duct 3-4 mm or more) and pain, decreased level of faecal elastase, but not lower than 150 mcg/g. The control group included patients (46/52.9%) who had previously been operated on according to the criteria of severe pain syndrome, significant expansion of the Wirsung duct (5-7 mm or more) and other severe clinical manifestations. The examination included EUS, CT, MRI, endogenous insulin, parathyroid hormone, CA 19-9, faecal elastase; determination of type IV collagen, a-SMA positive stellate cells; quality of life in the long term was studied based on the QLQ-C30 and EORTC QLQ PAN-28 questionnaires.

Results: In 38 (92.7%) patients of the main group in the long-term period (up to 5 years), the level of exocrine function remained at the preoperative one, there was no pain syndrome, the quality of life corresponded to healthy people's. In all patients of the control group, despite absence of pain, there was low level of the exocrine function of the pancreas, which correlated with low level of quality of life.

Conclusion: In CP patients with pancreatic ductal hypertension, earlier surgical treatment is required according to the proposed criteria to maintain the functional reserve of the pancreas and high level of quality of life.

P-09-14

P-suPAR may reflect the inflammatory response after pancreatic surgery

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Abstract

Background: Surgery related soft tissue trauma can activate inflammatory cascade that leads to possible subsequent complications. Plasma soluble urokinase-type plasminogen activator receptor (P-suPAR) is a biomarker elevated by several inflammatory conditions. P-suPAR is shown to remain unchanged in patients with bacteraemia despite of surgery, and in patients undergoing coronary bypass surgery. Elevated levels have shown to predict postoperative complications after major non-cardiac surgery. The purpose of this study was to measure P-suPAR values of patients undergoing pancreatic surgery procedure to investigate the inflammatory response and prediction of complications.

Methods: One hundred seventy-six patients planned to undergo pancreatic surgery for suspected malignant or premalignant lesion were recruited. Comorbidities, preoperative laboratory values, postoperative complications and final histopathology were registered. P-suPAR values were analysed preoperatively, and on postoperative days (POD) 1 and 3.

Results: Seventeen patients did not undergo pancreatic resection due to a metastasized or advanced disease. 133 patients [median age 67 (range 33-84) years, 50% male] underwent a pancreatic resection (85 pancreaticoduodenectomies, 26 distal pancreatectomies, 22 total pancreatectomies). P-suPAR values decreased significantly on postoperative days 1 [median 3.2 (IQR 2.5-3.9) ng/mL; p<0.001] and 3 [3.2 (2.7-4.1) ng/mL; p<0.001] compared to preoperative values [3.7 (3.1-4.7) ng/mL], unlike CRP or white blood cell count (WBC). Furthermore, P-suPAR on POD 1 was significantly lower in patients who developed a postoperative pancreatic fistula (POPF) [2.6 (2.1-3.4) ng/mL] compared to patients without POPF [3.2 (2.6-3.8) ng/mL; p=0.007]. Similar decreases in P-suPAR values were seen in postoperative acute pancreatitis (POAP) [2.5 (2.2-3.5) ng/mL] vs. no POAP [3.2 (2.7-3.9) ng/mL; p=0.027] and surgical site infection (SSI) [2.7 (2.3-3.7) ng/mL] vs. no SSI [3.3 (2.8-3.8) ng/mL; p=0.017].

Conclusion: P-suPAR level in POD 1 after pancreatic surgery is significantly lower in patients who develop POPF, POAP or SSI. P-suPAR is also decreased after pancreatic resection in all operated patients. This differs from previous findings after non-pancreatic surgery. Low P-suPAR levels may possibly be explained by stronger compensatory anti-inflammatory mechanisms following the initial inflammatory reaction after surgical trauma. This type of inflammatory profile is entitled to further investigation and interest.

P-09-15

The devil is not as black as he is painted: establishing a pancreatic surgery programme

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Abstract

Background: Right sided pancreatic resection and pancreatectomy are complex and challenging surgeries, which require specialized expertise and infrastructure. These can be a serious obstacle in establishing a pancreatic surgery programme at a hospital where these types of procedures were never performed before during its fifty years history.

Methods: The patients who underwent surgical treatment with curative intent for right sided pancreatic lesions from the beginning of the programme in January, 2021, were identified in the database. The demographic and postoperative data were analysed. Descriptive statistics were used to summarize data. The experienced pancreatic surgeon from a high volume centre was present during all operations and there was an opportunity for telemed consultation during all postoperative courses of patients.

Results: 10 patients were found to be candidates for Whipple procedure or total pancreatosplenectomy. Among them 8 (80%) patients had pancreatic head lesions, 2 (20%) - papilla of Vater cancer. We performed 7 Whipples and 3 total pancreatosplenectomies. The median operative time was 210 (IQR 195-215) minutes. The median blood loss was 150 ml (100 - 200). The mean ICU stay was 2.2±0.9 days, and mean POS was 13.5±7.7 days. Postoperative complications grade ≥IIIA occurred in 1 case and no one died during 30 days of follow up. No new equipment or additional fundings were needed to perform major pancreatic resections in the settings of the hospital where it never was done before. Radiological service provided an opportunity to do CT scan 24\7.

Conclusion: It is feasible to perform pancreatic surgeries with a low rate of complications and mortality in a centre with no prior experience. Our findings suggest that with dedication and a commitment to excellence, hospitals can provide high-quality care for patients with pancreatic lesions. Further studies with larger sample sizes and longer follow-up periods are needed to confirm these findings and assess the long-term outcomes of pancreatic surgery programmes at medical facilities with limited experience.

P-09-16

Personalised step-by-step surgical treatment of acute necrotizing pancreatitis with priority use of minimally invasive interventions

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Abstract

Background: Despite the huge progress in the understanding of pathogenesis of acute necrotizing pancreatitis (ANP) mortality and complication rates in it severe form remain high. Our purpose was to improve the efficacy of treatment of patients with ANP by implementing personalised tactic of surgical interventions.

Methods: The analysis of the treatment results of 1047 patients with ANP who underwent treatment with application of the elaborated approach has been carried out. Step-up minimal invasive approach was applied to patients with acute necrotic collection and liquefactive walled-off pancreatic necrosis, whereas in cases of solid walled-off

pancreatic necrosis we preferred one-step necrosectomy technique. Control group consisted of 182 patients to whom standard surgical treatment was applied. The following parameters were collected for each episode: length of hospital stay, mortality, occurrence of organ failure and local complications.

Results: Percutaneous interventions under the control of ultrasonography were performed in 402 (40.28%) patients, in 143 cases puncture and sanitation of the pathological focus was performed under the control of endoscopic ultrasound (EUS). Selective mini laparotomy and mini lumbotomy interventions were performed in 47 (4.49%) persons with limited localized focal lesions. In 21 patients with extended parapancreatic necrosis video-assisted retroperitoneal debridement (VARD) through the nephroscope was performed. Necessary for wide laparotomic interventions occurred in 20.92% and in in 7.55% we have to repeat them. Mortality in the main group of patients was 9.36% which was significantly lower than in control group.

Conclusion: Personalised approach by application of mini invasive interventions depending from clinical and morphological variants of disease improves the results of surgical treatment of ANP.

P-09-18

Whole 16S rRNA sequencing of the oral microbiome predicts postoperative pancreatic fistula – a prospective observational cohort study

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Abstract

Background: Postoperative pancreatic fistula (POPF) is a common and potentially severe complication following pancreas surgery. To date there is no predictor anticipating the occurrence of POPF. Recently, the orointestinal microbiome was found to have a great impact on pancreatic cancer and inflammatory pancreatic diseases. We aim to prospectively evaluate the orointestinal microbiome as predictor for POPF after surgery.

Methods: In an observational cohort study, 105 patients were recruited prospectively before planned pancreas surgery. Hereby, buccal, and rectal swabs were collected (in total 204 samples). After excluding patients with delayed surgery (> 1 week after recruitment), neoadjuvant chemotherapy and pancreatectomy as well as all samples that had not reached the desired sequencing depth, 74 buccal and 70 rectal samples (n= 74) were included in subsequent analysis. Microbial composition was detected by using Oxford Nanopore Technologies. For buccal samples 16S rRNA sequencing and for rectal swabs metagenomic sequencing was performed.

Results: Swab-based buccal classifiers performed much better than rectal swabs with patients having type B or C fistula (rPOPF; n=19) compared to patients with biochemical leak (BL) or no fistula (nPOPF; n=56). Significant differences between groups were detected for β-diversity (unweighted UniFrac, p-value = 0.003) and α-diversity (observed species, p-value = 0.004) in buccal but not in rectal swabs. Notably, even after considering of 67 potentially confounding variables, the results remain significant (p-value = 0.043). Interestingly, the BMI was the most obvious confounding factor. Four species were found to be differentially abundant in the rPOPF group: Streptococcus gorondii, Gemella haemolysans, Haemophilus parainfluenzae, Gemella sanguinis. Building a model with these species and the BMI resulted in an AUROC of 93.9 %.

Conclusion: Our results show that POPF can be robustly predicted by the oral microbiome in combination with BMI.

P-09-19

From the operating room to the biomedical engineering laboratory: preliminary results for the mechanical characterisation of the pancreatic tissue

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Abstract

Background: Post-operative pancreatic fistula (POPF) is the major cause of morbidity and mortality in pancreatic surgery. This work is part of a wide project aimed to create a realistic phantom of pancreatic tissue which could help surgeons to improve their expertise to perform pancreatic anastomosis and reduce the incidence of POPF. For this reason, it is fundamental to obtain a mechanical characterisation of the pancreatic tissue and the main pancreatic duct, in order to create a synthetic phantom as realistic as possible.

Methods: This study results from a close synergy between the Department of Chemistry, Materials and Chemical Engineering "Giulio Natta" of Politecnico di Milano and the Pancreatic Surgery Unit of Istituto Clinico Humanitas. Samples of human pancreatic tissue are retrieved during pancreatic resections and tested using a bioindenter machine (UNHT³ Bio, Anton Paar GmbH) a device for measuring local mechanical properties of soft and biological samples. The elastic modulus is calculated from the loading part of the indentation curve using Hertz's model, which is more appropriate for biological materials.

Starting from the results obtained, a 3D printing and polymer molding could be used to reproduce the anatomical details and viscoelastic properties of human pancreas.

Results: Starting from forces and displacements measured during indentation tests, the Hertz's model are used to calculate the Elastic modulus (EHz) of the pancreatic tissue. The tissues show a viscoelastic behaviour typical of all biological tissues, with an average EHz = 1 ÷ 3 kPa. There is also a decrease in the mechanical properties (EHz modulus) when the tests are carried out 24 hours after the retrieved.

Conclusion: A phantom which maintains the viscoelastic properties of real human pancreas would enable surgeons to improve their technical skills and shorten their learning curve to perform pancreatic anastomosis in the most appropriate way, with the reduction of the incidence of POPF. Our preliminary results aim to show how soft a material that wants to replicate the mechanical behaviour of the human pancreas should be in order to customize a realistic pancreatic synthetic tissue.

P-09-21

Influence of perioperative care factors on morbidity of pancreatoduodenectomy

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Abstract

Background: Pancreatoduodenectomy (PD) is a major surgical procedure with a high risk of complications. The aim of this study is to analyse our own cohort of patients to evaluate the impact of perioperative care factors on morbidity and mortality in patients undergoing PD.

Methods: The prospectively maintained database included patient demographic, histopathological, perioperative and postoperative data including perioperative care factors (preoperative nutritional preparation, albumin level, perioperative infusion therapy, early initiation of parenteral nutrition, total cumulative fluid balance in the first 3 postoperative days). The influence of individual factors on the incidence of postoperative complications assessed according to the Clavien-Dindo classification, the incidence of pancreatic fistula (POPF), postpancreatectomy haemorrhage (PPH) and delayed gastric emptying (DGE) was then analysed in the whole cohort.

Results: A total of 133 patients were included in the study, 80 (60.2%) males and 53 (39.8%) females, median age was 64.2 years. Severe morbidity (Clavien-Dindo III-V) occurred in 28 (21.1%) patients, POPF in 23 (17.3%), PPH in 12 (9.0%) and DGE in 34(23.6%) patients. The median length of hospitalization was 14 days. In univariate analysis, there was a statistically significant association of major morbidity and incidence of POPF and PPH with pancreatic duct width, duration of surgery, patient weight, and total cumulative fluid balance in the first 3 postoperative days. The dynamics of CRP levels in the first 3 postoperative days (cut-off 187 mg/l) proved to be a suitable predictive marker for early detection of postoperative complications.

Conclusion: Perioperative care factors are important in influencing the morbidity of pancreatic resection procedures. Restriction of perioperative intravenous fluid administration, implementation of the ERAS protocol for prehabilitation - improving nutritional status by sipping, as well as early response to CRP elevation and dynamics in the first postoperative days seem to be appropriate tools to reduce morbidity and mortality.

P-09-22

Liver cirrhosis increases mortality in patients undergoing pancreaticoduodenectomy: a systematic review and meta-analysis

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Abstract

Background: Liver cirrhosis (LC) has been traditionally considered a contraindication for major gastrointestinal procedures due to the associated morbidity and mortality in the postoperative period. The aim of this systematic review was to review the evidence on the impact of preoperative LC on post-pancreatoduodenectomy (PD) outcomes.

Methods: A literature review was performed on PUBMED, MEDLINE, EMBASE databases to identify studies that

assessed postoperative outcomes in patients with and without LC following PD. The meta-analysis was performed according to the PRISMA guidelines and a Mantel-Haenszel random effect model was used. The primary outcome was mortality following PD. The secondary outcomes included post-pancreatectomy haemorrhage (PPH), postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE), bile leak, ascites, and liver failure (LF).

Results: Six studies and a total of 985 patients (cirrhotics 182, non-cirrhotics 803) who underwent PD were included. According to Child-Pugh classification, 146 patients were Child-Pugh A, and 36 patients were Child-Pugh B. The indications for PD in the LC group were pancreatic adenocarcinoma (18.1%), chronic pancreatitis (10.4%), ampullary and periampullary tumours (7.7%), bile duct adenocarcinoma (1%) and other pathology. There was no difference in age and sex distribution between both groups. The hospital mortality rate was significantly higher in the cirrhotic patients compared to those in the control group (7.7% vs 1.7%) (OR 7.91, 95% CI 6.49 - 9.64, p=0.005). There was no statistically significant difference between the two groups in PPH (OR 1.24, 95% CI 0.48 - 3.20, p=0.583), POPF (OR 1.51, 95% CI 0.79 - 2.88, p=0.153), DGE (OR 1.21, 95% CI 0.58 - 2.53, p=0.463), bile leak (OR 1.50, 95% CI 0.73 - 3.07, p=0.196). The cirrhotic patients had a higher risk of developing ascites (24.7% vs 0%) (OR 37.58, 95% CI 8.42 - 167.65, p=0.0045) but the there was no difference in the development of LF between the two groups (5.5% vs 0%) (OR 22.59, 95% CI 0.54 – 949.55, p=0.07). There was higher risk of re-operation in the LC group compared to the control (17.7% vs 8.8%), but the difference was not statistically significant (OR 22.59, 95% CI 0.54-949.55, p=0.070).

Conclusion: Liver cirrhosis is associated with a significantly increased risk of mortality post-pancreatoduodenectomy.

P-09-23

Laparoscopic vs. open distal pancreatectomy - a single centre experience

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Abstract

Background: Comparison of open (ODP) and laparoscopic distal pancreatic resection (LDP) to assess the safeness of LDP.

Methods: Between 04/2015 and 09/2022 a total of 196 patients (159 ODP and 37 LDP) who underwent distal pancreatectomy at the Department of Surgery, Klinikum rechts der Isar, Technical University of Munich, were included. Clinicopathological data were analysed to compare the clinical outcome between both groups.

Results: There was no significant difference in the pancreatic fistula rate after LDP vs. ODP, although there was a trend toward a higher rate of Grade B/C fistula after of LDP (Grade B/C-Fistula 43.2% (LPD) vs. 29.5% (OPD) and no/biochemical fistula 56.8% vs. 70.7%, p=0.08). Complication rates according to Clavien-Dindo-classification (CDC) were similar (CDC ≥ 3, 35.1% vs. 39%) in both groups. Operation time was also comparable with 251 (ODP) vs. 237 (LDP) minutes, p=0.14. Hospital stay was significantly shorter in LDP group (12.5 vs. 15 days, p=0.04). Splenectomy rate was high in both groups with no difference (91.1% (OPD) vs. 92.6% (LDP) (p=1.0). There were also no difference in the age and sex of the included patients. Patients with pancreatic cancer were mostly often operated in open procedures (54.1% vs. 13.5%, p<0.001). NET and Cystic tumours were the most common diagnosis in LDP cohort (70.2%). In 8 cases, the laparoscopic procedure was converted to open approach. The diagnosis in these 8 cases were PDAC (2), NET (1), chronic pancreatitis (1) and cystic tumours (4). In this cohort, three patients developed type B fistula and one patient developed bile leakage, while the remaining 4 patients had no clinically relevant complica-

tions. Causes for conversion were adhesions (2), tumour/cyst size (3), massive obesity (1), pancreatic cancer (1) and iatrogenic injury to the main bile duct (1).

Conclusion: LDP is a safe operation, especially for non-cancerous pancreatic disease. The oncological safety of LDP for pancreatic cancer will be revealed in the upcoming randomised trials.

P-09-25

A retrospective, multicentre, nationwide analysis of the impact of splenectomy on survival of pancreatic cancer patients

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Abstract

Background: Splenectomy is regularly performed in total and distal pancreatectomy due to technical reasons, lymph node dissection and radicality of the operation. However, the spleen serves as an important organ for competent immune function, and its removal is associated with an increased incidence of cancer and a worse outcome in some cancer entities. The impact of splenectomy in pancreatic cancer is not fully resolved.

Methods: We therefore compared the outcome of 193 pancreatic cancer patients who underwent total or distal pancreatectomy with (Sp) or without splenectomy (NoSp) between 2015 and 2021 using the StuDoQ|Pancreas registry of the German Society for General and Visceral Surgery. In addition, we integrated our data into the existing literature in a meta-analysis of studies on splenectomy in pancreatic cancer patients.

Results: There was no difference between the Sp and NoSp groups regarding histopathological parameters, number of examined or affected lymph nodes, or residual tumour status. We observed a significantly prolonged survival in pancreatic cancer patients who underwent total pancreatectomy, when a spleen-preserving operation was performed (median survival: 9.6 vs. 17.3 months, p = 0.03). In this group, splenectomy was identified as an independent risk factor for shorter overall survival [HR (95%CI): 2.4 (1.18 – 4.9)]. In a meta-analysis of the existing literature in combination with our data, we confirmed splenectomy as a risk factor for a shorter overall survival in pancreatic cancer patients undergoing total pancreatectomy, distal pancreatectomy, or pancreatic head resection [HR (95%CI): 1.53 (1.11 – 1.95)].

Conclusion: Whenever technically possible, preservation of the spleen should be considered during total pancreatectomy for resection of pancreatic cancer, as the spleen seems to affect the long-term survival in this subgroup. The immunological reasons behind this observation deserve further investigation.

P-09-26

Pathologic tumour response to neoadjuvant therapy in resected pancreatic cancer: does it affect prognosis?

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Abstract

Background: Neoadjuvant therapy (NAT) + surgical resection has gained consensus in recent years as treatment strategy for pancreatic cancer (PC). Pathological response (PR) after NAT is generally assessed according to the College of American Pathologists (CAP) grading system, ranging from 0 (complete response) to 3 (no response). The aim of our study is to evaluate the prognostic role of PR after NAT + surgery for PC.

Methods: Patients undergone NAT and resection for PC between 2011 and 2020 were retrospectively evaluated. Clinical and pathological data were collected. Patients were categorized into 3 groups according to PR (0/1, 2, 3). Disease Free Survival (DFS) and Overall Survival (OS) were estimated. Univariate and multivariate survival analysis were performed in order to evaluate the prognostic role of PR.

Results: 112 patients were included in the study. PR was 0/1, 2 and 3 in 18 (15%), 79 (61%) and 29 (24%) cases, respectively. Chemotherapy regimens different from FOLFIRINOX and gemcitabine + nab-paclitaxel (OR 2.09 (0.60-3.58), p=0.006) and lymphovascular invasion (OR 2.09 (0.27-3.91), p=0.02) were associated to poor PR (PR-3). Median follow-up (range) was 25.8 (3.6-130.5) months. For PR-0/1, PR-2 and PR-3, median DFS was 45.8, 11.5, 4.6 months (p<0.0001), respectively, while median OS was not reached, 27.1 and 17.5 months (p=0.0006), respectively. At univariate analysis, PR-0/1 was significantly associated to better DFS and OS (HR 0.33 (0.17-0.67), p=0.002; HR 0.20 (0.07-0.54), p=0.002, respectively). At multivariate analysis, pancreaticoduodenectomy versus other surgical procedures (HR 0.50 (0.30-0.84), p=0.009), LNR (HR 27.14 (1.21-608.9), p=0.038) and lymphovascular invasion (HR 1.99 (1.06-3.76), p=0.033) were independently associated to DFS; moreover, pre-treatment CA 19.9 value (HR 1.00 (1.00-1.00), p=0.025), post-treatment resectability status (HR 0.51 (0.28-0.95), p=0.035), pancreaticoduodenectomy (HR 0.56 (0.32-0.99), p=0.050), severe morbidity (2.99 (1.22-7.55), p=0.017), LNR (HR 56.8 (2.08-1548.3), p=0.017), lymphovascular invasion (HR 2.18 (1.08-4.37), p=0.029) were independently associated to OS. PR did not reach statistical significance at multivariate analysis.

Conclusion: PR-0/1 is not frequent after NAT + surgery for PC (only 15% of cases). Large multicentre studies are needed to demonstrate the prognostic role of PR.

P-09-27

Metastasectomy of isolated metachronous pulmonary oligometastases of PDAC prolongs OS and DFS in patients following radical pancreatectomy

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Abstract

Background: Isolated metachronous pulmonary oligometastases (IMPO) develops in specific subgroup of radically operated PDAC patients following pancreatectomy. Curative metastasectomy in selected patients can prolong OS and DFS and can be performed repeatedly. This study presents uniqe single centre small cohort of patients with IMPO treated with lung resections following previous pancreas resections.

Methods: Retrospective analysis of single-institution database of PDAC patients following pancreatectomy performed between 2010-2019. Exclusion criteria were neoadjuvant therapy, postoperative complications leading to mortality and recurrence other than isolated pulmonary oligometastases. R0 and R1 were defined by Leeds protocol. Follow-up was held every three months with carbohydrate antigen (CA) 19-9 level monitoring and CT scans every 6 months. Elevation of CA 19-9 lead to FDG-PET/CT. When only pulmonary PDAC recurrence on PETCT was found, pulmonary metastasectomy was considered by institutional MDT. Long time interval between primary pancreatic surgery and pulmonary recurrence onset and good performance status of patient were considered as favourable parameters for pulmonary metastasectomy. OS and post-recurrence survival and RFS were calculated. The study followed the ethical standards of the Institutional Review Board of the University Hospital in Olomouc, (approval reference no. 159/16).

Results: In total 267 patients fulfilled inclusion criteria. Ninety-days mortality was 2.9%. Eight patients (3%) developed isolated pulmonary metastases with median survival of 74.9 months (10-110 months). In five of them successful lung resections were performed 54, 37, 31, 57 and 27 months following primary pancreas resection. Two patients died due to pulmonary progression with overall survival 96 and 68 months. Three patients are still alive - one patient underwent repeated lung resections 31, 55 and 75 months following primary pancreas resection, followed adjuvant systemic therapy, currently alive 83 months without recurrence, other are alive 87 and 36 months.

Conclusion: In PDAC patients, the treatment strategy for oligometastasis has been controversial. However, only a few cases of long-term survival after pulmonary metastasectomy for oligometastasis of PDAC have been reported so far and our small cohort support the strategy of individualised therapy. Metastasectomy may prolong survival after primary resection of the PDAC in cases with pulmonary oligometastases.

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P-09-28

A modular perfusion circuit with predetermined physiological parameters for the development and understanding of whole organ ex vivo pancreas perfusion: insights from a porcine study

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Abstract

Background: Whole organ ex vivo perfusion is a promising technology for the preservation of organs before transplantation. However, current perfusion systems lack the cost-effectiveness needed to be applicable to provide a feasible research platform. This study aimed to develop a novel modular perfusion circuit with predetermined physiological parameters for ex vivo pancreas perfusion.

Methods: Five porcine pancreata were resected from domesticated pigs at a commercial abattoir and perfused using our perfusion circuit. The circuit consisted of a modified organ chamber, oxygenator, and heat exchanger. The

physiological parameters, including temperature, oxygenation, flow, and pressure, were pre-set, and monitored throughout the experiment. Haematoxylin and Eosin (H&E) staining was performed with samples taken from the perfused pancreas and a control organ stored at a core temperature of 8°C.

Results: The multi-organ perfusion circuit maintained stable physiological parameters during the ex vivo perfusion of the pancreas. The pancreatic perfusion resulted in good preservation of the organ with minimal tissue damage.

Conclusion: The results of this study demonstrate the feasibility of a modular perfusion circuit with predetermined physiological parameters for ex vivo perfusion of the pancreas. This technology has the potential to develop locally ablative and diagnostic technologies using this as an initial investigative platform.

P-09-29

Minimally invasive versus open radical antegrade modular pancreatosplenectomy for pancreatic ductal adenocarcinoma: an entropy balancing analysis in a multicentre study

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Abstract

Background: The safety and efficacy of minimally invasive radical antegrade modular pancreatosplenectomy (MI-RAMPS) remain to be established in pancreatic cancer (PDAC)

Methods: Eighty-five open (O)-RAMPS were compared to 93 MI-RAMPS in a multicentre study. The entropy balance matching approach was used to compare the two cohorts, eliminating the selection bias. Three models were created. Model 1 made O-RAMPS equal to the MI-RAMPS cohort (i.e., compared the two procedures for resectable PDAC); model 2 made MI-RAMPS similar to O-RAMPS (i.e., compared the two procedures for borderline-resectable PDAC); model 3, compared robotic and laparoscopic RAMPS.

Results: O-RAMPS and MI-RAMPS showed "non-small" differences for BMI, comorbidity, back pain, tumour size, vascular resection, anterior or posterior RAMPS, multi-visceral resection, stump management, grading, and neo-adjuvant therapy. Before reweighting, O-RAMPS had fewer clinically relevant postoperative pancreatic fistulae (CR-POPF) (20.0% vs. 40.9%;p=0.003), while MI-RAMPS had a higher mean of lymph nodes (25.7 vs. 31.7;p=0.011). In model 1, MI-RAMPS and O-RAMPS achieved similar results. In model 2, O-RAMPS was associated with lower comprehensive complication index scores (MD=11.2;p=0.038), and CR-POPF rates (OR=0.2;p=0.001). In model 3, robotic-RAMPS had a higher probability of negative resection margins.

Conclusion: In patients with anatomically resectable PDAC, MI-RAMPS is feasible and as safe as O-RAMPS.

Results: We had 225 respondents: mostly adults, 69% females, 89% Caucasians with 74% residing in the USA. 42% of paediatric cohort and 50% of adults reported exocrine pancreatic insufficiency while 8% of paediatric cohort and 26% of adults reported DM. Type 3c DM was present in all paediatric cases and 45% of adult DM cases. Nearly 45% of the adult respondents reported night-time sweating but this was reported in about 13% of children (p=0.002). Other symptoms frequently reported by respondents included brittle nails in 32% of the cohort (33% of adults, 25% of children), brittle hair (32% of cohort; 33% adults, 21% children), hair loss (29% of cohort; 31% adults, 13% children) and dry eyes (35% of total cohort; 37% of adults, 17% children). Although, many respondents had dry eyes; diagnosis of Sjögren's syndrome was rare in 3.1% of the cohort; all adults. Iron deficiency anaemia was frequently reported in 25% of adult respondents and 18% of children. Hypothyroidism was reported in 9.3% of the cohort, Raynaud's syndrome in 4% and celiac disease in 3.1%.

P-09-30

Borderline resectable and locally advanced pancreatic cancer: resectability and survival after neoadiuvant therapy

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Abstract

Pancreatic adenocarcinoma (PDAC) remains one of the neoplasms with the poorest prognosis with an overall 5-year survival of 8% and which can reach 15-40% after radical surgery. The aim of the study is to evaluate the impact of neoadjuvant therapy in terms of conversion to resectability and overall survival in locally advanced (LA) and borderline resectable (BR) PDAC. The patient cohort was selected among patients with histological diagnosis of BR or LA PDAC in the period between January 2017 and December 2021. Each patient was discussed by a multidisciplinary team in accordance with NCCN resectability criteria, CA 19.9 values, comorbidities and performance status. Data from 60 consecutive patients were analysed. According to the resectability status defined by the radiological images, 40% were classified as BR and 60% as LAC. The chemotherapy schemes administered were mainly FOLFIRINOX (FFN) in 51.06% of cases and gemcitabine/nab-paclitaxel (GEMPAC) in 36.17% of patients. Other therapeutic schemes were administered in 12.77% of patients and included the use of gemcitabine in mono chemotherapy, FOLFOX and ibrutinib in the context of a randomised clinical trial. Radiological and biochemical response after administration of neoadjuvant therapy was found in 48.64% of patients, who were candidates for surgical exploration. Of these, 47.83% of cases were resected. In 36.4% of cases it was necessary to perform a venous vascular resection. Postoperative morbidity was 27.3%. Postoperative mortality was nil. Curative R0 resections were obtained in 63.6% of cases. Overall survival was 14.5 ± 2.13 months for patients who progressed; 19.92 ± 3.15 months for those responding to chemotherapy and 40.56 ± 4.32 months for those resected. The disease-free survival of patients who underwent resection was 26.51 ± 5.54 months. The use of chemotherapies other than FFN or GEMPAC was found to be statistically correlated with a worse prognosis (p - value < 0.05). The data published are promising and suggest that the use of polychemotherapy regimens with neoadjuvant intent represents a key point in the treatment of BR and LA PDAC. However, the percentage of response and downstaging after administration of these therapies is variable and does not always coincide with the effective resection of the tumour.

P-09-32

The significance of lymph node dissection at the left side of superior mesenteric artery (SMA) during Whipple's procedure for pancreatic head cancer

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Abstract

Background: The systemic dissection of the lymph node at the left side of SMA (No.14d/p-L) was not recommended for radical resection of pancreatic head cancer by current guideline. We aim to evaluate the prevalence and risk factors of positive lymph nodes at this station.

Methods: The clinical and pathological information of 103 consecutive cases of Whipple's procedure for pancreatic cancer by a single surgeon at the Pancreatic Centre of the First Affiliated Hospital with Nanjing Medical University during the year of 2022 were prospectively collected and analysed. All patients underwent systemic lymphadenectomy on the left-side of SMA (level-II dissection) during the surgery. Risk factors for positive No.14d/p-L lymph nodes were analysed with univariate and multivariate logistic regression.

Results: There were 69 male and 34 female patients, with median age of 63 (14) years old. Preoperative CT scan showed any form of arterial invasion in 16/103 patients, and 1 patient received neoadjuvant therapy. The median diameter of the tumour was 3.2 (0.8) cm, while the median number of harvested lymph nodes and positive lymph nodes were 25 (10) and 1 (3), respectively. The lymph node staging included N0 in 35 cases (34.0%), N1 in 43 cases (41.7%), and N2 in 25 cases (24.3%). The overall positive rate of No.14d/p-L lymph nodes was 31.1% (32/103), with the positive rates of No.14p-L and No.14d-L lymph nodes were 18.5% and 21.4%, respectively. The additional dissection of No.14d/p-L lymph nodes significantly increased the number of positive lymph nodes ($P<0.01$), and changed TNM staging in 5 patients, including 2 patients from stage IB to IIB, 2 IIA to IIB, and 1 IIB to III. Positive No.7/8/9/12 lymph nodes and tumour location were independent risk factors for No.14d/p-L lymph nodes metastasis.

Conclusion: Additional systemic lymphadenectomy at the left side of SMA during Whipple's procedure can facilitate more accurate staging for patients with pancreatic head cancer. Prophylactic clearance of lymph nodes at this area may be valuable, especially in patients with lymphadenopathy in other stations or with tumours close to the uncinate.

P-09-33

Robotic distal pancreatectomy in a patient with a heterozygous pathogenic variant in the PALB2 Gene

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Abstract

Background: Pathogenic variations in the *PALB2* gene have been associated with an increased risk of developing cancer at specific sites for nearly two decades. In the spotlight, breast, ovarian and pancreatic cancer. To date, there is no consensus in the literature on how to proceed in patients with pancreatic lesions and genetic alterations that increase the risk of malignancy. In this article, we demonstrate the process of diagnosis, follow-up and, mainly, the

multidisciplinary decision to intervene in a patient with a diagnosed genetic variation, previous breast cancer and a pancreatic lesion.

Case Presentation: The patient was diagnosed with breast cancer in 2019. She underwent resection and reconstruction in 2020 and also underwent genetic evaluation, which diagnosed a heterozygous pathogenic variation in the *PALB2* gene. Knowing this genetic alteration, after 2 years, during follow-up, a lesion in the tail of the pancreas was evidenced in a magnetic resonance cholangiopancreatography (MRCP). After a multidisciplinary discussion with oncologists, oncological surgeons, radiologists and geneticists, a robotic distal pancreatectomy was chosen. The histopathological analysis indicated that it was a cystic mucinous lesion. Patient was discharged after 5 days, with no evidence of fistula or other complications. She has currently completed 6 months of follow-up, with no new evidence of disease.

Conclusion: The treatment of pancreatic lesions associated with genetic alterations must be based on multidisciplinary opinions and decisions, in addition to being individualized for each case. The presence of a condition that is known to increase the incidence of malignant lesions may be indicative of a more interventional treatment.

P-09-34

Management of malignant gastric outlet obstruction (mGOO) due to pancreatic cancer in the era of EUS-gastroenterostomy: an international practice survey and case vignette study

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Abstract

Background: Malignant Gastric Outlet Obstruction (mGOO) has been standardly treated by surgical GastroEnterostomy (S-GE) or Endoscopic Stenting (ES). More recently, Endoscopic Ultrasound-guided GastroEnterostomy (EUS-GE) has emerged as a low-invasive alternative, supported by guidelines with surgical-range efficacy. Nevertheless, its worldwide diffusion is heterogeneous and advantages/disadvantages debated. The aim of this survey is to assess clinical decision-making of international specialists regarding mGOO and to explore current opinion regarding EUS-GE use.

Methods: An online survey was created exploring centres' experiences and physicians' opinions regarding indications, contraindications, benefits and risks of available treatments; 2 case vignettes explored clinical decision-making in different scenarios. The survey was spread through social networks and the EPC newsletter.

Results: Overall, 290 pancreatologists from 44 countries (5 continents) responded, of whom 35% surgeons and 65% gastroenterologists, 44% from centres managing ³20mGOO/year. The most frequently available treatment for mGOO was ES (91%), followed by S-GE, while EUS-GE was only available to 59% of responders, and only 10% declared proficiency in this technique. 68% referred an established gold-standard in their centres, but this differed by specialty, with ES, EUS-GE and S-GE being advised by 45%, 20% and 10% of gastroenterologists and 24%, 8% and 25% of surgeons. For 51% of responders, EUS-GE will become the primary treatment for mGOO. This percentage increases among gastroenterologists and high-volume centres. For 14%, EUS-GE spread will be limited in the future, or used only when ES fails (19%), with higher rates among surgeons. When choosing between alternatives, the main decision driver is life expectancy, followed by disease stage and patient's frailty, whereas potential future surgical

resectability does not contraindicate any treatment for 3/4 of responders. The main perceived advantages of EUS-GE were minimally invasiveness and high clinical efficacy, while the learning curve remains its main disadvantage.

Conclusion: This survey revealed significant differences in the management of mGOO, depending on specialties, local expertise and treatment volume, suggesting the lack of standardised algorithms. Despite great enthusiasm around EUS-GE, its availability remains suboptimal, with learning curve as the main barrier. Life expectancy and patients' frailty are likely to remain the main decision factors.

P-09-35

International survey of anticoagulation following porto-mesenteric vessel resection/reconstruction in pancreatic surgery

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Abstract

Background: Despite improvements in systemic therapies, survival following treatment for pancreatic ductal adenocarcinoma remains highest in patients following surgical resection. Multi-national trials have confirmed this finding in borderline resectable pancreatic cancer, where complication and survival rates following portal venous resection and reconstruction are comparable to those without vascular resections. While arterial resection is more controversial and associated with greater peri-operative mortality and morbidity, novel techniques and approaches have led to R0 resections in cases that would have been considered palliative only a few decades ago.

The porto-mesenteric vasculature differs considerably from systemic vasculature in vessel diameter, blood flow and pressure. Thrombosis is common in manipulated vessels, but post pancreatectomy haemorrhage a potentially life-threatening complication. A systematic, evidence approach to thromboprophylaxis could help reduce complications and mortality in this population.

Methods: An online survey was sent to individual members of the EPC asking about local experience with porto-mesenteric vascular resection, as well as assessment and practice of thromboprophylaxis. Responses were collected anonymously using Google Forms.

Results: Twenty-seven responses, from largely individual centres, across 9 European and 1 Asian nation were recorded, the majority from experienced pancreatic surgeons (>200 cases) 51.2% of which worked in a transplant centre. 63% would routinely use anticoagulation following vascular resection, but mostly without formal risk stratification (76.5%). In portal venous resection, unfractionated heparin was frequently (58.8%) used intra-operatively, and low molecular weight heparin following discharge (41.2%). DOACs (5.9%), coumarins (5.9%) or antiplatelet agents (11.8%) were rarely used. In cases with arterial resection or synthetic graft reconstruction, unfractionated heparin was always used and antiplatelet agents were more frequently prescribed (57.1%) following discharge. Type of therapeutic agent, dosage and duration of use varied widely between units.

Conclusion: Porto-mesenteric vascular resection is becoming a valuable tool in the treatment of pancreatic cancer, however the approaches to thromboprophylaxis vary widely and evidence base is limited. Studies need to address risk factors for thrombosis as well as establish type, dosage and duration of thromboprophylaxis in this population.

P-09-36

Performing robot-assisted pancreatoduodenectomy in octogenarian vs younger patients: a one-to-one case control study

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Abstract

Background: Over the last few years, as a result of rising life expectancy, there has been an increase in pancreatic cancer diagnoses, with a mean age of about 72 years. Data in the literature on surgery in elderly patients are still debated, since age is not a contraindication to surgery and thanks to improvements in surgical technique and perioperative care, an increasing number of patients are undergoing surgery. The aim of this study is to analyse the outcomes of robot-assisted pancreatoduodenectomy (R-PD) in octogenarian patients, with the main focus on serious postoperative complications 30-days after surgery, while the secondary objectives were length of hospital stay, mortality, and development of clinically relevant postoperative pancreatic fistula.

Methods: Data of patients who underwent R-PD at our Institution were prospectively collected from November 2018 to November 2022 and retrospectively analysed. Matching criteria used were: gender, age, BMI, ASA score, histological diagnosis, and tumour stage of the malignant tumours. Therefore, R-PD patients aged>80 years (over-group) were compared with a matchable group of R-PD patients aged <80 years (under-group) with a one-to-one case-control methodology.

Results: Starting from a whole series of 68 patients, a total of 13 cases in each of the two groups were selected for the retrospective matched cohort study. No differences in terms of postoperative complications were reported, being occurred in 6/13 (46.2%) in the under-group and in 4/13 (30.8%) in the over-group. Even pancreatic fistula was not significantly different, being occurred in 2/13 (15.4%) in the under-group and in 1/13(7.7%) in the over-group. A higher rate of medical complications was reported in octogenarian patients. Lastly, no difference in 30-day mortality (0/13 in both groups) and length of hospital stay was reported in the two groups.

Conclusion: As evidenced by our experience, advanced age should not be a restriction for robotic surgery in patients with pancreatic head tumours. In fact, R-PD is a feasible and safe procedure even in octogenarian patients.

P-09-38

Health-related quality of life after laparoscopic versus open distal pancreatectomy according to PROMIS-29 profile

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Abstract

Background: Limited data comparing health-related quality of life (HRQOL) after laparoscopic (LDP) versus open distal pancreatectomy (ODP) are available. The aim of this study was to assess the impact of minimally invasive ap-

proach on postoperative HRQOL after DP using the Patient-Reported Outcomes Measurement Information System (PROMIS), a validated tool developed to address the lack of universal measure of patient-reported outcomes.

Methods: Data from consecutive patients who underwent DP (2020-2022) enrolled in a prospective clinical trial (NCT04431076) were reviewed. Patients completed PROMIS-29 questionnaires preoperatively, at 15, 30, 90 days after surgery. Linear regression analysis adjusting for confounders including preoperative PROMIS scores, age, gender, ASA score, diagnosis, multivisceral resection, clinically relevant postoperative pancreatic fistula (CR-POPF) was used to estimate between-group differences in PROMIS domains T scores.

Results: Overall, 202 patients underwent DP (pancreatic cancer 41%, multivisceral resection 10%, CR-POPF 31%, median LOS: 6 days). LDP was performed in 118 patients, ODP in 86 patients.

At 15 postoperative days, the proportions of patients who recovered or improved preoperative physical function, social roles, fatigue, pain interference, sleep disturbance, anxiety, depression scores were 14%, 27%, 36%, 42%, 58%, 75%, 80%, respectively. At adjusted analysis, LDP was associated with higher physical function scores (mean difference 4.4, p=0.001) compared to ODP, while other HRQOL domains' scores were similar.

At 30 postoperative days, the proportion of patients who recovered or improved preoperative scores was 34% for physical function, 39% for social roles, 48% for fatigue, 51%, for pain interference, 68% for sleep disturbance, 78% for anxiety, 80% for depression. At multivariate analysis, LDP was associated with higher PF (mean difference 4.7, p=0.001) and SR (mean difference 4.6, p=0.004), lower anxiety (mean difference -3.6, p=0.016) and fatigue (mean difference -2.5, p=0.048) scores compared to ODP.

At 90 postoperative days, no significant differences in HRQOL PROMIS-domains were found betweenLDP and ODP patients.

Conclusion: According to PROMIS-29 questionnaire, minimally invasive surgery for DP resulted in improved physical and social functioning and reduced anxiety and fatigue up to 30 days after surgery compared to the open approach, while no difference was found for other HRQOL domains and in the longer term.

P-09-39

Reappraisal of residual tumour status on pancreaticoduodenectomy margins: a single-institutional cohort of 858 patients with resected pancreatic head ductal adenocarcinoma following a standardised pathological protocol

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Abstract

Background: The prognostic value of margin residual tumour (R) status for pancreatic ductal adenocarcinoma (PDAC) needs further detailed evaluation. We aimed to determine the influence of R status on overall survival (OS) and its relation to TNM staging system after pancreaticoduodenectomy (PD).

Methods: A consecutive cohort of PDAC patients undergoing PD was evaluated with a standardised pathology protocol. Prognostic factors were analysed by Cox regression analysis. Receiver operating characteristics curves and time-dependent area under the curve were utilised to compare prognostic prediction.

Results: R0 resection of circumferential resection margin (CRM-) was found in 296 (34.5%) patients; the superior

mesenteric vein (SMV) groove was most commonly involved (364 (42.4%)). R status independent prognostic factors were CRM (hazard ratio (HR) = 1.430), pancreatic neck (HR = 1.357), SMV groove (HR = 1.226) and uncinate process (HR=1.263). Involvement of the SMV groove margin maintained a significant impact on OS regardless of other margins involved whether separately or combined, and also to TNM stages. Following adjuvant therapy patients with an R1 <1mm CRM+ had a better overall survival than patients with an R1-direct margin (median: 21.37 vs: 14.23 months respectively), but not in patients without adjuvant therapy.

Conclusion: R0 resection is key is a key determinant of survival following PD. Involvement of the SMV groove margin was an independent dominant survival factor. Adjuvant therapy significantly improved OS in patients with R1<1mm status compared to R1 direct resections.

P-09-40

Surgical treatment of pancreatic neoplasia in children: a single-centre retrospective analysis of short-term outcomes

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Abstract

Background: Pancreatic neoplasia in children is rare. Limited data is available to guide care in paediatric population. We present a modern case series of patients undergoing surgical treatment for this uncommon condition.

Methods: This is a retrospective review of paediatric patients undergoing resection for pancreatic neoplasm at the National Cancer Institute in Ukraine between August, 2013 and February, 2023. Only patients under the age of 18 were included. Demographics, surgical parameters, and short-term outcomes were analysed.

Results: Overall, we included 14 patients with a median age of 11.5 years (range 1-15). Mean BMI was 19.6 kg/m2, none of the patients had any comorbidities. The tumour was located in the head of the pancreas in 8 (57.1%), and in the body/tail – in 6 (42.8%) cases. None of the patients required neoadjuvant treatment. 6 (42.8%) Whipple operations (WO), 4 (28.6%) distal pancreatectomies, 3 (21.4%) tumour enucleations, and 1 (7%) posterior RAMPS were performed. Laparoscopic approach was applied in 6 (42.8%) cases during the last five years. Postoperative histology revealed solid pseudopapillary neoplasm in 7 (50%) patients, serous cystadenoma in 2 (14.3%), neuroendocrine tumours in 2 (14.3%), pancreatic ductal adenocarcinoma in 1 (7%). There were two rare cases of mature cystic teratoma in a 2-year-old boy who underwent WO and pancreatic paraganglioma in an 8-year-old girl who underwent laparoscopic distal pancreatectomy. The median operative time was 300 min (range 75-380), blood loss – 125 ml (range 50-150). There were 2 (14.3%) complications Clavien-Dindo ≥3 in two cases, including laparoscopic reexploration, and ultrasound-guided drainage of abdominal fluid collection, both due to pancreatic fistula in patients after laparoscopic and open distal pancreatectomies. 4 (28.6%) patients underwent blood transfusion. Median length of hospital stay was 11 days (range 6-20). There was no perioperative mortality.

Conclusion: Surgical treatment remains the best chance for cure in patients with pancreatic neoplasms. These complex surgeries can be safely accomplished in the paediatric population. Advances in minimally invasive surgery allowed the transition to less invasive procedures in these patients.

P-09-41

Intraoperative Gram staining of bile protocol to prevent infectious complications in pancreaticoduodenectomy

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Abstract

Background: Infectious complications play a prominent role in pancreatoduodenectomy. Their incidence increases in cases with bacteria in bile at the time of the procedure. This situation is known as bacterobilia and mainly occurs in cases with prior preoperative biliary drainage (PBD). Perioperative antibiotic therapy plays an important role in the prevention of these complications. Altough prophylaxis is the recommended option, some authors propose continuing antibiotic treatment for the first few days following surgery, especially in patients with greater risk of bacterobilia. However, although prophylaxis may be insufficient in some cases, routine administration of broad-spectrum antibiotics can lead to increased bacterial resistance. In this context, we present a protocol implemented with the objetive of reducing infectious complications through a targeted and individualised antibiotherapy.

Methods: A prospective study analysing the incidence of infectious complications in pancreatoduodenectomy was performed, comparing 50 patients without PBD(Group 1) and 50 patients with PBD(Group 2). All patients received the same antibiotherapy protocol. Firstly, an intraoperative gram staining of bile was performed. If no microorganisms were detected antibiotherapy was limited to cefazolin prophylaxis. If bacterobilia was detected, targeted antibiotherapy was administered for five days: Piperacilline-Tazobactam for gramnegative-bacilli; Vancomicine for gram-positive-cocci; Metronidazole for grampositive-bacilli; Fluconazole for fungi (it could be modified according to the final culture result).

Results: The incidence of baterobilia was 13% in Group 1 and 90% in Group 2($p<0.05$). Enterobacter and Klebsiella were the most prevalent microorganisms in Group 1. Klebsiella, Enterococcus, Enterobacter and Escherichia coli were the most prevalent in Group 2. However, no differences were observed in postoperative infectious complications. In Group 1, the incidence of surgical site infection (SSI), organ/space SSI and sepsis was 6%, 6% and 0%. In the second group, the incidence of these variables was 10%, 10% and 6%, respectively. No differences were observed in the remaining morbi-mortality variables (pancreatic fistula, bleeding, mortality).

Conclusion: Intraoperative gram staining of bile fluid could be a useful tool to conduct personalised antibiotic therapy in pancreatoduodenectomy and contribute to the control of infectious complications.

P-09-42

Postoperative pancreatic fistula: is it possible to predict it appearance in the first two postoperative days?

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Abstract

Background: Postoperative pancreatic fistula (POPF) is one of the main complications after pancreaticoduodenectomy (PD). According to the International Study Group for Pancreatic Surgery, its diagnosis is based on the assessment of drain fluid amylase (DFA) levels in the third postoperative day, considering biochemical leak when DFA level greater than 3 times the upper normal amylase serum value and pancreatic fistula when it is accompanied by clinical relevance (Grade B and C). In this context, we present a study to analyse potential POPF risk factors in order to predict it appearance in the first two postoperative days.

Methods: A retrospective study in 70 patients who underwent PD was performed. The considered risk factors were ASA-score, preoperative biliary drainage, need for intraoperative blood transfusion, DFA level in the first and second postoperative (PO) day and the presence of systemic inflammatory response syndrome in the first 48 hours after the surgery.

Results: The incidence of POPF was 20% (71% biochemical leak, 8% Grade B and 21% Grade C). The presence of SISR after the surgery and intraoperative blood transfusion were related with the development of POPF ($p<0.05$). The cut-off value of DFA to predict the development of POPF was 1134 U/L in the first PO day and 965 U/L in the second PO day, according to ROC curves in a logistic regression analysis.

Conclusion: These results can be considered, in one hand, to intensify the treatment in order to try to minimise the effect of POPF since the first 48 hours after the surgery in high-risk patients. On the other hand, these results can help to select patients that can benefit from an enhanced recovery protocol (early drain removal) in case of low risk to develop POPF.

P-09-44

Prevention and mitigation strategies for postoperative pancreatic fistula after pancreatoduodenectomy

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Abstract

Background: To develop a mitigation strategies for reducing the occurrence of postoperative pancreatic fistula after pancreatoduodenectomy.

Methods: In the period 2015-2021 results of surgical treatment of 370 patients with resectable pancreatic and periampullary cancer undergoing pancreaticoduodenectomy were analysed. Since November 2018, we have been using new surgical strategies: intraoperative risk assessment of postoperative pancreatic fistula occurrence and application of our modification of pancreatic fistula risk score, assessment of the presence of sarcopenia before surgery, nutritional support in patients with sarcopenia and our surgical tactics depending on the risk of postoperative pancreatic fistula (and using external pancreatic stent in patients with high risk of postoperative pancreatic fistula occurrence). Proposed mitigation strategies were applied in 141 patients during the period from November 2018 till December 2021, it was the main group. The group of comparison included 229 patients, which were operated without using the developed surgical strategies in the period from January 2015 to October 2017.

Results: The level of grade B or C postoperative pancreatic fistula was in 64 of 229 (27.9%) patients in the comparison group, which is significantly higher than in the main group, where the grade B fistula occurred in 16 (11.3%) patients (c2= 14.2, p = 0.0002). In the main group, we did not observe grade C fistula. Level of postoperative complications was significantly lower in the main group, when complications occurred in 43 (30.5%) patients, in the comparison group complications occurred in 94 (41.0%) patients (c2=4.1, p=0.04). Due to the developed tactics, we reduced the mortality rate in the main group from 2.2% to 1.4% (c2= 0.27, p = 0.6).

Conclusion: The developed surgical strategies for prevention of POPF allowed us to significantly reduce the occurrence of postoperative pancreatic fistula from 27.9% to 11.3%, the number of postoperative complications from 41.0% to 30.5% and decrease mortality from 2.2% to 1.4%.

P-09-45

Clinical significance of radical surgical treatment of patients with locally advanced tumours right anatomical segment of pancreas

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Abstract

Background: Radical resection of pancreas during pancreatic ductal adenocarcinoma has a favourable effect on the patient's survival rate and disease prognosis. In our research we show that the most often positive is smv margin after pancreatoduodenectomy. The purpose of the study is to evaluate the criteria for the diagnosis of vascular invasion at the preoperative stage, to increase the proportion of R0 resections.

Methods: The study included 73 patients with locally advanced tumours of the pancreatic head operated on in the pancreatic surgery department from 2019 to 2022. The range of operations included: Whipple pancreatoduodenectomy, pylorus-preserving pancreatoduodenectomy, and total pancreatoduodenectomy. The presence or suspicion of vascular invasion, the size, and the stage of the tumour at the preoperative stage were diagnosed according to the data of MSCT, MRI, ultrasonography, and endosonography. Histological examination was carried out according to the recommendations of the College of American Pathologist 2020. The first group 44 of patients who were made pancreatoduodenectomy with resection of PV/SMV, and the second group 29 patients without vascular resection. In the second group, a positive venous (smv) resection margin, R1 resection, had all patients according to the planned

histological examination.

Results: During the preoperative examination, vascular invasion was suspected in 68.2% of patients in the first group, and 58.6% in the second, 58,6%, (x2 = 0,696; p = 0,403). According to histological examination, damage to the vascular wall was confirmed in 81.8% of cases among the first group of patients.

A comparative assessment of the indicators of the two groups indicates that there is no significant difference in tumour size (t = 1.38; p = 0.085), localisation, intraoperative data (operation time) (t = 1.19; p = 0,117), the number of postoperative complications (x2 = 0.027; p = 0.869), and the histological type of the tumour. Only intraoperative blood loss had statistical significant.

Conclusion: Performing a resection of PV/SMV during pancreaticoduodenectomy with pre- or intraoperative suspicion of vascular invasion allows to increase the number of R0 resections and improve the prognosis of the disease.

P-09-46

Provincial prospective audit of pancreaticoduodenectomy in China: an analysis of 1172 Cases in the year of 2021

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Abstract

Background: There is a lack of domestic or provincial level data regarding the outcomes after pancreaticoduodenectomy in China. The Jiangsu Provincial Pancreaticoduodenectomy Audit is established in March 2021 and is mandatory in 21 tertiary referral hospitals in Jiangsu Province, an economically developed province in eastern China.

Methods: Performance indicators and case-mix factors were chosen by taking reference from the literature and international peers. Definition and grading of complications followed the recommendation of ISGPS and/or Clavien-Dindo classification. Quality of the audit data was evaluated by cross-checking of interrelating variables in the database (postoperative fistula rate vs. interventional percutaneous drainage rate) and on-site validation with the original medical records. Centralized follow-up studies were carried out to evaluate the outcomes 90 days after surgery.

Results: From March 1, 2021 to December 31, 2021, 1172 cases of pancreaticoduodenectomies were registered, including 201 minimally invasive cases (17.2%) and 133 cases of combined resections (11.3%). Male to female ratio was 1.5 and the median age was 66 (15) years old. Preoperative biliary drainage was performed in 16.2% of the cases. Median surgery duration was 291 (115) min and 26.8% of the patients received intraoperative blood transfusion. The overall complications rate was 55.1% and severe complications (> grade II) rate was 15.1%. There were 11.7% and 2.2% of the patients received interventional treatments and re-operations after surgery, respectively. Median postoperative hospital stay was 16 (11) days. In-hospital mortality rate was 0.9% while 90-day mortality rate was 5.6%. Independent risk factors for 90-day mortality included age ≥ 70, ASA grade as III-IV and pathology as pancreatic cancer. The outcomes of pancreaticoduodenectomy in Jiangsu Province was comparable to the international benchmarks. On-site validation revealed 0.6%~10.7% of critical variables recorded were different from the original medical charts.

Conclusion: The provincial audit is a potentially powerful tool in quality control for pancreaticoduodenectomy. Good outcomes were reported in tertiary hospitals from Jiangsu, China. Mitigations shall be further implemented to improve the quality of the database.

P-09-47

Inadequate lymph node examination leads to misclassification and affects survival in resected pancreatic ductal adenocarcinoma

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Abstract

Background: Lymph node status is considered one of the strongest prognostic factors for survival in resected pancreatic ductal adenocarcinoma (PDAC). However, the minimum number of examined lymph nodes (ELN) required for adequate staging has not been established in PDAC. The objective of the study was to investigate the influence of ELN on staging and survival in different types of resection for PDAC.

Methods: 466 patients undergoing partial or total pancreatectomy for PDAC at two European university hospitals between 2007 and 2016 were retrospectively reviewed. Clinicopathological data were analysed to identify the minimum number of ELN that influence prognosis and lymph node status. Survival analyses were performed to verify adequate staging.

Results: 341 (73%) patients showed lymph node metastasis (N1/N2), whereas 125 (27%) patients had no lymph node involvement (N0). To detect lymph node involvement with a probability of 95%, at least 20 lymph nodes (LN) were required for examination in pancreaticoduodenectomy, ≥25 LN in distal pancreatectomy, and ≥22 LN in total pancreatectomy. With increasing number of ELN, the proportion of positive LN increased. In node-negative patients, survival was significantly worse when < 15 LN were examined, with median overall survival of 32 months (<15 ELN) vs. 65 months (≥15 ELN) (p=0.013). These survival differences were also detectable in patients with N1 lymph node status, but not with N2 status. The examination of <15 LN was a significant negative predictor for overall survival in multivariate analysis (HR 1.725, CI 95% 1.317 - 2.260, p<0.001).

Conclusion: The number of ELN in node-negative patients affects survival in PDAC. We identified possible misclassification of patients with N0 and N1, but not with N2 status when <15 LN were examined. Therefore, at least 15 LN must be examined for adequate staging. Standardised lymphadenectomy and thorough histopathological examination avoid false lymph node classification in PDAC.

P-09-48

Failure-to-resection after surgical exploration for pancreatic cancer: predicting unnecessary surgery to optimize patient selection

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Abstract

Background: The characteristics of patients who are excluded from pancreatectomy following surgical exploration for pancreatic cancer have been poorly scrutinized thus far. However, failure-to-resection (FTR, the proportion of patients undergoing surgical exploration only despite being deemed suitable for curative intent surgery) could provide fundamental insights for the optimization of treatment allocation.

Methods: 681 patients who underwent exploration for pancreatic ductal adenocarcinoma (2018 – 2020) were analysed. Preoperative characteristics associated with FTR were investigated, as well as postoperative course and survival predictors in the resected and non-resected cohort.

Results: 70 patients (10.3%) ultimately did not receive pancreatectomy, because of findings of unresectable (35.7%) or metastatic (64.3%) disease intraoperatively. FTR did not differ between patients receiving upfront or post-neoadjuvant surgery (9.5 vs. 10.9, p=0.611), nor did the incidence of metastases (67.9 vs. 61.9%; p=0.799). Preoperative NCCN-defined resectability status correlated with both resection completion (resectable: 93.9% vs. borderline 85.0% vs. locally-advanced disease: 59.1%; p<0.001) and R0 rate (60.1% vs. 46.9% vs 36.4%, respectively; p<0.001), being the strongest predictor of FTR in both the upfront (OR 11.30, 95%CI 2.99-42.9, p<0.001) and post-neoadjuvant surgery group (OR 6.83, 95%CI 2.23-20.94, p<0.001). Greater tumour size, male gender, poorer performance status and chemotherapy discontinuation were also associated to FTR after primary chemo-radiation therapy, while chemo regimen, RECIST response and Ca19.9 variation had poor prediction capability. Despite worse complication rate, patients receiving pancreatectomy displayed longer OS even when positive margin was achieved (R0: 36.9 months, vs. R1/R2: 25.6 months vs. exploration only: 11.8 months; Bonferroni p<0.001). Among non-resected patients, there was no substantial difference between those who were found being metastatic or locally advanced intraoperatively (10.8 vs. 14.4 months; p=0.10).

Conclusion: Resectability status defined from cross-sectional imaging still represents the most accurate parameter to inform curative surgery completion for pancreatic cancer, irrespective of preoperative treatment received and response. Novel biomarkers are needed to improve patient selection and surgical indication.

P-09-49

Comparison of total lymph node retrieval and survival with the standard Whipple procedure versus the pylorus preserving pancreatoduodenectomy in early pancreatic head tumours

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Abstract

Background: The Whipple procedure and the pylorus-preserving pancreatoduodenectomy (PPPD) are the two main surgical techniques used to treat pancreatic head tumours. While previous studies have shown similar lymph node retrieval rates between the two procedures, their impact on survival remains unclear. In this study, we aimed to compare the total lymph node retrieval and survival rates between the standard Whipple procedure and PPPD in patients with early (T1,T2) head pancreatic cancer tumours.

Methods: We conducted a retrospective analysis of patients who underwent either the Whipple procedure or PPPD for T1 and T2 tumours between 2012 and 2021 in our HPB unit. A total of 129 patients were included in the study. We compared the total lymph node retrieval and survival rates between the two groups using the Kaplan-Meier method and statistical tests.

Results: Our results showed that there was no significant difference in total lymph node retrieval rates between the Whipple procedure (mean: 23.36) and PPPD groups (mean:22.38) (p=0.158). Similarly, there was no significant difference in survival rates between the two groups.

Conclusion: Our study suggests that there is no significant difference in total lymph node retrieval rates or survival rates between the standard Whipple procedure and PPPD in patients with T1 and T2 tumours. These findings may help guide surgical decision-making and improve patient outcomes.

Our study has several limitations, including its retrospective nature. Further randomised prospective studies are needed to confirm our findings and explore the long-term outcomes of these two surgical techniques in larger patient populations.

P-09-50

The interplay between preoperative anaemia, intraoperative blood loss and transfusions in pancreatoduodenectomy: a question unresolved

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Abstract

Background: Preoperative anaemia, high Estimated Blood Loss (EBL) and intraoperative transfusions are considered independent contributors to adverse outcomes following pancreatic resection. The present study aid to unveil the interplay and possible dependency between such factors in determining subsequent complications.

Methods: 652 consecutive pancreatoduodenectomies (2017-2019) were analysed. Patient- and operative- factors were associated with postoperative outcomes using multivariable logistic regression and hierarchical models to

detect interactions. Moreover, Hb variation between preoperative and POD3 timepoints was modeled using longitudinal data linear models.

Results: Anaemic patients (44.5%) received more intra (x2.5) and postoperative transfusions (x1.5) but did not exhibit poorer outcomes. Overall, Hb showed a constant decline across preoperative timepoints, with a median 21% drop (equating to a net 2.6 mg/L loss). Hb trends were influenced by anaemia, high EBL and transfusions, but trajectories did not correlate with overall complications - except for the need of subsequent transfusions ($p<0.001$). Median EBL was 490mL, with 89 patients (13.7%) receiving intraoperative transfusions and only 16% showing Hb restoration. While increasing EBL was associated with intra/postoperative transfusions ($p<0.001$), multivariable models did not show any association between EBL and overall complications after adjusting for the interaction with both preoperative anaemia and transfusions. Conversely, intraoperative transfusions were associated with pancreatic fistula (OR 2.63) and renal failure (OR 2.81), while both transfusions and greater perioperative Hb drift predicted severe complications (ORs 2.35 and 0.06, respectively), PPH (ORs 3.27 and 0.01) and postoperative transfusions (ORs 3.37 and 0.01). Of note, intrinsic pancreatic characteristics such as soft texture and diminutive duct were persistently associated with worse outcomes.

Conclusion: Anaemia and EBL seem not to influence complication development per se after PD. Conversely, intraoperative transfusions and greater Hb decline - which are dependent on the above mentioned contributors and may indicate reduced tissue perfusion - are associated with poorer outcomes. These results call for future studies investigating the role of pancreatic hypo-perfusion in complication development and guiding goal-directed clinical approaches.

P-09-51

Factors affecting prognosis after pancreatectomies for pancreatic cancer: a multivariate analysis

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Abstract

Background: Pancreatic cancer is the seventh leading cause of cancer death with very poor prognosis, while surgery remains the most curative option. In this retrospective study, we aimed to identify the prognostic factors affecting survival after pancreatectomies for pancreatic cancer during 2012-2021.

Methods: In this retrospective study, we analysed data from patients been operated in the HPB unit of our tertiary hospital the last decade, during 2012-2021. A total of 231 patients were included in the study. The factors included in univariate analysis were: gender, age, histological type, neoplasm grading, tumour size, organ of origin, lymph node (LN) status (total LN, negative LN, LN ratio), vascular invasion, perineural invasion, R status, T and N status, neoadjuvant chemotherapy, existence of bile stent and bilirubin levels. Then we conducted a multivariate analysis using Cox regression to determine which factors were independently associated with survival.

Results: In univariate analysis, factors like age, sex, neoadjuvant chemotherapy, total number of LNs and negative LNs were not statistically significant. Tumour size and differentiation were statistically significantly correlated with worst overall survival ($p=0.001$). Histological findings like microvascular and perineural invasion were statistically significant ($p=0.001$, $p=0.006$) as well as the N status ($p=0.048$), LN ratio ($p=0.002$). The surgical margins expressed as the R status was also a significant factor with R1 resections having much worse survival ($p=0.009$). However, on multivariate analysis, only differentiation of the tumour was found to be statistically significant ($p=0.004$). Patients

with well-differentiated tumours had a significantly better prognosis than those with poorly-differentiated tumours.

Conclusion: Our study suggests that tumour differentiation is the most important prognostic factor for survival after pancreatectomies in pancreatic cancer patients. The other factors that were identified in the univariate analysis may still be clinically relevant. Further prospective studies are needed to validate our findings. Our study has several limitations including sample size, retrospective design and lack of study other clinical variables that may affect survival.

P-09-52

Posterior-inferior approach retrograde spleen-preserving left pancreatectomy: how I do it

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Abstract

Background: Spleen-preserving left pancreatectomy is technically difficult for tumours in the region of distal pancreata and splenic hilum, especially for open Kimura technique in obese patients.

Methods: Here we describe a novel technical modification for spleen-preserving left pancreatectomy, which simplify the surgical manipulations and promote the feasibility of spleen and splenic vessels preservation.

Procedure: The colicosplenic ligament was dissected and splenic flexure of the colon was freed first, exposing the inferior border of the pancreatic body-tail and spleen. Other ligaments holding the spleen to the retroperitoneal space, including the splenorenal ligament and the phrenocolic ligament, were also dissolved to mobilize the spleen. The gastrosplenic ligament was preserved. After the pancreatic tail was detached along the Gerota's fascia, the whole region of pancreatic body-tail and spleen can be alleviated from the retroperitoneal space to the plane of the incision with gauze pads placed behind. This manoeuvre turned a deep, awkward surgical field to a shallow, easy one, making ligation and dissection of the tiny branches of the splenic vessel more straightforward and controllable. Bleeding from the splenic vessel can be easily managed. The dissection of the pancreatic body-tail can always start from the tip of the tail, where there would be no tiny vessels in that area. Resection of the left pancreas as well as the tumour could be continued in a retrograde manner.

Conclusion: Our novel modification is very useful in open spleen-preserving left pancreatectomy, as well as other open surgeries in the proximal part of greater curvature of the stomach.

P-09-53

Pancreatectomies in a tertiary hospital during the period 2012-2021: a retrospective study

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Abstract

Background: Pancreatic surgery is one of the most challenging parts of general surgery and is recommended to be performed by surgeons with high expertise and with high volume of patients. In this study we present the experience of our HPB surgical unit on pancreatectomies during the last decade between the period 2012-2021.

Methods: We conducted a retrospective analysis of patients who underwent pancreatectomy in our HPB surgical department during the period 2012-2021. A total of 356 patients were included in the study. We compared gender, age, the type of pancreatectomy, histological type of the specimen and margin status (R).

Results: The median age of patients underwent pancreatectomy was 65.3 years, the male/female ratio was 199/157. From these patients 134 underwent Whipple procedure, 107 pylorous-preserving pancreatoduodenectomy (PPPD), 82 distal pancreatectomy, 25 total pancreatectomy and 8 enucleation of pancreatic neuroendocrine tumour (NET). The histological type was mainly adenocarcinoma (231 cases), next most common type was pancreatic NET (33 cases), Intraductal papillary mucinous neoplasm (IPMN) in 22 cases, chronic pancreatitis in 22 cases, solid pseudo-papillary neoplasm (SPN) in 6 cases, other benign neoplasms in 23 cases and other carcinomas in 11 cases. Our R0 resections were 227. Post-operative complications of Clavien-Dindo scale 3 or more presented in 52 cases. The 30 day mortality was 5.1% (18 patients). The mean length of stay in the hospital was 15 days and the median was 11.5 days. The 5-year survival of patients with pancreatic adenocarcinoma was 22%, while of those patients with NET was 71%.

Conclusion: Our results are in terms with international centres of excellence surgery units. Further prospective studies should be performed to validate our findings. Pancreatic surgery should be performed only in centres of excellence worldwide because of its highly expertise.

P-10-01

Pancreatic neuroendocrine neoplasms in patients with more than 75 years of age: a single centre experience

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Abstract

Background: With increasing median survival and wider use of diagnostic radiology methods there is an increase in findings of neuroendocrine tumours in elderly patients. Surgery, even in this case, plays an important curative role.

Methods: Clinical records of patients > 75 years-old who were diagnosed with pancreatic NET (p-NET) from 1979 to 2021, were retrieved retrospectively. We evaluated the reasons for excluding surgery as well as the postoperative outcome of patients undergoing surgery.

Results: 42 patients were enrolled (20 M/22 F, mean age 80 years) out of 397 observed (10.6%). Six patients had a Functioning-pNET (F-pNET - 5 insulinomas and 1 gastrinoma), 36 cases had a Non Functioning -pNET (NF-pNET; 85.7%). Nineteen patients had a pancreatic head tumour and 23 in the body-tail. All patients with F-pNET and 14/36 with NF-pNET underwent surgery, thus 20/42 cases underwent surgery (47.6%). Six enucleations, 5 pancreaticoduodenectomies and 9 distal pancreatectomies were performed. Sixty-four % of patients who underwent surgery had a low-stage tumour (S1/2-without lymph-node involvement). Overall surgical morbidity was 15%: 1 pancreatic fistula grade B and 1 delay gastric emptying occurred; 1 case had acute postoperative heart failure. Average hospital stay was 10 days (range 7-21). Mean follow-up of was 6 years, 10/20 pts died, only 4 due to disease progression (2 with lymph-node metastases, 2 with hepatic metastases at diagnosis). Among 22 patients who did not undergo surgery, 9 pts were not operated on because of the small size of the tumour, 5 patients refused surgery and 8 patients had major comorbidities.

Conclusion: Elderly patients with p-NET need be carefully selected to undergo surgery. In case of pancreatic resection in our experience, the postoperative morbidity is very low, and the results are excellent.

P-10-02

Outcome of pancreatic NETs with liver metastases surgically treated: a single centre experience

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Abstract

Background: Surgery for pancreatic NETs (pNETs) with Liver Metastases (LM) is still debated, particularly in non-functioning tumours. Claimed as an operation which results in a longer survival, debulking or partial resection of LM is so far a procedure not widely accepted.

Methods: We reviewed our series of pNETs observed by our Pancreatic Unit from 1980 to 2020 to identify patients with LM. Follow-up to December 2022. Among 375 pNETs diagnosed, 67 (17,7%) had LM. Sixteen (23.8%) patients had a functioning primary pNET. 26 primary pNETs were in the head, 11 were multiple/diffuses. 39 patients underwent resective surgery, 25 of them had synchronous LM. Fourteen patients who had pancreatic resection without distant metastases, had recurrence with LM after a mean DFS of 95 months (8 years).

Results: 39 patients underwent surgery; pancreaticoduodenectomy was perfomed in 12 cases (with 6 hepatic resection/ablation), distal pancreatectomy in 21 patients (with 13 hepatic resection/ablation), in 2 cases a total pancreatectomy was made and 4 cases had other procedures. Postoperative mortality occurred in 2 patients for liver failure and MDR infection. Twenty-eight patients with pNET did not undergo pancreatic resection; in two cases, surgery was performed for palliation (gastric/biliary by-pass), in 9 cases for laparoscopic biopsy of LM. Among 25 patients operated with LM, 4 patients are still alive after mean time of 166 months (14 years), while 21 patients died after a mean time of 53 months (4 years). In this subgroup of 25 patients, the real 3, 5 and 10 years survival were 56, 39, and 25% respectively. In 12 cases, post-operative therapy with somatostatin analogues (SSA) was made. Only 2 cases were treated with postoperative chemotherapy. Out of 14 resected patients who recurred with LM after a mean DFS of 95 months, 8 patients are alive 176 months after surgery, and 5 patients died after 139 months. Only 1/28 non-operated patient is alive after 155 months, while 27 non-operated patients had a mean OS of 43 months.

Conclusion: In pNETs with LM a long survival may be achieved even when a R2 LM resective surgery is perfomed.

P-10-03

Long-term health-related quality of life after surgery of pancreatic neuronendocrine neoplasms: a single centre experience of 32 years

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Abstract

Background: Pancreatic Neuroendocrine Neoplasms (pNEN) often have a good prognosis. We evaluated health-related quality of life (HRQoL) after a pancreatic resection in open surgery for a pNEN.

Methods: 104 patients who underwent a pancreatic resection for a pNEN between May 1990 and April 2022 in our centre were enrolled. Clinical data were retrieved from clinical charts, while the QoL data were collected prospectively. The EORTC QoL questionnaires QLQ-C30, QLQ-GI.NET21 and QLQ-PAN26 were filled by the patients from September 2021 to December 2022. Results were expressed in a scale 0-100 in percentage values, higher scores

represent a better outcome of functional scales and a worse outcome for symptomatic scales. Six major clinical domains were selected as outcome variables: global QoL, physical function (PF2), social function (SF), disease related worries (DRW), pain and upper-GI symptoms. These domains were evaluated according to seven clinical variables: gender (M/F), age (<65/≥65), grade at histology (1/2), type of pNEN (functioning/nonfunctioning), comorbidities (no/single/multiple), type of surgical resection, and pancreatic function (normal/diabetes/impaired exocrine). Wilcoxon and Kruskal-Wallis test were used for data analysis.

Results: There were 41M/63F, mean age 63 yrs.; 63.5% were affected by multiple comorbidities. 57% were non-functioning and 70% were G1 tumours. 54% underwent standard resection, 83% maintained a normal pancreatic function after surgery. Data show good HRQoL results (median 83.3%; IQR 58.3-100%). Regarding DRW, a minority showed concerns about their health status (med 26.7; IQR 13.3-33.3), while their physical (med 94.4; IQR 77.8-100) and social (med 88.9; IQR 77.8-94.4) functions were slightly affected. Pain (med 9.5; IQR 0-19.1) and upper GI symptoms (med 3.9; IQR 0-9.1) were rarely reported. We observed statistically significant results for QoL (worse in women, p=0.04, and in elderly, p<0.001), PF2 (worse in women, p<0.001, and in elderly, p<0.001), pain (worse in women, p=0.02, and in elderly, p=0.002); upper-GI symptoms were worse in elderly (p=0.016), and standard surgery affected both SF and DRW (p=0.03 and p=0.04, respectively).

Conclusion: In patients who underwent a pNEN resection, gender, age and type of surgery seem to affect slightly HRQoL; however, a good HRQoL was generally reported.

P-10-04

Evaluation of treatment appropriateness in patients submitted to surgery for non-functioning pancreatic neuroendocrine tumours (NF-PanNETs)

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Abstract

Background: Currently available preoperative prognostic factors for non-functioning pancreatic neuroendocrine tumours (NF-PanNETs) still struggle to predict properly tumour aggressiveness, making an adequate management of these lesions hard to be achieved. Aims of this study were: i) to evaluate treatment appropriateness in patients submitted to surgery for NF-PanNETs, and ii) to investigate preoperative features predicting under- or over-treatment in this setting.

Methods: Patients who underwent curative surgery for NF-PanNETs at a referral centre for NETs (San Raffaele Hospital, 2002-2022) were retrospectively analysed. Treatment appropriateness was categorised as appropriate treatment, over-treatment, and under-treatment. The absence/presence of features of aggressiveness at final histology and the occurrence of disease relapse within one year from surgery were considered to define treatment appropriateness.

Results: Overall, 384 patients were included. Of these, 230 (60%) received an appropriate treatment, 129 (34%) an over-treatment and 25 (6%) an under-treatment. Treatment appropriateness was significantly associated with the type of diagnostic work-up (p=0.034). The combination of high-quality imaging (Computed Tomography and/or Magnetic Resonance Imaging), endoscopic ultrasound and ^{68}Gallium Positron Emission Tomography was the most frequent diagnostic work-up performed in patients included in the appropriate treatment group. Over-treated patients showed the highest frequency of lesions located in the pancreatic body-tail (p=0.012), and presented the smallest tumour size (p<0.001) at imaging evaluations. The year of surgical resection was found to be strongly

correlated with treatment appropriateness (p<0.001), with a significant increase of appropriately treated patients after 2015. Surgical resection performed before 2015 (p<0.001), radiological tumour diameter <25.5mm (p<0.001) and pancreatic body/tail tumour location (p=0.018), were identified as independent predictors of over-treatment. Radiological tumour size was the only independent determinant of under-treatment (p=0.016). A significant poorer disease-free survival (p<0.001), overall survival (p<0.001) and disease-specific survival (p<0.001) rates were observed among the under-treated patients.

Conclusion: Over-treatment occurs in almost one-third of patients undergoing surgery for NF-PanNETs. However, over the last decade, the percentage of appropriately treated patients has been steadily increasing. A more careful assessment of lesions located in the pancreatic body-tail and/or with a radiological diameter <25.5mm should be performed in the attempt to further improve treatment appropriateness.

P-10-05

The use of quantitative contrast-enhanced endoscopic ultrasound in the evaluation of pancreatic neuroendocrine tumours: can we move from quality to quantity? A proof-of-concept study

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Abstract

Background: Contrast enhanced EUS (CE-EUS) is a pivotal tool for the diagnosis of pancreatic focal lesions, especially for pancreatic cancer (PC) and pancreatic neuroendocrine tumour (pNEN). The enhancement after contrast medium injection is usually assessed qualitatively, although dedicated software has recently been developed that provides an objective quantitative assessment using perfusion parameters. Our aim was to evaluate quantitatively the enhancement of pancreatic solid lesions at CE-EUS.

Methods: Seventy-three patients (51 PC and 22 pNET) who underwent CE-EUS and EUS-guided fine needle aspiration (EUS-FNA) were included. Quantitative analysis of tumour vascularization was performed with a commercially available software (Vuebox®). Time-intensity-curve (TIC) were created and several parameters were evaluated including the average contrast signal intensity (MeanLin), peak enhancement (PE), rising time (RT), fall time (FT), time to peak (TTP), mean transit time (mTT), Wash-in Area Under the Curve (WiAUC), Wash-in Rate (WiR), Wash-in Perfusion Index (WiPI), Wash-out Area Under the Curve (WoAUC), Wash-out Rate (WoR), and WiAUC + WoAUC (WiWoAUC). Univariate and multivariate analysis were conducted. Patient-level and tumour-level characteristics were evaluated.

Results: Univariate analysis showed that several parameters (PE, WiR, WiAUC, WiPI, WoAUC and WiWoAUC) were statistically significantly associated with pNET. At univariate analysis pNET diameter was associated with mTT (p<0.001)

Conclusion: Quantitative enhancement evaluation in CE-EUS is still at dawn but in the future, it could potentially predict early tumour behaviour and drive therapeutic choices.

P-10-06

Efficacy and safety of capecitabine and temozolomide (CAPTEM) in advanced gastro-entero-pancreatic neuroendocrine neoplasms (GEP-NEN): a systematic review and meta-analysis

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Abstract

Background: Gastro-entero-pancreatic neuroendocrine neoplasms (GEP-NEN) are heterogeneous tumours, with multiple therapeutic options for advanced stages. The combination of capecitabine and temozolomide (CAPTEM) is increasingly used for advanced GEP-NEN, but evidence on results is sparse. We conducted a systematic review and meta-analysis to assess efficacy and safety of CAPTEM in advanced GEP-NEN

Methods: We included studies enrolling patients with any grade GEP-NENs undergoing CAPTEM. A meta-analysis with random effects model, progression-free survival (PFS) as primary endpoint and severe adverse events (SAEs) rate as secondary endpoint was performed. Different treatment schedules were considered. The heterogeneity (I2) was interpreted by meta-regression analysis considering the following covariates: study type and design, sample size, metastatic disease rate, rate of primary pancreatic NENs, previous treatments, and study quality.

Results: A total of 22 studies with 788 patients (age range 29-64 years; male proportion range 46.9-65%, primary pancreatic site range 14-100%) were included. All but 1 study, being a RCT, were retrospective. The median CAPTEM cycles number was 6.9 (IQR 4.5-8). The cumulative PFS was 14.7 months (12.9-16.5), with high heterogeneity (I2=99%). Study type and design, previous treatments, and quality of the studies did not affect PFS. Although not significant, PFS was higher in patients with non-pancreatic primary tumours and in post-2017 trials. The pooled SAEs rate was 17.6% (10.1-25). There was no publication bias.

Conclusion: CAPTEM is an effective combination, with similar PFS and a safety profile compared to other agents. Further investigation in RCTs or in sequence studies is advisable.

P-10-07

Diagnostic work-up and surgical management of insulinoma - a retrospective analysis from a tertiary referral centre

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Abstract

Background: Insulinoma is a multifaceted disease posing several challenges in terms of clinical presentation, diagnostic work-up and surgical management. The aim of this study was to describe diagnostic work-up, surgical management and postoperative outcomes of patients with insulinoma.

Methods: All consecutive patients who underwent surgery for insulinoma at San Raffaele Hospital (Milan, Italy) between 2008 and 2022 were included.

Results: Overall, 98 patients were included. The median delay between presenting symptoms and insulinoma diagnosis was 10 months (IQR 4-21). Insulinoma diagnosis was made at our Institution in 45 patients, 20 of whom referred within 6 months from symptoms onset. In this subgroup, the median interval between symptoms presentation and insulinoma diagnosis was 4 months (IQR 2-6), as compared to 14 months (IQR 10-26) in patients (*n*=25) who referred to our institution after 6 months from symptoms onset (*P*<0.001). The insulinoma was localised preoperatively in all the cases. All patients underwent ≥1 high-quality imaging: computed tomography (CT: *n*=87, sensitivity 84%), magnetic resonance imaging (MRI: *n*=55, sensitivity 85%) and endoscopic ultrasound (EUS: *n*=79, sensitivity 100%). MRI identified the tumour in 8 patients with negative CT. EUS localized the insulinoma in 3 patients with negative CT and negative MRI. Parenchyma-sparing resections were performed in 41 patients. Contact with major vessels, lesion close to the main pancreatic duct ore embedded in the pancreatic parenchyma (*n*=14), contact with major vessels (*n*=9) and suspect of malignancy (*n*=4) were the main reasons to perform a formal resection. The rate of clinically relevant postoperative pancreatic fistula was similar between patients who underwent enucleation/central pancreatectomy and those submitted to pancreaticoduodenectomy/distal pancreatectomy (*n*=8/41, 20% *versus* *n*=17/57, 30%, *P*=0.248).

Conclusion: An early referral to high-volume centres is important for reducing diagnostic delay in patients with insulinoma. The diagnostic work-up of insulinoma frequently requires several imaging modalities to be performed, with EUS being the most sensitive one. Parenchyma-sparing surgery for insulinoma should be performed whenever technically and oncologically feasible.

P-10-09

Mechanisms of CUX1-induced tumour progression in neuroendocrine tumours of the pancreas

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Abstract

Background: Pancreatic neuroendocrine tumours (PanNET) are a group of heterogeneous malignancies. We previously identified the transcription factor Cut homeobox 1 (CUX1) as an important mediator of tumour progression and therapy resistance in PanNET. Based on our preliminary data, the aim of this work is to characterize the underlying molecular mechanisms of CUX1-induced tumour progression to identify potential targets for therapeutic intervention.

Methods: In the two PanNET cell lines BON-1 and QGP1 transient CUX1 knockdown was performed by transfecting cells with siRNAs. For stable knockdown, CUX1 oligonucleotides corresponding to gene specific small hairpin RNA sequences were cloned into the pGreenPuro lentivector. The CUX1-p200 gene was cloned into the pCDH overexpression vector. Western blotting assay performed to investigate CUX1 expression levels. To assess effect on apoptosis, TUNEL assay was used. RNA sequencing was performed to provide insight into the transcriptome of PanNETs. To further characterize the impact of CUX1 KD, gene set enrichment analysis (GSEA) based on sequencing data was

accomplished. Seahorse assay performed to measure oxygen consumption rate upon CUX1 knockdown. Mass spectrometry was performed in order to confirm RNA sequencing data.

Results: Transiently CUX1 KD in PanNET cells showed an upregulation of apoptosis. The RNA sequencing data displayed numbers of mRNAs, lncRNAs and miRNAs, which are differentially expressed (FDR < 0.05) upon CUX1 KD. LINC02404 and hsa-miR-1197 are interesting candidates that are upregulated with CUX1 KD. GSEA identified E2F targets, G2M checkpoint as well as MYC targets as top depleted and hypoxia, oxidative phosphorylation and TNFA signalling as top-enriched pathways in CUX1 KD cells. Mass spectrometry following by western blotting analyses displayed downregulation of HAT1 upon CUX1 KD.

Conclusion: Our results suggest that CUX1 could behave as an oncogenic factor in PanNET via modulating a complex network of protein-coding and non-coding RNAs. Further experiments such as lncRNA pull down and miRNA mimic transfection are needed to elucidate the mechanisms in detail and to propose targets for therapeutic intervention in CUX-1 overexpressing PanNET.

P-10-10

Malignant insulinoma - single centre experience

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Abstract

Background: Insulinoma are rare pancreatic tumours. The incidence is low about 1 – 2 per 1 million inhabitants per year. Majority of the tumours are benign, malignant form are diagnosed in less than 10 %. The diagnosis of malignant insulinoma is based on local invasion and distant metastases. The prognosis is relatively poor only about 50 % patients survive 5 years.

Methods: We retrospectively reviewed the records of patient undergoing surgery due to insulinoma in 23 years (2000 – 2022). We have performed 112 surgeries. The diagnosis was based on Whipple trias as in cases of benign insulinoma and on infiltrative or metastatic growth. We identified 6 patients with malignant insulinoma.

Results: There is 6 % of malignant insulinomas in our series. More patients were males (4 : 2). The localisations were more frequent in the head of the pancreas (3 cases). Left pancreatectomy with splenectomy was performed in cases localised in body and tail of the pancreas. The Whipple procedure and excision + Roux Y anastomosis was performed in the two of insulinomas in the head of pancreas. In the last case only explorative laparotomy was possible. One patients died shortly after surgery, two of them 5 and 6 years after surgery and three of them are still alive 5, 11 and 18 years after surgery. These results are better than in literature, because nearly all of our patients survive minimally 5 years.

Conclusion: It is difficult to diagnose preoperatively malignant form without metastases. The diagnostic workflow is same as in benign type. Surgery is treatment of choice for both types of insulinoma. We can achieve long-term survival in malignant cases too

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P-10-11

Always look behind the rock: a case of an insulinoma hidden by a pancreatic stone

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Abstract

Background: Among pancreatic NET insulinomas are the most insidious to diagnose and often their preoperative radiologic localisation fails because of their small size and lower expression of somatostatin receptors.

Case Report: We present the case of a 59-years-old woman, without relevant past medical history, who presented with symptomatic hypoglycaemia (diplopia, blurred vision, palpitations, weakness). Plasma fasting tests revealed blood glucose level < 50 mg/dL, increased plasma insulin level (≥6 µU/ml) and increased C peptide level (≥0.2 nmol/l), suggesting the presence of an insulinoma. Therefore**,** imaging studies were started to localize the tumour. An abdominal computed tomography scan (CT) was performed showing two millimetric cystic lesions in the body of the pancreas and a stone in the tail, confirmed by a subsequent magnetic resonance (MRI). A 68Gallium-PET didn't highlight any suspected areas. An endoscopic ultrasound (EUS) was then performed, showing a lobular pattern of the pancreatic parenchyma in toto without evidence of focal lesions. The two cystic lesions in the body of the pancreas were interpreted as branch ducts Intrapapillary Mucinous Neoplasm without any worrisome features. Elastography showed no alterations in the parenchymal elasticity. Thus, nothing was going in the direction of detecting the insulinoma. However, looking at the tail of the pancreas the presence of a shadow cone revealed a calcific area of about 10 mm which, after contrast administration and Hi-Flow magnification, showed itself surrounded by unusual rich vascularization. An EUS-guided fine needle biopsy (FNB) on this area was performed and the histologic report described many cells aggregates with chromatin granules and immunohistochemistry positive for synaptophysin, thus confirming the diagnosis of a pancreatic neuroendocrine neoplasm. A laparoscopic distal splenopancreatectomy was performed. Final histopathological report revealed the presence of a well differentiated and functional neuroendocrine tumour of the pancreas (G1, chromogranin A +, synaptophysin +, insulin +) producing calcified matrix.

Conclusion: Calcifications in pancreatic neuroendocrine tumours are rarely seen radiologically but this finding should be watched carefully especially when searching for very small tumours like insulinomas. EUS study with the use of contrast agent was crucial for our diagnosis as it revealed a typical hyper-enhanced vascular pattern around the calcification, which guided the subsequent biopsy.

P-10-12

The impact of metformin, insulin, and diabetes on the progression of pancreatic neuroendocrine tumours (PNETs)

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Abstract

Background: Little is known about prognostic factors for the outcome of pancreatic neuroendocrine tumours (PNETs) but previous studies suggested a potential positive effect of metformin use, and a potential negative effect

of diabetes and insulin use. Most of previous evidence includes heterogeneous cohorts, a factor that might have impacted the interpretation of results in terms of prognosis. Our aim is to investigate the role of metformin, insulin, and diabetes in the progression of operated PNETs in a high-volume centre in Sweden.

Methods: A single-centre, retrospective cohort study was conducted at Umeå University Hospital, Umeå Sweden. We included consecutive patients with PNETs operated between 2001 and 2020. All diagnosis were histological confirmed. We collected demographic and exposures. We evaluated continuous variables with t-test or Mann Whittney and categorical variables with chi-square test. Potential factors impacting the overall and progression free survival were analysed through an adjusted univariable cox regression model.

Results: Overall, 54 patients were included, 61.1% males, mean age 66 years; 22 of which (44.8 %) with DM, mean duration of diabetes 48 months (23-149). Metformin was used by 11 patients (21.2%), insulin by 13 patients (25.5%). Metformin users vs non-users displayed non significantly different mortality rates (0% vs 22%, p=0.09), non-significantly different disease specific mortality (0% vs 5.9%, p=0.4), and non-significantly different post-operative recurrence (27.3% vs 22.0%, p=0.7). Likewise, insulin users vs non-users displayed non significantly different mortality rates (23.1% vs 13.2%, p=0.4), non-significantly different disease specific mortality (0% vs 5.7%, p=0.4), and non-significantly different post operative recurrence (30.8%vs 21.1%, p=0.4). Overall survival was not affected by insulin use (HR=1.5, 0.3-7.2 95% CI, p=0.5) nor by the presence of DM (HR=0.9, 95% CI 0.2-4.1, p=0.9).

Conclusion: This study could not confirm any significant association between DM, the use of metformin, or insulin and the progression of operated PNETs.

P-10-13

Histology matters: incidence of major thrombotic events in pancreatic neuroendocrine tumours (PNETs) compared to pancreatic ductal adenocarcinomas (PDACs)

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Abstract

Background: Pancreatic neuroendocrine tumours (PNETs) can develop cancer-related medical complications during the long-standing clinical course. Cancer is a known risk factor for thrombosis and the need of anticoagulants in an outpatient clinic setting can be assessed through the Khorana score. Pancreas localisation is associated with higher risk, but the Khorana score does not distinguish between PNETs and pancreas ductal adenocarcinoma (PDAC). The aim of the study is to assess the incidence and prevalence of major thrombotic events (MTE) in operated PNETs vs PDAC.

Methods: Retrospective case-control on a cohort of patients operated at Umeå University Hospital, Umeå, Sweden between 2001-2020. Cases (PNETs), and consecutive age (±10 years) matched controls (PDAC) were compared for demographics, exposures, cancer characteristics, MTE at the time of diagnosis and during follow-up. Statistical analysis: student's t-test, Mann Whitney test, univariable Cox regression analysis.

Results: 53 cases and controls were included, 60.4% males. Overweight and obesity were significantly more prevalent in cases than in controls (53.1% vs 42.0 and 10.2% vs 8.0%, respectively p=0.04). A previous history of cancer and active cancer was more frequent in cases than in controls (30.2% vs 11.5%, p= 0.01, 36.4% vs 3.8%, p= 0.009), respectively. The rate of pre-operative MTE was not statistically significant (20.8% vs 11.3%, p=0.1), as well the previous use of aspirin, other antiplatelet drugs, and anticoagulants (32.7% vs 24.5%, p=0.3; 5.9% vs 9.4%, p=0.4;

and 33.3% vs 18.9%, p=0.09, respectively). The rate of post-operative MTE was statistically lower in cases than in controls, 11.3% vs 0%, p=0.01. At univariable Cox regression analysis cases displayed less risk of developing major cardiovascular events (HR=0.13, 0.05-0.36, 95% CI, p=0.0001).

Conclusion: The post-operative risk of MTE is significantly lower in PNETs compared to PDAC. Different pancreas histotypes might display different risk and deserve further risk-stratification before the administration of parenteral anticoagulants.

P-11-01

Accompanying cancer of other site may be a new prognosticator in patients with branch duct intraductal papillary mucinous neoplasm unfit for surgical treatment

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Abstract

Background: This study was done to elucidate the clinico-radiologic predictive factors for cancerous change detected by disease progression (PD) mainly defined by interval increase in cyst size and morphology, for branch duct intraductal papillary mucinous neoplasm (BD-IPMN) patients with relatively long-term follow-up.

Methods: Analyses were performed for 135 patients with BD-IPMN enrolled from July 2010 to October 2020, in whom the communication between the cystic lesion and pancreatic duct was confirmed by either endoscopic ultrasonography (EUS), magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP).

Results: During the mean ± SD follow-up period of 59.4 ± 29.2 months, PD was noticed in 28 (20.7%) of 135 BD-IPMN patients. Among 135 patients, 8 (5.9%) displayed cancerous change. By univariate analyses, tumour location of head and uncinated process, septated/multilocular cyst morphology, baseline cyst size ≥30 mm, presence of interval increase in cyst size, baseline cyst wall thickening ≥2 mm, baseline presence of mural nodules, and accompanying cancer of other site were significant predictive factors for cancerous changes in BD-IPMN patients. A Cox forward stepwise linear regression model revealed that mural nodule (OR 58.210, 95% CI 6.649 ~ 509.594, p <0.01) and accompanying cancer of other site (OR 8.463, 95% CI 1.745 ~ 41.039, p <0.01) were significant and independent predictive factors for cancerous change in BD-IPMN patients.

Conclusion: A considerable proportion of patients with BD-IPMN showed PD and cancerous change during the long-term follow-up. Mural nodule and accompanying cancer of other site were significant and independent predictive factors of cancerous change in patients with BD-IPMN.

P-11-03

Preliminary clinical exome evaluation of intraductal papillary mucinous neoplasm patients by next generation sequencing

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Abstract

Background: Intraductal papillary mucinous neoplasm (IPMN), as one of the most prevalent pancreatic cystic tumours, is characterised by cystic papillary growths and dilation within the pancreatic ductal system. The prevalence of individuals with IPMN is approximately 0.001% to 0.002%.The molecular mechanism of IPMN is not fully understood, but its increasing incidence and confirmed potential role in progression to invasive adenocarcinoma of the pancreatic ducts drawing research attention to early and non-invasive diagnosis. Genomic screening could be an effective method to identify genetic predisposition in high-risk populations.

Methods: Eight blood samples from IPMN patients (mean age 71 ± 9; 3 males) underwent clinical exome sequencing analysis. Library preparation and sequencing were performed using Clinical Exome Solution v2 (Sophia Genetics) and the MiSeq platform (Illumina). The clinical exome panel comprised the coding regions and ±5bp of exome flanking regions of 4,490 genes. Alignment, annotation, and variant filtering (MAF <0.05 and coding sequences) were carried out with Sophia DDM software (v. 5.10.32).

Results: Considering all patients, an average of 6,662 retained variants were found, focusing our analysis on virtual panels. According to the literature and GO, virtual panels related to inflammation (204 genes), obesity (38 genes), diabetes (170 genes) and pancreatic cancer susceptibility (51 genes) were designed. For inflammation panel, rare variants in Apoliprotein and Toll Like Receptor families were identified in at least two patients. For diabetes panel we found one variant in two patients for *TUB transcription factor* and *Neuronal differentiation 1*; two variants in *ATP binding cassette A4* were identified in two different patients and three patients are carriers of one variant in *Potassium channel J11* gene. For pancreatic cancer susceptibility panel, we identified at least two patients with rare variants in the following genes: two different variants in *ATM kinase*, in *Docking protein 2*,in *Pancreatic* and *Duodenal Homeobox1* and one variant in *BRCA1*. For obesity panel no rare variants were found.

Conclusion: This study highlighted that different patients share more than one rare genetic variants in inflammation, diabetes, and pancreatic cancer susceptibility panels. These genomic characteristics of IPMN highlight the complex dynamics of the disease providing opportunities for early detection and intervention.

P-11-06

Serous cystadenocarcinoma of the pancreas: a review of the current literature

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Abstract

Background: Serous Cystadenocarcinoma of the pancreas is a rare entity originally described in 1989. To date, only a small number of case studies appear in the literature. Serous cystadenocarcinomas are defined by histologic characteristics similar to benign serous cystadenomas; however, they also include local invasion or metastasis to distant parts of the body. The goal of this study is to identify the current literature on serous cystadenocarcinoma of the pancreas and describe characteristics of both the tumour and patient population.

Methods: Pubmed, Scopus, Web of Science, and Embase were queried for publications relating to serous cystadenocarcinoma of the pancreas. Systematic review software was used to examine the initial 1285 publications retrieved, and identify 36 pertinent papers for analysis. Data was collected from these papers and analysed using

Graphpad Prism v9.4.1.

Results: Thirty-six papers from 1989 to 2022 were evaluated. A total of 38 patients with serous cystadenocarcinoma were identified. The mean age was 63.6 years old. The majority of patients were female (71.1%), with the most common presenting symptom being abdominal pain. The majority of tumours were microcystic (35, 92%) and were located in the body and tail of the pancreas (31%), with local invasion (73.7%) and/or distant metastasis (36.8%) at the time of presentation. Management included surgical resection for all patients, including those with metastatic disease. Recurrence was 25% with a mean dormant period of 56 months. The mortality rate at time of last follow-up was 16% (6).

Conclusion: Serous cystadenocarcinoma of the pancreas is a slow growing tumour with favourable outcomes even when recurrence or distant metastasis is present.

P-11-07

The potential benefit of laparoscopy in distal pancreatectomy for cystic lesions in the enhanced recovery after surgery era: a multicentre propensity-score matched analysis

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Abstract

Background: The increasing detection rate of pancreatic cystic neoplasms favours the early resection of these tumours which, when localized in the body and tail of the pancreas, could be treated with a laparoscopic approach. To understand the possible advantages of laparoscopic surgery in the setting of cystic neoplasm, we performed a propensity score matching (PSM) analysis on patients treated at two high-volume centres for pancreatic diseases.

Methods: 294 patients who underwent distal pancreatectomy for cystic disease at two different institutions (San Raffaele Hospital and Verona Hospital) were retrospectively analysed. A 1:1 PSM was performed for successful laparoscopic surgery with adjustment for background characteristics. Aims of the study were to analyse length of hospital stay, time to functional recovery and morbidity after surgery.

Results: Overall, 294 patients were analysed, 148 (50.4%) underwent laparoscopic approach and 146 (49.6%) the open approach. The main indication for surgery were mucinous cystic neoplasms, followed by intraductal papillary mucinous neoplasms and serous cystic lesions. Variables included in the propensity model included age, gender, BMI, ASA score, vascular and multivisceral resections After PSM, two balanced groups of 67 patients were analysed. Patients who received a successful laparoscopic surgery showed a reduced in-hospital morbidity (calculated with the comprehensive complication Index, median 9 [IQR 0-21] vs 21 [IQR 0-30]), and no difference was observed in terms of pancreatic surgery related complications (delayed gastric emptying, pancreatic fistula). In addition, patients who underwent laparoscopic resection had a shorter length of hospital stay (8 days [IQR 7-11] vs 9 days [IQR 7-12], p=0.049) and reduced time to functional recovery (6 days [IQR 5-9] vs 7 days [6-10], p=0.047).

Conclusion: Laparoscopic distal pancreatectomy showed lower in-hospital morbidity, shorter length of stay and a faster recovery after surgery compared to open distal pancreatectomy. These results support the feasibility and safety of the laparoscopic approach for pancreatic cystic lesions.

P-11-08

Role of pancreatic ductal adenocarcinoma risk factors in intraductal papillary mucinous neoplasms progression.

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Abstract

Background: Intraductal papillary mucinous neoplasms (IPMNs) are often precursors of pancreatic ductal adenocarcinoma (PDAC), with an estimated progression rate between 19-40%. Therefore, the ability to identify IPMN patients with a high risk of progression into invasive cancer could be instrumental to improve PDAC early detection and patient survival. It has been proposed that PDAC risk factors play a role in IPMN progression, but definitive results are absent. In this study, genetic and non-genetic PDAC risk factors were tested in a group of IPMN patients under surveillance.

Methods: The study population consisted of 354 IPMN patients enrolled by two Italian centres. IPMN progression was defined based on the development of worrisome features and/or high-risk stigmata during patient follow-up. All patients were genotyped for 30 known PDAC risk loci that were analysed individually and grouped in a polygenic score (PGS) in relation to IPMN progression. In addition, the ABO blood group and non-genetic PDAC risk factors (cigarette smoking, diabetes status, body mass index (BMI), and family history of PDAC) were analysed.

Results: The analyses of the genetic polymorphisms showed suggestive associations of two variants rs1517037 (HR=1.54, 95% CI 1.05-2.25; P=0.027), rs10094872 (HR = 0.72; 95% CI 0.53-0.98; P=0.035) with risk of IPMN progression. However, after correction for multiple testing, none of the variants showed a statistically significant association. Furthermore, the PGS and the ABO blood group were not associated with progression. Instead, statistically significant associations were observed for the number of packs of cigarettes smoked per year (HR = 1.49, 95% 1.06-20.09, P= 0.021), and obesity (HR=2.52, 95%CI 1.25-5.06, P= 0.01).

Conclusion: In conclusion, this study is the first attempt to investigate the presence of shared genetic background between PDAC risk and IPMN progression. The results suggest the absence of a common genetic background, while cigarette smoking and BMI show robust associations with IPMN progression towards malignancy. The biological mechanism linking these two risk factors to progression could be chronic pancreatic inflammation, of which both factors are strong promoters.

P-11-09

Recurrence, recurrence patterns and management of recurrence after resection for invasive IPMN: data from 466 consecutive patients from a multicentre international cohort study

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Abstract

Background: Recurrence patterns and treatment of recurrence post resection of invasive IPMN are poorly explored. This present international multicentre cohort study aims to identify recurrence patterns and management of first and second recurrence in a large cohort of patients.

Methods: Patients undergoing pancreatic resection for invasive IPMN between January 2010 to December 2020 at 23 centres were identified. Multivariate logistic regression models, Kaplan-Meier analysis and cox-proportional hazards models were utilised to determine predictors of recurrence and survival, including the impact of adjuvant chemotherapy.

Results: 466 patients with median age of 70 (27-92) and M:F ratio of 1.17:1 were included. Recurrence occurred in 45.5% (212/466) patients. Early recurrence (within 1 year) occurred in 20.2% (94/466) patients. Fifty-eight (12.4%) of patients experienced a loco-regional (pancreatic bed/peri-pancreatic tissue) and 177 (37.8%) of patients experienced distant recurrence (liver=66, lung=58, peritoneal=40 and lymph node=33, other=35). Poor differentiation (HR 4.45, p=0.002), lymphovascular invasion (HR 1.86, p=0.017) and splenic resection (HR 6.3, p<0.001) were independent predictors of recurrence. Colloid component (HR 0.44, p=0.045) and higher Charlson CI (HR 0.53, p=0.037) were negatively associated with recurrence.

One hundred and twenty patients with recurrence received further treatment. The majority (n=92) received chemotherapy, 12 were treated with radiotherapy, 6 with surgery and 1 multi-modal therapy. OS from diagnosis of recurrence was significantly higher in those treated (33.3 months vs 9.1 months (p<0.001). In patients with distant

recurrence, OS was significantly improved by treatment (65.2 months vs 36.0 months, p<0.001). In patients with loco-regional recurrence, OS was improved (77.7 months vs 41.8 months, p=0.061) but this was not significant. Treatment of a second recurrence was not associated with improved OS.

Conclusion: Recurrence after resection for invasive IPMN is high. Although it is not possible to identify optimal treatment strategy for recurrence, treatment of recurrence is associated with improved overall survival and should be considered.

P-11-10

Diagnostic challenges of pancreatic acinar cystic transformation: a single-centre retrospective study of 64 patients

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Abstract

Background: Pancreatic acinar cystic transformation (ACT) was first described in 2000. It is initially supposed pre-neoplastic nature was reconsidered in the WHO Classification 2019. Its current management prone to a non-surgical approach, and so rare cases of histopathological diagnosis have been obtained since. Radiological diagnostic criteria have been proposed to differentiate ACT from Branch-duct Intraductal Papillary Mucinous Neoplasms (BD-IPMN) (Delavaud et al., 2014): 1) ≥5 cysts, 2) clustered peripheral small cysts, 3) cyst calcifications and 4) no communication with the main pancreatic duct. The objectives of this study were to describe the clinical and radiological characteristics of patients with a presumed diagnosis of ACT in imaging and to assess the role of these known radiological criteria in case of possible differential diagnoses.

Methods: In this single-centre retrospective study (2003-2021), consecutive patients with a presumed diagnosis of ACT in the coding database were included. Patients without an available imaging (CT or MRI) for expert radiological centralized review were excluded. A group of "typical" diagnosis of ACT was defined as the absence of differential diagnosis to be evoked. A group of "doubtful" diagnosis of ACT was defined as other possible differential diagnoses.

Results: A total of 64 patients were included (35 male patients [55%]). Median age of diagnosis was of 60 (IQR 47-67) years. ACT diagnosis was "typical" for 35 (55%) patients and was "doubtful" for 29 (45%) patients. In the "typical" group, 91.4% of patients presented ≥3 radiological criteria versus 96.6% in the "doubtful" group (p=0.61). There were more calcifications and <10 cysts in the "doubtful" group compared to the "typical" group (86% versus 66%, p = 0.041 et 24% versus 6%, p = 0.06, respectively). In the "doubtful" group, the main differential diagnoses evoked were: 16 (55%) BD-IPMN and 7 (24%) calcified chronic pancreatitis (CCP). A pathological confirmation of ACT was obtained for three patients from which two were in the "doubtful" group.

Conclusion: ACT displays a heterogenous morphological presentation reflecting a challenge for accurate diagnosis. The published diagnostic radiological criteria seem not to be helpful, especially in case of calcifications or/and <10 cysts.

P-11-11

Adjuvant chemotherapy does not impact on survival outcomes after resection for Invasive IPMN: data from 466 consecutive patients from an international multicentre cohort study

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Abstract

Background: The role of adjuvant chemotherapy following pancreatic resection for invasive IPMN remains controversial with no clear guidance. This present large multinational cohort study explored outcomes of patients who did and did not receive adjuvant chemotherapy following resection for invasive IPMN.

Methods: Patients undergoing pancreatic resection for invasive IPMN between January 2010 to December 2020 were identified from 23 centres. Multivariate logistic regression models, Kaplan-Meier analysis and cox-proportional hazards models were utilised to determine predictors of recurrence and survival, including the impact of adjuvant chemotherapy.

Results: 466 patients underwent pancreatic resection for IPMC. Median age was 70, 53.9% (n=252) were male. The majority of tumours were in the head of the pancreas (72.7%) with 56.6% of patients (n=264) undergoing a Whipple's pancreatoduodenectomy. Two hundred and twenty-seven patients (50.9%) received adjuvant chemotherapy.

The common chemotherapy regimens used were Gemcitabine (60.6%), Gemcitabine-capecitabine (26.4%), Folfirinox (10.1%), other (16.3%). The predictors of adjuvant chemotherapy use were poor differentiation (p=0.009), Peri-neural invasion (p=0.021), tumour in the pancreatic head (p=0.02) and stage of the tumour according to the AJJC classification. There was no benefit seen with adjuvant chemotherapy in incidence of recurrence (p=0.097) [local p=0.039) or distant (p=0.11)]. Further subgroup analysis found that no benefit was seen recurrence rates in all pathological subtypes of invasive IPMN [Gastric (59.6% vs 37.5%, p=0.04), Intestinal (45.1% vs 25.0%, p=0.037), Pancreatico biliary 56.1% vs 37.5%, p=0.026) and Oncocytic (40.0% vs 50.0%, p=0.653)].

No one chemotherapy regimen was found to be more effective than others (p=0.086).

Conclusion: This large multicentre series demonstrates that adjuvant chemotherapy is not associated with improved disease-free survival in patients with invasive IPMN. These results would support the need for a prospective randomised controlled trial to evaluate definitively the role of adjuvant chemotherapy in these patients.

P-11-12

IPMN progression over time: modifiable risk and protective factors

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Abstract

Background: IPMNs are mucin producing subtypes of pancreatic cysts considered a potential precursor of pancreatic cancer. The molecular mechanism and the biological factors involved in IPMN progression are still unknown. In previous studies, modifiable risk factors (e.g., smoking) and protective factors (e.g., ACE-Inhibitors) have been evaluated in order to slow down or prevent the IPMN progression. The aim of this study is to evaluate the association between modifiable risk factors (smoking history and alcohol intake) and the use of common prescribed drugs (aspirin, ACE-Inhibitors, angiotensin-II-receptor antagonists, and statins) and the progression of IPMN.

Methods: This is a monocentric retrospective cohort study performed at Fondazione Policlinico A. Gemelli-IRCCS. Patients with a radiological assessment at time 0 and a radiological follow-up (performed with the same technique as time 0) at 3 years were included in the study. Demographics data (sex, age, weight and height), IPMN characteristics (type of IPMN and radiological characteristics at baseline), lifestyle factors (smoking and alcohol intake) and drugs intake (aspirin, ACE-I, ARBs, and statins) were collected. Clinical and radiological features at 3 years follow-up were recorded to detect IPMN progression (defined as occurrence of high-risk stigmata and/or worrisome features). Statistical analysis was performed with SPSS 20. Descriptive data are reported as mean/median ± standard deviation and range, or percentage. Categorical data were compared using the χ_2 test. A multivariate regression analysis was performed. p values <0.05 were considered statistically significant.

Results: 126 patients were enrolled in the study. Smoking (OR 5.7, p 0.036, IC95% 1.11-29.04), heavy alcohol intake (OR 4.8, p 0.027, IC95% 1.10-9.50) and ARBs use (OR 3.52, p 0.048, IC95% 1.85-14.50) were associated with IPMN progression. Statins intake was associated with a lower risk of IPMN progression (OR 0.154, p 0.043, IC95% 0.021-0.978). Body weight, aspirin, ACE-I and low alcohol intake were not statistically significant.

Conclusion: Smoking, heavy alcohol and ARB-I intake are considered risk factor while statins use is considered a protective factor for IPMN progression. Main limitations of this study are the retrospective design and the small cohort size. Prospective trials are needed to confirm these data.

P-11-13

Impact of age, comorbidities and relevant changes on surveillance strategy of intraductal papillary mucinous neoplasms: a competing risk analysis

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Abstract

Background: Appropriateness of surveillance for branch-duct intraductal papillary mucinous neoplasms (BD-IPMNs) is debated. We aimed to combine different categories of risks of IPMN progression and of IPMN-unrelated mortality to improve surveillance strategies.

Retrospective analysis of 926 presumed BD-IPMNs lacking worrisome features (WF)/high risk stigmata (HRS) under surveillance. Charlson Comorbidity Index (CACI) defined the severity of comorbidities. IPMN relevant changes included development of WF/HRS, pancreatectomy or death for IPMN or pancreatic cancer. Pancreatic malignancy-unrelated death was recorded. Cumulative incidence of IPMN relevant changes were estimated using the competing risk approach.

Results: 5-year cumulative incidence of relevant changes was 17.83% and 1.6% developed pancreatic malignancy. Low-, intermediate- and high-risk groups for IPMN relevant changes were identified with a 5-year cumulative incidences for IPMN relevant changes of 13.73%, 19.93% and 25.04%, respectively. Age ≥75 (HR: 4.15) and CACI >3 (HR: 3.61) were independent predictors of pancreatic malignancy-unrelated death. 5-year cumulative incidence for death for other causes was 15.93% for age ≥75+CACI>3 group and 1.49% for age < 75+ CACI ≤3. 5-year cumulative incidence of IPMN relevant changes were 13.94% in patients with age< 75+CACI≤3 compared with 29.60% in those with age ≥75+CACI>3. In this group 5-year rate of malignancy-free patients was 95.56% with a 5-year survival of 79.51%.

Conclusion: Although the occurrence of relevant changes during surveillance of low risk BD-IPMNs is not uncommon, malignancy rate is low and survival is significantly affected by competing patients' age and comorbidities. IPMN surveillance strategy should be tailored based on these features and modulated over time.

P-11-14

Contrast-enhanced endoscopic ultrasound in the differential diagnosis of pancreatic cystic lesions

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Abstract

Background: The differential diagnosis of some pancreatic cystic lesions remains difficult. In these cases, contrast-enhanced endoscopic ultrasound (CE-EUS) was proven to be useful. This study aims to evaluate the accuracy of CE-EUS for diagnosing pancreatic cystic lesions with a suspicion of risk factors for malignancy.

Methods: A retrospective analysis of patients with suspected pancreatic cystic neoplasms who underwent a CE-EUS at the University Hospital Olomouc from January 2020 - February 2022 was performed. The final diagnosis of cystic lesion was then confirmed using other cross-sectional imaging methods, cytologic, and biochemical findings by EUS fine needle aspiration, postoperative histology, or the long-term follow-up of the patients.

Results: During the study period, EUS was performed in a total of 167 patients with a pancreatic cystic lesion. 29 patients (17.4%) were then referred for CE-EUS for suspected risk features. Enhancement was observed in 9/29 patients (31%), from which 4 patients were operated on with a confirmation of a premalignant or malignant diagnosis. Twenty patients (69%) were without enhancement, from which one patient (5%) was operated on with a confirmation of premalignancy. The remaining 19 patients were referred to follow-up. In this group, 2 (10.5%) patients had a premalignant cystic lesion, and 17 (89.5%) patients had a benign diagnosis. No complications were reported during the procedure. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CE-EUS were 70%, 89.5%, 77.8%, 85% and 82.8%, respectively.

Conclusion: CE-EUS is a feasible and safe method used for the differential diagnosis of suspected pancreatic cystic neoplasms to guide further treatment. However, the results are limited by a low number of provided CE-EUS, and a prospective randomised study with more patients is necessary to confirm these results.

P-11-16

Role of endoscopic ultrasound to identify morphological features predictive of malignancy in patients undergoing surgical resection for presumed IPMN

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Abstract

Background: Intraductal papillary neoplasm of the pancreas (IPMN) are common in general population. IPMNs can be classified into three morphological types (Main-duct/MD, Branch-duct/BD and Mixed-type/MT) and ranging from low-grade dysplasia (LGD) to invasive carcinoma (IC). Identification of high-grade dysplasia (HGD)/IC has a strong clinical value. The aim of this study is to evaluate the accuracy of endoscopic ultrasound (EUS) to predict malignancy.

Methods: This is a retrospective study including consecutive patients undergoing preoperative EUS before surgery for IPMNs from 2015 to 2019. Several EUS features were considered: 1) Presence of worrisome feature(WF), high-risk stigmata(HRS) or macroscopic solid component (MSC) at diagnosis; 2) Pancreatic duct (PD): PD dilation, thickened walls of PD (TW-PD), presence and dimension of PD nodules (PDN), contrast-enhancement (CE)/ real time elastography (RTE) on PDN. 3) Cysts: dimension >30 mm, TW, CE on walls, presence/dimension of mural nodules (MN), CE/RTE on MN.

Results: We enrolled 105 patients (median age: 71 years, male sex: 60.9%). The final histological diagnosis was LGD in 38.1%, HGD in 26.6% and IC in 35.3%. EUS predictors of HGD/IC at univariate regression were TW-PD (p=0.03) and PDN dimension (p=0.01). Predictor factors of IC were WF (p=0.002), HRS (p=0.001), or MSC (p<0.001) at diagnosis, PD dilation (p=0.04), rigid pattern of PDN on RTE (p=0.04) and rigid pattern of MN on RTE (p=0.02).

Conclusion: EUS is able to predict the invasive behaviour of IPMNs selected for surgery. Interestingly, some factors associated with aggressiveness as TW-PD or EUS-RTE, are not mentioned in current international guidelines.

P-11-17

Recognition of GNAS and KRAS mutations in endoscopic ultrasound – fine needle aspiration (EUS-FNA) fluid samples from the main pancreatic duct (MPD) accurately discriminates intraductal papillary mucinous neoplasm (IPMN) from benign conditions with MPD dilatation

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Abstract

Background: Pre-surgical discrimination of main-duct IPMN from benign conditions with dilated MPD is an often unmet need to avoid unnecessary surgery while not missing therapeutic opportunities. *GNAS* and *KRAS* mutations from EUS-FNA intracystic samples are highly specific of IPMN. EUS-FNA fluid sampling from dilated MPD can be a valuable approach for molecular analysis to recognize IPMN with main duct involvement. We aimed to evaluate the diagnostic yield of *GNAS* and *KRAS* mutation analysis in EUS-FNA fluid samples from the MPD to recognize IPMN in patients with dilated MPD.

Methods: Patients with *GNAS* and *KRAS* testing of pre-operative EUS-FNA fluid samples from dilated MPD where retrospectively collected. Only lesions surgically resected were included. *GNAS (R201H and R201C)* and *KRAS (exons 12 and 13)* point mutations were analysed by droplet-digital PCR and cold-PCR, respectively.

Results: Fifteen patients were included (age: 57.8 years; female/male: 3/12): 10 patients (67%) with IPMN (4 main-duct IPMN and 6 mixed-type IPMN; 4 of whom had coexisting findings of chronic pancreatitis - CP -), 4 (27%) CP without IPMN and 1 (6%) MPD obstructive dilatation, based on the pathological report of the surgical specimen. Median MPD diameter was 10mm (range: 4-20mm). Point mutations in *GNAS* and/or *KRAS* were present in 8/10 (80%) IPMNs (*GNAS* mutations in 8/8, *KRAS* mutations in 2/8). *GNAS/KRAS* mutations were not present in any non-IPMN conditions (5/5). Cytology of EUS-samples was available in 9/10 patients with IPMN and in 5/5 patients without IPMN. *GNAS/KRAS* mutations were present in 6/7 (86%) IPMN with mucinous cytology and in 2/2 (100%) IPMN with non-mucinous cytology. The presence of *GNAS/KRAS* mutations was not associated with age, sex, side branch cysts coexistence, CP association, MPD diameter, grade of dysplasia or histologic subtype of IPMN. Sensibility, specificity and global diagnostic yield of *GNAS/KRAS* analysis for IPMN diagnosis were 80%, 100% and 86.7%,

respectively.

Conclusion: Identification of *GNAS/KRAS* mutations in EUS-FNA fluid samples from the MPD is highly accurate for IPMN recognition in patients with dilated MPD. However, more studies with larger sample size are needed to confirm these results.

P-11-18

Progression of the branch duct intraductal papillary mucinous neoplasm: parametric time-to-event analysis, using frailty models and ancillary parameters of hazard curves

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Abstract

Background: The rate of changes for BD-IPMNs during the follow-up has always been reported using non-parametric or semi-parametric models. The aim of the present study was to describe the natural history of BD-IPMN using parametric time-to-event models.

Methods: A prospectively maintained database, including 588 patients with BD-IPMN without high-risk stigmata, was analysed. All patients were managed according to Fukuoka guidelines, and patients who underwent surgical upfront at the time of diagnosis were excluded. The change was defined as the occurrence of worrisome features or high-risk stigmata during the follow-up. The hazard function was obtained using parametric analysis. The following parameters were analysed as covariates: age, sex, symptoms, comorbidity, ca 19.9 levels, enhancing or thickened wall (ETW), non-enhancing mural nodule (NEMN), Wirsung size between 5-9 mm (W5-9), pancreatitis, multifocal cysts, and cyst size. The covariates effect was reported as accelerated failure time (AFT). Several curves were built Weibull, lognormal, exponential, generalized gamma, and Gompertz. The gamma frailty (LR test) and Akaike information criterion (AIC) were used to compare the curves.

Results: The median follow-up was 50 months (33-75, IQR). The patients who experienced a change during the follow-up were 178 (30.3%), with a median of 44 months (23-73, IQR). The following parameters significantly reduced the time to progression: increased Ca 19.9 levels (-0.64; -1.04 to -0.24, AFT); ETW (-0.95; -1.43 to -0.47, AFT); NEMN (-1.01; -1.92 to -0.08, AFT); W5-9 (-0.53; -1.05 to -0.01, AFT). The model that best represents the BD-IPMN progression is the lognormal curve, having no frailty (LR=0; p=1.000) and the smallest value of AIC (884). Age at the diagnosis (increasing) was the only parameter that modified the shape of the curve, significantly reducing the risk of progression (ln sigma =0.4; p=0.004).

Conclusion: The risk of change during the follow-up for BD-IPMN was influenced by the type of worrisome features at the time of diagnosis. The progression model can be assimilated to a lognormal curve with a higher risk at the start of the observation.

P-11-19

Diabetes mellitus and metabolic factors: “weighing” the risk of malignancy in IPMNs

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Abstract

Background: It is well established that diabetes mellitus (DM) can be associated with pancreatic diseases and this relationship has been extensively studied regarding pancreatic ductal adenocarcinoma. The connection between DM and intraductal papillary mucinous lesions (IPMNs), as well as the role of other metabolic factors in these patients, is less well known.

Methods: Patients who underwent pancreatic resection for histologically proven IPMNs between 2010 and 2019 at San Raffaele Hospital were included. Patients with other concomitant gastro-intestinal tumours or who underwent neoadjuvant chemotherapy (CT) for invasive IPMN were excluded. Preoperative, operative, and histological data were prospectively collected and retrospectively analysed.

Results: Among 318 patients included in this study, 81 (25.5%) presented preoperative DM, either as a chronic disease (54 pts), as new onset/worsening DM as a symptom of the pancreatic lesion (35 pts) or, in 8 cases, with both a chronic disease and a worsening glycaemic control at the moment of IPMN diagnosis. Diabetic patients were older (median age 73 vs 68 years, p<0.001), more frequently male (67.9% vs 51.5%; p=0.010), had a higher rate of previous myocardial infarction (17.3% vs 7.2%; p=0.008) and of peripheral vascular disease (12.3% vs 4.6%; p=0.016). They more frequently underwent total pancreatectomy than non-diabetic patients and developed postoperative duodeno-jejunal fistula more frequently (11.9% vs 0.8%; p=0.004). Also, when comparing patients with low/intermediate-grade IPMN with those with high-grade/invasive IPMN, the latter were shown to have a higher rate of diabetes (31.2% vs 13.6%; p=0.001), both new-onset/worsening DM (13.5% vs 5.8%; p=0.041) and, although this did not reach significance, chronic DM (20.5% vs 11.7%; p=0.053). Furthermore, levels of preoperative haemoglobin, glycosylated haemoglobin, albumin and C-reactive protein were significantly different between patients with benign and malignant IPMNs.

Conclusion: Diabetes mellitus and other metabolic factors are intricately linked to pancreatic diseases, including IPMN. Their role in this disease, especially in the risk of malignant transformation, should be further investigated.

P-11-20

The role of EUS in diagnosis and management of pancreatic cystic neoplasms: intention-to-treat analysis

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Abstract

Background: International Guidelines suggest endoscopic ultrasonography (EUS) as surveillance and diagnosis tool for pancreatic cystic neoplasms (PCNs). The aim of this study was to assess if EUS diagnosis and treatment indication differed from those given after clinical and radiological evaluation alone.

Methods: All patients who underwent EUS for a presumed PCNs at the Verona University Hospital between 2019-2021 were retrospectively reviewed. Management indication pre- and post-EUS, regardless of the clinical pathway eventually chosen for the patient, were compared. A cyst was deemed suitable for surgery or surveillance according to the International Guidelines, while for surveillance discontinuation if the presumed diagnosis was serous cystic neoplasm or other rare benign/non neoplastic cysts.

Results: The cohort included 354 patients. The most frequent indication to perform EUS was a presumed intraductal papillary mucinous neoplasm (IPMN) (62.4%) regardless of the presence of worrisome features or high-risk stigmata (HRS). EUS changed presumptive diagnosis in 36.9% of patients. A change in diagnosis did not always entail a change in treatment indication. Indeed, EUS changed treatment indication in 28.5% of patients in the overall cohort, more frequently in IPMN without HRS (35.6%). In those patients, EUS suggested surveillance discontinuation or surgery in 11.4% and 24.2% respectively. Notably, EUS changed diagnosis in 22.2% presumed serous cystic neoplasm (SCN) and in all these cases changed treatment indication, too. Those were all unilocular or macrocystic lesions.

Conclusion: A change in diagnosis after EUS is not necessarily clinically relevant. EUS indicated a treatment change in more than one third of IPMN without HRS and in all presumed SCN that presented as unilocular or macrocystic lesions. These two populations are ideally the ones that could benefit the most from undergoing EUS. Future analyses need to evaluate how often EUS indication are followed by clinicians.

P-11-21

Pancreatic cystic neoplasms: still high rates of preoperative misdiagnosis in the guidelines and EUS era

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Abstract

Background: A wrong diagnosis of nature is common in pancreatic cystic neoplasms (PCNs). The aim of the current study is to reappraise the diagnostic errors for presumed PCNs undergoing surgery.

Methods: All pancreatic resections performed for presumed PCNs at the Verona Pancreas Institute between 2011 and 2020 were analysed. "Misdiagnosis" was defined as the discrepancy between preoperative diagnosis of nature and final pathology, while "Mismatch" as the discrepancy between the preoperative suspect of malignancy (or its absence) and final pathology. Features considered suggestive for malignancy at preoperative work-up were defined according to the International Guidelines (Pancreatology, 2017) and the European Guidelines (Gut, 2018). Diagnostic errors considered "clinically relevant" implied a potential over- or under-treatment for the patient.

Results: A total of 601 patients were included. Endoscopic Ultrasound (EUS) was performed in 301 (50%) patients. Overall misdiagnosis and mismatch were 19% and 34% respectively, with no significant benefit for those patients who underwent EUS. The highest rate of misdiagnosis was reached for cystic neuroendocrine tumours (61%) and the lowest for solid pseudopapillary tumours (6%). Several diagnostic errors had clinical relevance, including 7 (13%) presumed serous cystic neoplasms eventually found to be other malignant entities, 50 (24%) intraductal papillary mucinous neoplasms (IPMN) with high-risk stigmata (HRS) revealed to be non-malignant, and 38 (33%) IPMN without HRS revealed to be malignant at final pathology. A preoperative presumption of malignant mucinous cystic neoplasm was correct in only 20 (16%) patients.

Conclusion: Despite not always clinically relevant, diagnostic errors are still common among resected PCNs when applying International Guidelines. New diagnostic tools beyond EUS are needed to refine diagnosis of those lesions at higher risk for unnecessary surgery or accidentally observed nevertheless being malignant.

P-11-22

Guiding the way: a comparative analysis of IPMN management in two European centres

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Abstract

Background: While determining an appropriate course of treatment for an intraductal papillary mucinous neoplasm (IPMN), it is imperative that clinical, radiological, and histological results be considered. Many international recommendations for the administration of the IPMN have been formulated and accepted by the relevant bodies. This study was conducted with the goal of analysing and comparing the diagnostic accuracy of the evidence-based guidelines that were published in 2017 International, Fukuoka, and 2018 European for the identification of malignant IPMN in two European centres: The University Clinical Centre of Serbia and University Medical Medical Centre, Ljubljana, Slovenia.

Methods: Evaluations will be performed on a total of 111 consecutive resected patients who had been diagnosed with IPMN out of which 74 are recruited from the University Clinical Centre of Serbia and 37 had been diagnosed with IPMN at the University Medical Centre, Ljubljana. The purpose of this study is to compare the outcomes of these patients. The absolute and relative indications, as well as high-risk stigmata and worrisome features of risk linked with cancer, will be retrospectively analysed. Moreover, the sensitivity, specificity, positive (PPV), and negative predictive values will be investigated (NPV). In this study, the sensitivity of absolute and relative indications for resections will be determined according to both criteria, and the experiences of two different European centres will be compared.

Conclusion: Using the previous experiences of both centres, the study will provide guidelines for selecting individuals for resection.

P-12-01

Clinical development of a blood biomarker using apolipoprotein-A2 isoforms for early detection of pancreatic cancer

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Abstract

Background: We previously reported apolipoprotein A2-isoforms (apoA2-i) as candidate plasma biomarkers for early-stage pancreatic cancer. The aim of this study was the clinical development of apoA2-i as plasma biomarkers for pancreatic cancer.

Methods: We established a novel sandwich enzyme-linked immunosorbent assay (ELISA) using specific antibodies against the unique sequences of the C-terminal amino acids of apoA2-i, which was produced under the Quality Management System for in vitro diagnostics. Clinical evaluation of the assay was performed with predefined endpoints before measurement using 2732 plasma samples that were retrospectively collected, and the clinical equivalence and significance of apoA2-i were compared with that of CA19-9. The primary end point was comparison of the area under curves (AUCs) of receiver operating characteristic analysis between apoA2-i and CA19-9. Secondary end points were reproducibility of the specificity, of apoA2-I, evaluation of sensitivity, and improved sensitivity with combination assay using apoA2-i and CA19-9 compared with single assay of CA19-9 for detecting pancreatic cancer. This was a prespecified retrospective study.

Results: The primary end point of the AUC of apoA2-ATQ/AT [0.879, 95% confidential interval (CI): 0.832–0.925] for distinguishing between pancreatic cancer (n = 106) and healthy controls (n = 106) was higher than that of CA19-9 (0.849, 95%CI: 0.793–0.905), and achieved the primary endpoint predefined before measurement. The cut-off apoA2-ATQ/AT (59.5 µg/mL) was defined based on 95% specificity in 2000 healthy samples, and the reproducibility of specificities was confirmed in two independent healthy cohorts as 95.3% (n = 106, 95%CI: 89.4–98.0) and 95.8% (n = 400, 95%CI: 93.3–97.3). The sensitivity of apoA2-ATQ/AT for detecting stage I (47.4%) and I/II (50%) pancreatic cancer was higher than that of CA19-9 (36.8% and 46.7%, respectively). The combination of apoA2-ATQ/AT (cut-off, 59.5 µg/mL) and CA19-9 (37 U/mL) increased the sensitivity for diagnosing pancreatic cancer to 87.7% compared with 69.8% for CA19-9 alone.

Conclusion: ApoA2-ATQ/AT has equivalent or better clinical performance compared to CA19-9, and shows promise as a blood biomarker for use in clinical practice.

P-12-02

Are serum insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 2 (IGFBP-2) levels useful in chronic pancreatitis (CP) and pancreatic adenocarcinoma (PDAC) differentiation?

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Abstract

Background: IGF-1 and IGFBP-2 form a network involved in PDAC development. The role of IGFs in promoting pancreatic cancer cell proliferation, survival and migration is well established and their ability to stimulate tumour growth and metastasis is well documented.

The aim of the study was to evaluate if IGF-1, IGFBP-2 and IGF-1/IGFBP-2 ratio may be useful in PDAC and CP differentiation.

Methods: The study included 137 patients: 89 patients with PDAC and 48 patients with CP. The subjects were all tested for the levels of IGF-1, IGFBP-2, using the ELISA method (Corgenix UK Ltd R&D Systems) and CA 19-9 in serum. Additionally, the IGF-1/IGFBP-2 ratio was calculated.

Results: The IGF-1 serum level equalled 52.12 +/- 33.13 ng/ml in PDAC vs. 74.23 +/- 48.98 ng/ml in CP; p=0.0053. Mean level of IGFBP-2 was respectively equal to 305.95 +/- 194.58 ng/ml in PDAC vs. 485.43 +/- 299 ng/ml in CP; p=0.0002. Mean CA 19-9 serum concentration was 434.95 +/- 419.98 U/ml in PDAC vs. 78.07 +/- 182.36 U/ml in CP; p=0.0000. Mean IGF-1/IGFBP-2 ratio was 0.213 +/- 0.14 in PDAC vs. 0.277 +/- 0.33 in CP; p=0.1914. Diagnostic usefulness of indicators for the purpose of PDAC and CP differentiation was assessed by means of AUROCs comparison. AUROCs of IGF-1, IGFBP-2 and IGF-1/IGFBP-2 ratio ranged below 0.7, which is lower than the AUROC of CA 19-9 (0.7953; 0.719 within 95% CI). Together CA 19-9 & IGFBP-2 AUROC also ranged below 0.8. When age was included, AUROC increased to the 0.8632 and its 95% confidence interval held above the 0.8 limit. The division of patients into groups with early and late stages of PDAC does not improve the sensitivity of the markers used.

Conclusion: Presented results indicate that CA 19-9 is a marker presenting high potential for the PDAC and CP differentiation. The introduction of additional variables to the model, such as the serum level of IGF-1 or IGFBP-2, slightly increased the sensitivity in differentiating CP from PDAC. The IGF-1/IGFB-2 ratio turns out to be a good marker of pancreatic diseases, but insufficient for the purpose of CP and PDAC differentiation.

P-12-03

Increased risk of pancreatic cancer among 141,387 diabetic patients treated with DPP-4 inhibitors analysed with common data model

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Abstract

Background: Dipeptidyl peptidase 4 inhibitors (DPP-4i) are incretin-based anti-diabetes drugs, which have been introduced recently. It is concerned that, however, that DPP-4i might cause pancreatic cancer or pancreatitis due to the pleiotropic effects for the exocrine pancreas. In this study, the association between pancreatic cancer and DPP-4i was investigated based on common data model (CDM), an emerging tool for real world data (RWD) analysis.

Methods: The electronic hospital record (EHR) of diabetic patients treated with DPP-4i from 2006 to 2019 was pooled into CDM and compared with those with sodium-glucose cotransporter inhibitors (SGLT)-2i as the control. The enrolment assessment window was considered 6 months. The blackout and washout periods were defined as 2 and 56 days, respectively.

Results: Each cohort of DPP-4i and SGLT-2i consisting of 141,387 and 13,378 patients was formed. Pancreatic cancer was identified in 2,803 (2.14%) patients from the DPP-4i cohort and 129 (1.07%) from the SGLT-2i cohort, which showed statistical difference (P < 0.0001). The odds ratio was 2.02 (95% confidential interval: 1.69-2.41) with fixed and random effect models.

Conclusion: The study suggests there is increased risk of pancreatic cancer for patients treated with DPP-4i.

P-12-04

Pathologic complete response following preoperative chemotherapy vs. chemoradiotherapy in pancreatic ductal adenocarcinoma: a systematic review and meta-analysis

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Abstract

Background: The impact of additional radiotherapy on survival and pathologic response is still widely debated in patients treated with neoadjuvant treatment in pancreatic ductal adenocarcinoma (PDAC). The aim of this study was to compare the rates of pathologic complete response (pCR) in patients resected for PDAC after neoadjuvant chemotherapy (ChT) vs. chemoradiotherapy (CRT), and secondarily, to compare the R0 resection rate and overall survival (OS).

Methods: The study protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO CRD42022341466) on July 3rd 2022. A systematic review was conducted on MEDLINE/PubMed, Embase, Cochrane, Web of Science and Google Scholar, for studies published between 2012 and 2022. All studies reporting clinical outcomes of patients with PDAC following neoadjuvant therapy were considered eligible for inclusion. A meta-analysis comparing the rate of pCR, R0 resection rate, and 3-year OS following ChT vs CRT in patients was performed. The overall quality of evidence was evaluated using a GRADE approach.

Results: Of 4003 potentially relevant studies and 19 studies eligible for full-text assessment, 5 studies were included in the systematic review and in the meta-analysis. Among the 5 included studies, published between 2016 and 2022, 2 were retrospective single-centre studies, 2 were retrospective multi-centre studies, and one was a prospective phase II multi-centre RCT. Overall, 433 ChT patients and 770 CRT patients were included in the meta-analysis. Among patients treated with ChT only the most frequent regimen was FOLFIRINOX (80.0%), followed by gemcitabine+nab-paclitaxel (9.1%), while among those who underwent CRT the most common regimen was FOLFIRINOX+RT (49.2%) and gemcitabine+RT (33.9%). A statistically significant increased rate of pCR and R0 resections were found in CRT patients (OR 3.38, 95% CI 1.51-7.57, p=0.003, and OR 1.52, 95% CI 1.14-2.02, p=0.004, respectively), whereas 3-year OS (OR 1.08, 95% CI 0.77-1.52, p=0.64) did not differ significantly among groups.

Conclusion: CRT may have a positive impact on pathologic response and R0 resection rate, whereas a survival benefit was not reported, possibly due to the occult micrometastases and distant metastases that impact on survival of PDAC patients.

P-12-05

Characteristic analyses of early-onset pancreatic cancer: a survey of international publications

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Abstract

Background: Early-onset pancreatic cancer (EOPC) is relatively rare. The research on EOPC is somewhat obscure, and the specific clinical and molecular characteristics of this condition are debated. Therefore, we conducted a survey of these topics from international publications.

Methods: A search was performed in PubMed for articles related to EOPC that were published between January 2007 and January 2022. We assessed the basic features of EOPC research and the clinical and molecular characteristics of this condition.

Results: A total of 27 articles were included. A total of 18.5%, 18.5%, and 63% of papers were published from 2007-2011, 2012-2016, and 2017-2022, respectively. The age cutoffs for EOPC were 40 years (3.7%), 45 years (29.6%), 50 years (48.1%), 55 years (11.1%), and 60 years (7.4%), and 18.5% of papers included a single EOPC cohort. Of the papers, 81.5% focused on clinical data analysis. A total of 25.9%, 22.2%, and 22.2% of papers showed that EOPC is likely to receive more treatment (including surgery, radiation, and chemotherapy), have a higher predominance in males, and be at an advanced stage, respectively. EOPC presented more smoking, alcohol use, frequently located in the head of pancreas, and lower Charlson/Deyo comorbidity score from 14.8%, 7.2%, 7.2%, 7.2% papers, respectively. EOPC seemed to have more family history of pancreatic neoplasia, privately insured patients, each was discussed in just one article. A total of 66.7% of papers compared survival outcomes between the two groups. EOPC presented no differences, better survival, and worse survival from 29.6%, 29.6 and 7.4% of the papers, respectively. A total of 18.5% of the papers studied the distinctive molecular characteristics of EOPC: lower frequency of somatic single-nucleotide variant in CDKN2A, increased expression of FOXC2, enriched RAS wild-type, higher mutation rates of SMAD4, increased activation of TGF-β pathway, and higher expression levels of phospo-GSK3 in EOPC.

Conclusion: EOPC is a rare subgroup with distinctive clinical and molecular features. However, there was no uniformity in the age cut-off or survival outcomes of EOPC compared to their counterparts. The molecular characteristics need further investigation. This study may help researchers better understand the research on EOPC and its characteristics.

P-12-06

Peripheral and portal venous KRAS ctDNA detection as independent prognostic markers of early tumour recurrence in pancreatic ductal adenocarcinoma

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Abstract

Background: KRAS circulating tumour DNA (ctDNA) has shown biomarker potential for pancreatic ductal adenocarcinoma (PDAC) but has not yet been applied in clinical practice. We aim to improve the clinical applicability of ctDNA detection in PDAC and to study the impact of blood-draw site and time point on the detectability and prognostic

role of KRAS mutations.

Methods: 221 blood samples from 108 PDAC patients (65 curative, 43 palliative) were analysed. Baseline peripheral and tumour-draining portal venous (PV), postoperative and follow-up bloods were analysed and correlated with prognosis.

Results: Significantly higher KRAS-mutant detection rates and copy numbers were observed in palliative compared to curative patients' baseline blood (58.1% vs. 24.6%; p=0.002; and p<0.001). Significantly higher KRAS-mutant copies were found in PV blood compared to baseline (p<0.05) samples. KRAS mutation detection in pre- and postoperative and PV blood was significantly associated with shorter recurrence-free survival (RFS; all p<0.015) and identified as independent prognostic markers. KRAS ctDNA status was also an independent unfavourable prognostic factor for shorter overall-survival (OS) in both palliative and curative cohorts (HR:4.9, P=0.011; HR:6.9, P=0.008).

Conclusion: KRAS ctDNA mutation detection is an independent adverse prognostic marker in curative and palliative PDAC patients at all sites of blood-draw and is a strong follow-up marker. The most substantial prognostic impact was seen for PV blood, which could be an effective novel tool for identifying prognostic borderline patients - guiding future decision-making on neoadjuvant treatment despite anatomical resectability.

P-12-07

Dermatological paraneoplastic syndrome in pancreatology: clinical case

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Abstract

Background: The most common among paraneoplastic syndromes (PNS) are dermatological problems, occurring in 55-65% of cancer patients. We describe the clinical observation of dermatological paraneoplastic syndrome.

Methods: A 58-year-old patient was examined.

Results: The patient complained on periodic slight itching, weight loss over the past year by 8 kg, periodic pain in the left hypochondrium and epigastric region. In 2014, laparoscopic cholecystectomy (cholelithiasis) was performed. In 2015, during hospitalization due to exacerbation of chronic pancreatitis, a pancreatic head cyst was found. An objective examination revealed multiple seborrheic keratomas (3-15 mm); the dermatologist's conclusion: Leser-Trelat syndrome. In dynamics (two years later), abdominal pain, itching and nausea increased; according to the results of endoscopic ultrasound and MRI, there was a moderate increase in size of cystic formation of the pancreas; fine needle biopsy results: mucinous cystic neoplasia with signs of malignancy. A pylorus-preserving pancreatoduodenal resection was performed, the diagnosis of pancreatic mucinous cystadenocarcinoma was established. During the last year, the patient's daughter began to develop skin changes similar to those of the mother. At present, a thorough examination revealed no pathology of the pancreas.

Conclusion: The dermatologic PNS are the "mirrors", looking into you can find signs of various malignant neoplasms, including pancreatic. However, PNS is not always a manifestation of a cancer diagnosis, because PNS can also precede to neoplastic pathology.

P-12-08

Diagnostic accuracy of ki-67 labelling index in endoscopic ultrasonography-fine needle aspiration cytology and biopsy of pancreatic neuroendocrine neoplasms

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Abstract

Background: The present study aimed to compare the diagnostic accuracy of the ki-67 labelling index (LI) between the endoscopic ultrasonography-fine needle aspiration cytology/biopsy (EUS-FNAC/FNB) and the surgical specimen of pancreatic neuroendocrine neoplasm (PanNEN).

Methods: Conventional meta-analysis and diagnostic test accuracy (DTA) review were performed using 17 eligible studies. In the DTA review, the sensitivity, specificity, diagnostic odds ratio (OR), and area under the curve (AUC) of the summary receiver operating characteristic (SROC) curve were calculated. In addition, subgroup analysis was conducted based on EUS-FNAC and FNB, WHO grade, and tumour size.

Results: Overall concordance rate of WHO grade by ki-67 LI between the EUS-FNAC/FNB and the surgical specimen was 0.767 (95% confidence interval [CI] 0.713–0.814). Concordance rates of the EUS-FNAC and EUS-FNB subgroups were 0.741 (95% CI 0.681–0.794) and 0.839 (95% CI 0.738–0.906), respectively. In the DTA review for WHO grade 3, the sensitivity and specificity were 0.786 (95% CI 0.590–0.917) and 0.998 (95% CI 0.987–1.000), respectively. The diagnostic OR and AUC of the SROC curve was 150.220 (95% CI, 46.145–489.000) and 0.983, respectively. The sensitivity and specificity were the highest in WHO grade 1 and grade 3 subgroups, respectively.

Conclusion: Concordances of WHO grade by ki-67 LI were higher between EUS-FNAC/FNB and surgical specimens. The identification of the ki-67 LI can be useful for predicting the WHO grade of PanNEN in EUS-FNAC/FNB.

P-12-09

Immunomodulatory effects and response prediction of FOLFIRINOX chemotherapy in pancreatic ductal adenocarcinoma patients: implications for combination therapies

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Abstract

Background: FOLFIRINOX is currently one of the best chemotherapy combinations available to treat pancreatic ductal adenocarcinoma (PDAC). However, its clinical utility is limited by high toxicity and poor long-term survival outcomes. Thus, further increasing its systemic and local efficacy through multimodal treatment and early response prediction is desirable. This study aims to investigate the impact of one cycle of FOLFIRINOX on peripheral immune cells and plasma proteins to ultimately guide more effective immuno-based combinational therapies and, ideally, to identify an early biomarker predictive for FOLFIRINOX response.

Methods: Immune cell profiling (flow cytometry) and proteome profiling (Olink Proteomics) was performed on

blood and plasma samples from 86 PDAC patients of all disease stages. Samples were collected one day before and two weeks after the first FOLFIRINOX cycle. Datasets were subjected to Principal Component Analysis after which Linear Mixed Effect Models were fitted that corrected for confounding factors. Analyses were stratified by time (before vs on-treatment) and radiological response after four cycles of FOLFIRINOX (disease control (DC) and progressive disease (PD)).

Results: Unsupervised clustering of flow cytometry data demonstrated increased proliferation and activation of B cell subsets upon treatment. After correcting for covariates, FOLFIRINOX increased the expression of markers involved in T-cell activation and the frequency of proliferating NK(T) cells. In addition, antigen-presenting cells became more activated. Similarly, proteome analysis revealed that FOLFIRINOX diminished several tumour-cell-related pathways and enhanced pathways related to adaptive immunity, immune effector processes, T-cell activation and differentiation, and immunoglobulin production. Stratification by FOLFIRINOX response revealed high levels of activation markers on CD4+ and CD8+ T-cells in DC compared to PD patients. Contrarily, PD patients showed increased levels of inhibitory markers by B cells and CD4+ and CD8+ T-cells. Finally, proteome analysis revealed high levels of BACH1, ITGB6, MYO9B, PRDX3, SIT1, and VEGFA, and low levels of GAL in PD compared to DC patients pre-treatment.

Conclusion: One cycle of FOLFIRINOX has immunomodulatory effects that may form a theoretical foundation for developing (immune-based) combination therapies that harness the immune system in PDAC patients. In addition, several plasma proteins have great potential to predict progression under FOLFIRINOX before starting treatment.

P-12-10

Metabolite profiles in plasma distinguish between patients with periampullary cancer and benign pancreatic disease

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Abstract

Background: Periampullary cancer is a collection of cancers located in the surroundings of ampulla of Vater, in the head of the pancreas, the duodenum and the distal bile duct. The cancers are all serious malignancies with different frequency, prognosis, and treatment. Distinguishing them preoperatively has proven challenging. Further, to differentiate these cancers from benign periampullary disease is not without difficulties. During the last decade, blood-based metabolites have shown promising results as a diagnostic tool to differentiate periampullary cancers from benign disease.

Methods: The level of 28 metabolites in blood plasma from 117 patients with preoperatively suspected pancreatic cancer were established using LC-MS/MS analysis. After pathology evaluation, 72 patients were diagnosed with periampullary cancer and 45 with benign pancreatic disease. Testing of associations between metabolites, consensus clustering based on metabolite profiles, and survival analyses were performed.

Results: More than half of the metabolites were significantly different between the benign and the malign samples (p-value <0.05). Lower levels were found for all the significantly different metabolites in the malign samples, Glutamic acid with higher expression in the malign samples being an exception. Using consensus clustering, the metabolite profiles separate the samples into two clusters, mainly consisting of malign and benign samples, respectively.

Using Cox regression model, high plasma Phenylalanine was found to be associated with increased overall survival (HR=0.50, CI 0.30-0.83, p-value < 0.01).

Conclusion: Metabolite profiles in plasma from patients with malign and benign periampullary disease were significantly different, can distinguish malign from benign disease preoperatively and are possible preoperative biomarkers for periampullary cancer.

P-12-11

Bile analysis in patients with bile duct obstruction

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Abstract

Background: Although bile is a promising sample for biliary disease, there has been limited interest except proteomic analysis. The composition of bile is supposed to show the close correlation with the condition of bile duct and cholangiocyte, which is crucial for modifying the primary generated bile from canaliculi. We aimed to investigate the component of bile and evaluate its potential value as biomarker for malignant biliary tract obstruction.

Methods: We enrolled patients who underwent endoscopic nasobiliary drainage (ENBD) for bile duct obstruction at Korea university Guro hospital from May 2020 to July 2021. The bile was collected through the 3-way connector of ENBD tube, the day after endoscopic retrograde cholangiography and was investigated for sodium, potassium, chloride, acidity, protein, albumin, glucose, amylase and the rate of bacterial culture growth. We divided patients to two groups as the cause of biliary tract obstruction and compared the difference of bile components.

Results: A total of 253 patients were included in the study, 50 patients have malignant bile duct obstruction (18 biliary tract cancer, 14 bancreas cancer, 6 ampulla of Vater cancer, 4 gallbladder cancer, 1 lymphoma, 1 angiosarcoma, 5 other metastatic cancer, 1 unknown origin) and 203 patients have a benign cause. The mean chloride concentration of bile was significantly high in malignant group (115.88 vs 108.72 mmol/L, p<0.0001), but the mean sodium concentration was lower (146.68 vs 150.46 mmol/L, p=0.0007) than benign group. The higher amylase level (>500 U/L) of bile was associated with benign group (p=0.004). There was no difference in protein, albumin, potassium, acidity (pH) and the rate of cultures growth between two groups.

Conclusion: The bile chloride concentration was increased in malignant obstruction. It is thought that decreased chloride/bicarbonate anion exchange in cholangiocyte is involved in malignant cholangiopathy.

P-12-12

The added value of blood glucose monitoring in high-risk individuals undergoing pancreatic cancer surveillance

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Abstract

Background: New-onset diabetes (NOD) is associated with the development of pancreatic ductal adenocarcinoma (PDAC) and is suggested as potential biomarker to detect PDAC at an earlier stage. International guidelines rec-

ommend routine glucose measurements in pancreatic surveillance of high-risk individuals (HRIs), however, little is known about its added value in addition to imaging. Therefore, this study evaluates the added value of longitudinal glucose measurements as a diagnostic biomarker for PDAC in high-risk surveillance cohorts.

Methods: HRIs with a CDKN2A germline pathogenic variant participating in pancreatic cancer surveillance who had ≥ 1 fasting blood glucose (FBG) and/or HbA1c measurements were included in this study. Individuals with diabetes mellitus at baseline, less than 3 years of follow-up and all follow-up after pancreatectomy were excluded from the study. Data was collected on demographics, FBG- and HbA1c measurements, MRI- and EUS examinations, and pathology reports. Univariate multivariable logistic regression was performed to assess the relationship between NOD and PDAC, with adjustment for sex, age and smoking history. To quantify the diagnostic performance of NOD as a marker for PDAC, receiver operating characteristic (ROC) curve and area under the curve (AUC) were computed.

Results: In total, 220 HRIs were included in the analysis. Median age was 61 (IQR 53-71) years, 62.7% of participants were female, and the mean BMI was 26.2 (4.12 SD). More than half (54.1%) of the studied cohort had a positive smoking history and the median amount of glucose measurements per person was 7 (IQR 5-12). During the study period, 26 (11.8%) HRIs developed NOD, of whom 5 (19.2%) later developed PDAC. The other 23 (82.1%) PDAC cases remained NOD-free. Multivariable analysis showed no statistically significant relationship between NOD and PDAC (OR 1.21; 95% CI, 0.39-3.78). A statistically significant association was exclusively observed between age and development of PDAC (OR 1.05; 95% CI, 1.01-1.1). Furthermore, NOD did not differentiate between HRIs with- and without PDAC (AUC 0.54; 95% CI, 0.46-0.61).

Conclusion: This study demonstrated no added value for longitudinal glucose monitoring in HRI participating in an imaging-based pancreatic cancer surveillance program.

P-12-13

Impact of nationwide implementation of best practices in pancreatic cancer care (PACAP-1): a stepped-wedge cluster randomised controlled trial

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Abstract

Background: Implementation of new cancer treatment strategies are often suboptimal and slow. We aimed to implement best practices in pancreatic cancer care nationwide and assess the impact on overall survival (OS).

Methods: Nationwide multicentre stepped-wedge cluster randomised controlled trial comparing implementation of best practices with usual care (May 22, 2018 – July 9, 2020). Best practices included adequate use of perioperative and palliative chemotherapy, pancreatic enzyme replacement therapy (PERT), referral to a dietician, and metal biliary stents. A 6-week implementation period in all 17 Dutch pancreatic centres and their regional referral networks was performed. Primary outcome was 1-year OS. Secondary outcomes included best practice implementation and quality of life (EORTC global health score).

Results: Overall, 5887 patients diagnosed with pancreatic cancer were included; 2939 after implementation of best practices versus 2641 before. One-year OS was 3.8 vs 3.7 months (HR 0.98, 95%CI 0.88-1.08). Use of neoadjuvant

(11% vs 11%) and adjuvant chemotherapy (48% vs 51%) did not change, while use of palliative chemotherapy did (24% vs 30%, OR 1.38, 95%CI 1.10-1.74). Use of PERT increased (34% vs 45%, OR 1.64, 95%CI 1.28-2.11), the number of patients referred to a dietician remained similar (59% vs 63%, OR 1.16, 95%CI 0.92-1.45). Use of metal biliary stents instead of plastic stents increased (74% vs 83%, OR 1.78 95%CI 1.13-2.80). Quality of life did not differ (AUC 43.9 versus 42.8, median difference: -1.09, 95%CI -3.05-0.94).

Conclusion: Nationwide implementation of best practices in pancreatic cancer care did not improve 1-year survival. Despite improvement of some nationwide practices, still the majority of patients received no cancer-directed treatment. This study emphasizes the poor survival in a real-world population, and need for improved awareness and treatment options.

P-12-14

Quantification of perineural invasion in pancreatic ductal adenocarcinoma: proposal of a severity score system

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Abstract

Background: Perineural invasion (PNI) is the neoplastic invasion of nerves, a common feature of pancreatic ductal adenocarcinoma (PDAC), which correlates with an aggressive tumour behaviour even in the early stages of disease. PNI is considered as a present vs absent feature and a severity score system is missing. The aim of this study was to develop a scoring system for PNI and to correlate it with other pathological and prognostic features.

Methods: This monocentric retrospective study included PDAC patients undergoing surgical resection at San Raffaele Hospital between January 2015 and December 2018. Patients with incomplete pathological data or follow-up were excluded. Overall, 356 PDAC patients (47,8% females, median age 68 years) were analysed. PNI was scored as follow: 0: absent; 1: presence of neoplasia along nerves <3 mm; 2: neoplastic infiltration of nerve fibres ≥3 mm and/or massive perineural infiltration and/or presence of necrosis of the nerve bundle. The correlation between the proposed scoring system and other pathological features, disease free survival (DFS) and disease specific survival (DSS) were analysed. Uni- and multivariate analysis for DFS and DSS were performed.

Results: PNI was found in 72.5% of the patients. 38.2% of patients received neoadjuvant treatment, and there was a trend towards a reduction of PNI severity after neoadjuvant treatment, although not statistically significant (p=0.061). PNI score significantly correlated with tumour size, presence of lymph node metastases, vascular invasion, surgical margins status and tumour differentiation grade (p<0.001). PNI severity score significantly correlated also with decreasing DFS and DSS at univariate analysis (p<0.001). At multivariate analysis, the presence of lymph node metastases was the only independent predictor of DFS (p<0.001, HR 2.235) and of DSS (p<0.001, HR 2.902) together with tumour grade (p=0.002, HR 1.6677) and ASA score 3 (p=0.001, HR 1.697).

Conclusion: The increasing severity of PNI score strongly correlates with worsening of the most used pathological features in PDAC. Moreover, it has a prognostic role in terms of DFS and DSS. A prospective validation is needed to fully understand the role of PNI in PDAC.

P-12-15

Nutritional indices in an inpatient advanced pancreatic cancer treatment

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Abstract

Background: Systemic inflammation and nutritional parameters have been studied as possible prognostic factors in pancreatic cancer. As patients start chemotherapy with more aggressive as well as effective treatment, the indices and ratios containing nutritional parameters might be useful in predicting the amount of potentially received first-line treatment courses. The study aimed to analyse the correlation between nutritional status parameters and indices and the number of multi-agent treatment courses received at the inpatient chemotherapy department in treatment naïve patients.

Methods: In patients with locally advanced non operable or metastatic pancreatic cancer, pre-treatment parameters (Charlson comorbidity index (CCI), complete blood count, total protein, albumin, bilirubin) were collected and nutritional ratios and indices (neutrophil-to-lymphocyte (NLR), platelet-to-lymphocyte (PLR), lymphocyte-to-monocyte (LMR), prognostic nutritional index (PNI), nutritional risk index (NRI), HALP (haemoglobin, albumin, lymphocyte, protein), prognostic immune nutritional index (PINI), systemic inflammation score (SIS), systemic immune-inflammation index (SII)), were calculated in 158 patients with APC. The parameters were tested in attempt to assess the correlation between them and the number of multi-agent first-line inpatient treatment courses received.

Results: Out of 158 patients, 72 were men (45.5%) and 89 had with metastatic disease (56.3%). Mean number of inpatient received courses was seven. Kendall rank correlation coefficient test was statistically significant for CCI (-0.15), haemoglobin (0.129), erythrocyte (0.129), total protein (0.174), and albumin levels (0.178) as well as for PNI (0.179), NRI (0.150), HALP (0.145), PINI (0.187), and SII (-0.13) ($p<0.05$). There was a trend to statistical significance also in neutrophil (-0.1, $p=0.052$) and lymphocyte counts (0.104, $p=0.06$) and LMR (0.101, $p=0.067$).

Conclusion: Nutritional and systemic inflammation indices predict the number of multi-agent chemotherapy treatment courses received at the inpatient chemotherapy department.

P-12-16

Add-on oxaliplatin after treatment failure of nanoliposomal irinotecan plus fluorouracil and leucovorin in metastatic pancreatic adenocarcinoma – a retrospective study

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Abstract

Background: Nanoliposomal irinotecan (nal-IRI) plus fluorouracil and leucovorin (NalFL) is the standard therapy for gemcitabine-failed metastatic pancreatic adenocarcinoma (PDAC). However, treatment beyond the progression of NalFL has not yet established. We evaluated the outcomes of add-on oxaliplatin after failure of NalFL.

Methods: Consecutive patients who applied for the National Health Insurance-covered nal-IRI in our hospital be-

tween January 2019 and February 2023 were initially screened with the criteria of metastatic PDAC and failure of gemcitabine. Patients who had been treated with add-on oxaliplatin to NalFL (NalFLOX) after progression of NalFL were identified.

Results: We identified 29 patients with a median age of 66 years (range, 48–77 years). Stage IV disease was diagnosed in 18 patients initially. Before NalFL, a median of 1 (range, 0–3) palliative chemotherapy regimen had been given. The median time to treatment failure (TTF) after starting NalFL was 2.5 months with response rate (RR) of 3.4% and disease control rate (DCR) of 48.3%. ECOG PS of 0–1 was identified in 16 patients before NalFLOX. Oxaliplatin was added to NalFL due to imaging or clinical progression in 18 and 11 patients. For NalFLOX, the median starting dose and maximum dose were 55 (range, 40–70) mg/m^2 and 60 (range, 50–70) mg/m^2 for nal-IRI, and 60 (range, 50–70) mg/m^2 and 60 (range, 50–85) mg/m^2 for oxaliplatin. Fluorouracil was principally infused for 24 hours. The RR of NalFLOX was 6.9% with DCR of 37.9% and TTF of 2.8 months. Comparing patients with PS of 0–1 to 2-3, the median overall survival (OS) of NalFLOX was 8.8 months versus 3.9 months (P <0.001). The median OS of NalFLOX was 7.7 months versus 3.6 months (P = 0.001) in patients without and with prior exposure to platinum, while no prognostic significance in terms of prior exposure to fluoropyrimidine or nab-paclitaxel was found. The adverse events of NalFLOX were well tolerated.

Conclusion: Add-on oxaliplatin beyond the progression of NalFL in metastatic PDAC was of moderate efficacy and manageable toxicities. Further prospective studies may be warranted to explore this regimen in patients with acceptable PS but heavily pretreated PDAC.

P-12-17

The impact of different gemcitabine-based first-line regimens, gemcitabine plus nab-paclitaxel or S-1, on the efficacy of second-line liposomal irinotecan in patients with metastatic pancreatic cancer

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Abstract

Background: Liposomal irinotecan plus 5-fluorouracil and leucovorin (Nal-IRI + 5-FU/LV) provided survival benefit for patients with metastatic pancreatic cancer who were refractory to gemcitabine-based treatment, mainly gemcitabine plus nab-paclitaxel (GA) in current real-world practice. The efficacy and safety of nal-IRI + 5-FU/LV for metastatic pancreatic cancer with first-line treatment of gemcitabine plus S-1 (GS) had not been reported and was explored in this study.

Methods: Total 177 metastatic pancreatic cancer patients receiving GA or GS followed by nal-IRI + 5-FU/LV as the second-line treatment were identified from a multicentre retrospective cohort in Taiwan from 2018 to 2020. Of which, 85 patients received first-line GS treatment and the other 92 patients received first-line GA treatment. The comparisons regarding demographic characteristics, overall survival (OS), time-to-treatment-failure (TTF) and adverse events were done between GS and GA groups.

Results: The median OS was 15.0 months [95% confidence interval (CI), 12.2-17.8] of GS group and 15.9 months (95% CI, 13.3-18.5) of GA group with P=0.58. The median age of GS group was elder compared to GA group (67

versus 62 years, P<0.001), whereas more liver metastasis was noted in GA group (78 % versus 51%, P<0.001) and more patients in GA group received pre-emptive nal-IRI dose reduction (P=0.03) compared to GS group. The TTF (3.1 versus 2.8 months) and OS (6.1 versus 4.2 months) after nal-IRI treatment were similar between GS and GA group with P=0.36 and P=0.83, respectively. More patients in GS group encountered mucositis during nal-IRI treatment (15% versus 4%, P=0.02).

Conclusion: The treatment efficacy of second-line nal-IRI were similar regardless of different first-line gemcitabine-based regimens. The first-line treatment of GS followed by nal-IRI treatment after failure to gemcitabine is an alternative sequence for patients with metastatic pancreatic cancer.

P-12-18

GATA6 expression modulates the immune phenotype in patients with (borderline) resectable pancreatic cancer

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Abstract

Background: GATA6 is essential for maintaining the classical phenotype in pancreatic adenocarcinoma (PDAC), and high expression is associated with a favourable prognosis. The immune system plays a vital role in cancer prognosis by preventing or promoting tumourigenesis. Although some reports suggested an association between GATA6 and tumour immunity in PDAC, the exact role of GATA6 in modulating the immune response remains unclear. This study aims to investigate the immune phenotypes associated with GATA6 expression in treatment-naive and neoadjuvant chemo-radiotherapy (nCRT) treated PDAC patients.

Methods: This study included 85 resected PDAC patients from the randomised controlled PREOPANC trial, who were assigned to receive gemcitabine-based nCRT (n = 42), or immediate surgery (n = 43). Both treatment groups were scheduled to receive adjuvant gemcitabine. Immunohistochemistry staining classified patients into low, moderate, and high GATA6 expression groups. Additional stainings validated GATA6 as a marker for classical-type PDAC following nCRT. The immune transcriptome was examined using spatial immune transcriptomic profiling by NanoString technologies.

Results: Among the treatment-naive tumours, 26% were GATA6high and 29% were GATA6low. In contrast, among the nCRT-treated tumours, 21% were GATA6high and 42% were GATA6low. Treatment naïve GATA6high tumours showed a less inflammatory TME characterised by a low abundance of M2 macrophages and CD8+ T cells. Furthermore, pro-tumoural pathways related to interleukin (IL-4/-10/-13/-17), inflammatory (IL2-STAT5, IL6-JAK-STAT3), and KRAS signalling activities were reduced in GATA6high tumours. GATA6high tumours were significantly associated with prolonged overall survival in the entire cohort (hazard ratio (HR) 0.44; 95% CI: [0.22 to 0.85]). This association was similar after stratifying by treatment (nCRT: HR 0.21 [0.06-0.74], treatment-naive: HR 0.60 [0.27-1.32]), although not significant in the treatment-naïve tumours. The association in the entire cohort remained significant after correcting for potential confounders (HR 0.41 [0.21-0.80]). In addition, multivariate models showed no interaction between GATA6 expression and gemcitabine-based (neo)adjuvant treatment.

Conclusion: This study reveals that treatment-naive PDAC tumours with varying GATA6 expression have distinct immune phenotypes. The presence of GATA6 is associated with a shift towards a less pro-tumoural environment which may contribute to the favourable prognostic role of GATA6. This immunological shift was absent in patients that received nCRT.

P-12-19

Risk factors for developing impaired nutritional status in pancreatic cancer patients: A systematic review and meta-analysis

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Abstract

Background: Impaired nutritional status has an increased incidence in certain gastrointestinal cancers and is associated with altered prognosis and quality of life. The mechanisms of development are incompletely elucidated and there is no efficient treatment to prevent its occurrence and progression. We performed a systematic review and meta-analysis to investigate the risk factors that contribute to impaired nutritional status in patients with gastrointestinal cancer. We report here the results on pancreatic adenocarcinoma (PDAC) cases only.

Methods: We conducted the systematic search in 3 databases (PubMed, Embase and Central) on 21.10.2022 with no restrictions. We included in the analysis studies that fit the following PECO (population, exposure, comparison, outcome) framework: P: pancreatic cancer patients, E/C: any of the evaluated biomarkers, O: impaired nutritional status, as defined in each article. A random-effects model yielded the pooled odds ratios (ORs) and 95% confidence intervals (CIs). The risk of bias was assessed with the QUIPS tool.

Results: Twenty-eight articles comprising 18359 patients were included in the analysis. The overall quality of the articles was good, and most of them were at low risk of bias. Presence of biliary obstruction (OR 2.05 [CI 1.72 to 2.45]) and metastases (OR 1.79 [CI 1.19-2.70]), ECOG ≥2 (vs. ECOG<2) (OR 12.83 [CI 1.59 to 103.81]) and pancreaticoduodenectomy (vs. distal pancreatectomy) (OR 2.15 [CI 1.49 to 3.09]) were associated with significantly higher odds of impaired nutritional status in PDAC. Moreover, we observed clinically relevant point estimation of odds for increased risk of nutritional status impairment in head (vs. other) tumour location (OR 1.27 [CI 0.91-1.77]) presence of diabetes mellitus (OR 1.58 [CI 0.65 to 3.83]) and presence of hypertension (OR 1.87 [CI 0.32 to 10.81]), however we found these odds not significant.

Conclusion: Biliary obstruction, metastatic stage, pancreaticoduodenectomy, and ECOG ≥2 confer an increased risk for impaired nutritional status to PDAC patients. These factors may be included in a nutritional risk screening tool personalised for pancreatic cancer. (The last two authors equally contributed).

P-12-20

Accuracy of endoscopic ultrasound-guided tissue sampling for the cyto-histological diagnosis of solid pancreatic tumours: analysis of a large prospective registry

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Abstract

Background: Endoscopic ultrasound (EUS)-guided sampling is considered the gold standard for the cyto-histological diagnosis of solid pancreatic tumours. Development of new needles over the last years has improved the diagnostic accuracy of EUS-sampling. Aim of our study was to evaluate the accuracy of EUS-sampling for the cyto-histological diagnosis of solid pancreatic tumours in clinical practice.

Methods: Patients who underwent EUS-sampling for the evaluation of solid pancreatic tumour over the last 13 years were identified from a prospectively collected EUS registry and included in the study. EUS was performed with linear Pentax echoendoscopes and Hitachi systems. Tissue acquisition was performed with standard cytology needles (19-gauge, 22-gauge, and 25-gauge) and core needles [ProcoreTM, Franseen and Fork-Tip] (19-gauge, 20-gauge, 22-gauge, and 25-gauge). Samples were collected in a cytological solution (Cytolit®) and processed for cyto-histological evaluation. Results are shown as mean ± standard deviation and percentages. Diagnostic accuracy for malignancy was analysed using the histopathological analysis of the surgical specimens, and the clinical and radiological long-term follow-up in non-operated patients, as gold standard.

Results: 1072 patients were included in the study (mean age 67.6 years, range 17-92, 596 male). Size of solid pancreatic lesions was 33.4 ± 15.2 mm. 617 tumours were located in the head of the pancreas, 339 in the body, 83 in the tail and 33 in the uncinate process. Cytology needles were used in 543 patients (50.7%) and core needles in 529 (49.3%). Mean number of needles passes was 1.7 ± 0.8. On-site evaluation of samples was done in 224 (20.9%) cases. 916 (85.4%) masses were finally classified as malignant, whereas 156 (14.5%) were considered benign. Global sensitivity, specificity and overall accuracy for malignancy were 86.5%, 100% and 88.4%, respectively. Obtained sensitivity and overall accuracy were higher with core needles compared with cytology needles (89.4% vs 83.5%, and 90.7% vs 86.2%, respectively).

Conclusion: EUS-guided sampling is an accurate technique for the cyto-histological diagnosis of solid pancreatic tumours. Diagnostic yield reached in clinical practice is superior with core needles than with cytology needles.

P-12-21

Pre-diagnostic phase of pancreatic cancer: what should we pay to attention?

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Abstract

Background: Pancreatic adenocarcinoma, despite its low incidence, is the fourth leading cause of cancer-related death in Europe. Its poor prognosis is justified by the diagnostic delay and the lack of effective therapies. Our objec-

tive was to analyse the symptoms presented by patients with a diagnosis of pancreatic cancer before the diagnosis in order to see if there is a possibility of improving early diagnosis.

Methods: Retrospective descriptive study of a section of patients diagnosed with pancreatic adenocarcinoma between 07.01.2020 – 08.31.2022. Retrospective follow-up of the guide symptom for which the study of pancreatic cancer begins.

Results: 100 patients were included, male (58%) and median of 65 years old. Toxic habits: Alcohol (30%) and tobacco (64%).

The predominant initial symptom was epigastric pain (46%) either by itself or associated with a general syndrome (16%); jaundice (27%). Another symptoms (17%). Asymptomatic 10%.

61% of the patients had consulted medical services before the diagnosis for said symptomatology. 48% did so with their general practitioner (GP), 12% with their GP and the emergency department simultaneously and 1% only with the emergency department.

The predominant place of diagnosis was a hospital (70%), 11% were incidental findings in imaging tests done for another reason, 9% in outpatient clinics and 7% in primary health care.

36% of the patients had DM at the time of diagnosis, of which 62% were long-standing diabetics (>3 years). In 50% of diabetic patients there is hyperglycaemic decompensation (6 months before diagnosis).

The median from the onset of symptoms until being assessed at a medical service was 16 days and the median of diagnostic delay from the onset of symptoms to diagnosis was 5 weeks. Patients who were not admitted to the emergency department had a diagnostic delay of an average of 3 weeks. Less than 10% were resectable at diagnosis. The median survival was 6 months.

Conclusion: In a disease with a median survival of 6 months, a diagnostic delay of 5 weeks is significant. More than half of the patients consulted with their GP. A diagnostic algorithm should be created for increasing the suspicion of pancreatic cancer and improving early diagnosis.

P-12-22

Integration of metabolome and microbiome omics layers toward pancreatic cancer risk prediction

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Abstract

Background: Pancreatic cancer (PC) is projected to become the second most mortal type of cancer by 2030. Sever-

al factors increase the PC risk. However, these conditions are not enough to define high-risk populations towards preventive interventions. Oral and gut microbiota have been associated with PC risk, and a gut microbiota signature has shown to be a good predictor of PC risk. Preliminary studies point out that the metabolomic profile is associated with PC risk and can be used for further stratification. Our purpose was to build an integrative predictive model based on microbiome, jointly with serum, stool, and urine metabolome features, to identify PC high-risk population

Methods: The PanGenMic population was selected on the basis of oral, blood, urine, and stool samples availability with a total of 44 PC cases and 38 hospital controls. All subjects had metabolomics data generated with NMR assays quantify metabolite's concentration in stool (25 metabolites) and urine (25 metabolites), and with liquid/gas chromatography technology to quantify serum's metabolites (470-2000 metabolites). Oral and faecal samples were processed to extract and sequence the bacterial 16S (250 and 290 ASVs, respectively). Zero inflation was managed through pseudocounts, missing values were imputed following bayesian strategy, and Z-score normalization was implemented. A Kernel-based Bayesian regression model was fitted to obtain both the univariate layer risk score and the integrated risk score. All analyses were adjusted for sex, age, centre, analytical batch, and diabetes mellitus. The predictive ability of the models were evaluated with the area under the ROC curve using a cross-validation approach.

Results: The combined 7 layers of data showed an AUC of 0.80 (SD 0.11). The best-case combination included, serum gas (i.e. best univariate predictor) plus faecal microbiota and metabolome (i.e. lowest correlation to serum gas), with an AUC of 0.83 (SD 0.09).

Conclusion: This is the first study that compares and combines metabolome and microbiome performance into PDAC risk prediction. Regarding predictability, metabolome outperformed microbiome. The combination of faecal metabolomic + faecal microbiomic + serum gas metabolomic's risk score provided the greatest AUC, pointing to the translational potential of this assay for the sake of applicability.

P-12-23

Artificial intelligence approaches to predict pancreatic ductal adenocarcinoma risk

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Abstract

Background: The ability to predict accurately the individual risk to develop pancreatic ductal adenocarcinoma (PDAC) is crucial for the implementation of prevention. Using classical epidemiological approaches, only a small number of risk factors have been identified. Therefore, this study aimed at testing different machine learning (ML) methods to predict the occurrence of PC.

Methods: A total of 964 variables (genetic and non-genetic), 816 pancreatic cancer cases and 302,644 controls from the UK biobank cohort, were used to develop a predictive model for PDAC. Six different ML predictive models (Random Forest, AdaBoost, XGBoost, CatBoost and DeepForest) were tested using two different sets of variables (those significant under a Bonferroni threshold and those significant using a threshold of $p<0.05$). The predictive performances of the models were evaluated using the area under the receiver operating characteristic (ROC) curve (AUC), accuracy, precision, recall and F1-score. Finally, SHapley Additive exPlanation (SHAP) were used on the best ML models to identify the most important features for the model and explain what is the focus of the prediction.

Results: Among the 5 models tested, for the first group of variables, (n=81), XGBoost had the best comprehensive predictive performance, with an AUC of 0.94 and a recall of 0.79 for cases; whereas, for the second group of variables, (n=258), CatBoost performed best in term of prediction, with an AUC of 0.96 and a recall of 0.81 for cases. Using SHAP to visualize the interpretation of the ML models, we found that age and a polygenic risk score (PRS) (i.e., a score computed considering all genetic variants associated with PDAC) contributed the most to the prediction performance of the XGBoost and CatBoost models. The other variables that explained the model were, standing height, smoking status, and weight.

Conclusion: ML showed high specificity and sensibility to predict PDAC occurrence even with a relatively small number of PDAC cases, increasing the number of patients tested in the model will however, be instrumental to apply them in a clinical setting.

P-12-24

Combined IL6R inhibition and immunotherapy as a novel neoadjuvant therapeutic approach in murine pancreatic cancer: a preclinical study protocol

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Abstract

Background: Neoadjuvant therapy (neoTx) is critical for the surgical treatment of pancreatic cancer, especially for borderline resectable (BRPC) and locally advanced (LAPC) cases. Immunotherapy has become increasingly important in improving the treatment response of cancer patients, especially when combined with agents targeting immune inhibitory pathways. In our previous studies, we observed that gemcitabine as neoTx in mice with R0-resectable pancreatic ductal adenocarcinoma (PDAC) induced by electroporation technique led to decreased tumour size and volume, increased overall survival rates and decreased propensity for metastasis. We also showed that resistance to pembrolizumab (Anti-PD-1), an immune checkpoint inhibitor, could be overcome by its combination with an interleukin-6 receptor inhibitor (tocilizumab).

Study protocol & expected results: We hypothesize that a combined neoTx treatment (pembrolizumab, tocilizumab and gemcitabine) could improve resectability in a novel murine PDAC model.To test this hypothesis, we will generate R0-resectable murine PDAC in CD11b Cre;IL-6 fl/fl mice using orthotopic and electroporation models. Following tumour development, pembrolizumab (1-8W), tocilizumab (3-6W) and gemcitabine (3-6W) treatment will be initiated. The effect of treatment on tumour tissue and pain will be evaluated by USG and Von-Frey test. The primary outcome parameter planned to be obtained from the study will be overall survival and secondary outcome parameters will be pain and disease-free survival.

Conclusion: We believe that successful neoTx in BRPC and LAPC cases will indirectly increase the chances of surgical treatment, overall survival rates and disease-free survival in PDAC patients. A combined neoTx strategy with an interleukin-6 receptor inhibitor and anti-PD-1 therapy may have a significant impact on the outcomes of BRPC and LAPC patients. The translational research approach of this study may help to provide a novel, more effective treatment option for PDAC patients and thus address an unmet clinical need.

P-12-25

Investigating possible relationships between pancreatic cancer and hypothyroidism

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Abstract

Background: Studies have demonstrated that exogenous thyroid hormone enhances cell proliferation of pancreatic ductal adenocarcinoma (PDAC), prompting the suggestion that patients taking the hormone may be expected to have a worse prognosis. The purpose of our study is to investigate the prevalence of hypothyroidism among PDAC patients and its possible association with clinical endpoints.

Methods: A total of 634 consecutive patients who underwent pancreatic surgery or were diagnosed with metastatic-locally advanced PDAC between 2012 and 2021 in three Italian hospitals were enrolled, data on hypothyroidism and levothyroxine treatment were collected. Overall survival (OS) curves were constructed using the Kaplan-Meier method and differences were analysed by log-rank-test (Mantel-Cox). To determine the potential association of different clinical factors, a Cox-proportional-hazards model analysis was performed.

Results: Fifteen percent of our PDAC patients had hypothyroidism treated with levothyroxine. The prevalence of hypothyroidism was comparable in metastatic patients and those undergoing radical resection. PDAC patients with hypothyroidism had a significantly higher proportion of women. Cox-proportional-hazards model analysis showed a significantly higher hazard ratio (HR) for death associated with age and T-status in patients undergoing radical resection (HR=1.7; 95%CI=1.1-2.6; p=0.013 and HR=1.7; 95%CI=1.1-2.7, p=0.021) and increased CEA in metastatic patients (HR=2.018; 95%CI=1.2-3.5; p=0.011). In the metastatic setting, median survival did not differ, whereas PDAC patients with hypothyroidism undergoing radical resection had a poorer outcome, with a trend toward a statistically significant difference (p=0.06).

Conclusion: Our study highlighted a higher incidence of PDAC in patients with hypothyroidism treated with levothyroxine compared with the overall population. In addition, we observed a shorter OS in PDAC patients undergoing radical resection with hypothyroidism, which suggests the value of additional studies to establish the possible contribution of thyroid hormone to PDAC outcomes.

P-12-26

A profile of long-term pancreatic cancer survivors

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive disease with a five-year overall survival (OS) of less than 10 percent. The phase III PRODIGE study reported the longest median OS for patients with PDAC, it was 54.4 months. The aim of this study was to examine the clinicopathological characteristics of long-term survivors of PDAC.

Methods: We retrospectively analysed a total of 532 consecutive patients who underwent pancreatic surgery or diagnosed metastatic/locally advanced PDAC treated between 2012 and 2021 in three Italian hospitals. Long-term survival patients were defined if OS was more than 54.4 months. We examined differences in clinical and pathological parameters between the group of Long-Term Survivals and Not Long-Term Survivals. Moreover, we used univariate and multivariate COX regression models to predict the influence of specific factors with OS. Values less than 0.05 were considered statistically significant, the p-value was tested bilaterally.

Results: Statistically significant differences were noticed in a variety of clinical and pathological features between the two groups. 5.6% of our PDAC patients survived in the long-term. Notably, long-term surviving patients were more often younger than 50 years of age (p=0.001), had less vascular (p=0.001) or perineural (p=0.02) invasion, less elevated CA 19-9 at diagnosis (p<0.001), were more frequently undergoing radical surgery (p=0.001) with subsequent adjuvant chemotherapy (p<0.001), and were less frequently metastatic at diagnosis (p=0.007). No differences were observed between the two groups with regard to sex, primary tumour site, hypothyroidism, T stage, N stage, or elevated CEA at diagnosis. Cox proportional hazards model analysis of the whole cohort showed that the occurrence of distant metastasis and elevated CA 19-9 at diagnosis were associated with a significantly higher HR for death (HR=2.1; 95%CI=1.1-4; p=0.02 and HR=1.6; 95%CI=1.1-2.3; p=0.017, respectively). In contrast, adjuvant chemotherapy after surgery was associated with a significantly lower HR for death (HR=0.39; 95%CI=0.25-0-61; p<0.001).

Conclusion: We therefore conclude that in our series, the presence of distant metastasis, elevated CA 19-9 at diagnosis, and the absence of adjuvant chemotherapy after surgery are independent negative predictors for survival in PDAC patients.

P-12-27

Longitudinal changes in body composition and metabolic markers prior to diagnosis of pancreatic ductal adenocarcinoma

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Abstract

Background: Alterations in body composition and metabolic factors may serve as a potential biomarker for early-detection of pancreatic ductal adenocarcinoma (PDAC). This study aimed to capture the longitudinal changes occurring in body composition and metabolic factors preceding a diagnosis of PDAC.

Methods: All patients (≥18 years) diagnosed with PDAC between 2000 and 2021 were identified. We collected data on demographics, comorbidities, PDAC characteristics, all abdominal CT scans and blood-based markers up to 3 years prior to date of diagnosis (index date). We applied a fully-automated abdominal segmentation algorithm previously developed by our group (Weston et al. Radiology 2019) for three-dimensional quantification of body composition on CT scans. We plotted spline regression of body composition and metabolic factors over time and applied paired samples T-test to compare values between time-periods (3 to 6 month intervals).

Results: We included 1825 PDAC patients in body composition analysis, of which 581 (31.8%) had ≥2 pre-diagnostic CT exams. For analysis of longitudinal trends of blood-based markers, 4846 patients were included. Mean age at diagnosis was 68.4 (SD 11.3) years, 43.6% were female and the mean BMI was 27.0 (SD 5.5). The distribution of PDAC stage was as follows: 12.5% stage I, 32.6% stage II, 19.7% stage III, and 35.2% stage IV. Prior to a PDAC diagnosis, we observed significant decreases in visceral fat volume, subcutaneous fat volume, total cholesterol and LDL. Concurrently, patients developed significant increases in HbA1c, fasting blood glucose and white blood cells prior to a clinical PDAC diagnosis. The most substantial changes occurred in fasting blood glucose and white blood cells with a 21.8% and 25.2% increase, respectively. Most body composition and metabolic markers showed a linear decreasing or increasing trend over time to diagnosis of PDAC.

Conclusion: This study identified significant alterations in a variety of soft tissue and metabolic markers that occur in the development of PDAC. These metabolic changes may become apparent prior to two years before diagnosis, which may serve as a significant window of opportunity for early detection.

P-12-28

Cigarette smoking impairs the response to mFOLFIRINOX in patients with pancreatic ductal adenocarcinoma

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Abstract

Background: Although pancreatic cancer (PDAC) patients are mostly treated with chemotherapy, studies analysing the impact of "patient-related factors" such smoking on response to polychemotherapy are scanty. Data obtained in

other tumours and on PDAC models suggest that smoking may induce molecular changes toward a more aggressive phenotype in pancreatic cancer cells. Our aim was to investigate whether smoking affects response to polychemotherapy.

Methods: A database of consecutive PDAC patients prospectively enrolled at a tertiary centre at time of diagnostic EUS-guided biopsy was queried for patients treated with first-line polychemotherapy. Demographic data, risk factors, stage and follow-up data were recorded. Patients-related factors associated with disease control rate (DCR) at 6 months (SD+PR as per RECIST criteria), PFS and OS were investigated by means of statistics for categorical and continuous variables, Kaplan-Meier curves and Cox regression analysis.

Results: Of 339 consecutively enrolled PDAC patients, 212 were included in the analysis; patients' stage: resectable=25, borderline-resectable=75, locally advanced=62, metastatic=50. Treatments were nab-Paclitaxel+Gemcitabine (AG) (n=89), PAXG (Cisplatin, Capecitabine, Nab-Paclitaxel, Gemcitabine)(n=62), mFOLFIRINOX (n=61). The DCR at 6 months was 66.9% (65% for AG, 69% for PAXG, 67% for mFOLFIRINOX). Stage (not Ca19-9) was the only factor significantly associated with worse PFS (HR=1.3; 95%CI: 1.2-1.5; p=0.0010) and OS (HR=1.3; 95%CI: 1.1-1.7; p=0.009) in the whole cohort. Mean PFS and OS were not different in ever smokers/current/heavy vs never smokers. In the subgroup of patients treated with mFOLFIRINOX, the DCR was 43% in current smokers and 75% in never+ex-smokers. In a multivariate Cox regression analysis adjusted for stage and age, in patients treated with mFOLFIRINOX, heavy smoking (>20 pack-years) was associated with worse PFS (median 6 vs 13 months; HR=2.6; 95% CI 1.1-6.3; p=0.03). Smoking status was not associated with DCR and PFS in patients treated with AG or PAXG. Diabetes, BMI, aspirin or statin use and presence of a biliary stent were not associated with response to polychemotherapy.

Conclusion: Cigarette smoking seems associated with a worse response to first-line mFOLFIRINOX in PDAC patients. Whether this is due to the reduced tolerability to the chemotherapy or to molecular changes induced by smoking warrants further investigation.

P-12-29

Heterotaxy syndrome with agenesis of the dorsal pancreas: a dark twisted turn of events

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Abstract

Background: Heterotaxy syndrome is a rare and heterogeneous congenital entity, defined by a disruptive internal arrangement of thoracic and abdominal organs across the left-right body axis associated with several congenital malformations, including pancreatic agenesis. Abdominal pain, diabetes mellitus, and pancreatitis were described in association with agenesis of the dorsal pancreas.

Methods: We report the clinical case of a 42 years-old woman, an active smoker (18 pack-years), with insulin-treated diabetes mellitus, recurrent abortions, and a family history of renal malformation. She was referred to the outpatient gastroenterology clinic for chronic abdominal pain and constipation.

Results: Initial laboratory studies and colonoscopy were unremarkable. Due to the progressive worsening of abdominal pain with de novo anorexia and weight loss, an abdominal CT revealed features compatible with heterotaxy syndrome, including intestinal malrotation (without usual identification of Treitz ligament), polysplenia, and dorsal pancreatic agenesis. In the pancreatic topography, proximally to the superior mesenteric artery origin, a 3.6cm hypodense mass was identified. No cardiovascular, hepatobiliary, renal, or systemic vessel abnormalities were de-

scribed. No chromosomal abnormalities were detected in karyotype. An abdominal MR confirmed dorsal pancreatic agenesia and described a posterior 4.5cm (long axis) lesion in the cephalic-pancreatic region involving the celiac trunk and superior mesenteric artery. A fine-needle aspiration biopsy performed by endoscopic ultrasonography established the diagnosis of pancreatic adenocarcinoma. Diagnosis of locally advanced, unresectable pancreatic lesion was assumed in multidisciplinary discussion, and systemic chemotherapy with gemcitabine monotherapy was proposed due to poor performance status. An acute thrombotic event with visual acuity impairment occurred during treatment, and local progression and metastatic liver disease were documented. Further clinical deterioration with uncontrolled pain and upper gastrointestinal occlusion determined exclusive symptomatic treatment, and the patient died within five months of diagnosis.

Conclusion: This is a rare case of heterotaxy syndrome with dorsal pancreatic agenesis and pancreatic adenocarcinoma, diagnosed in a young woman with chronic abdominal pain and obstipation workup. Chronic pancreatitis and compensatory hypertrophy of the pancreatic head were previously associated with dorsal pancreatic agenesis. However, the pathway to pancreatic carcinogenesis is not understood or proven.

P-12-30

Diagnostic delay at diagnosis and time-to-treatment in pancreatic cancer influence overall survival

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Abstract

Background: Pancreatic adenocarcinoma (PDAC) usually presents aspecific symptoms leading to a long diagnostic delay (DD). Furthermore time-to-treatment (TTT) depends on several factors including time for examinations, histological confirmation and/or oncological evaluation. Our aim was to investigate: a)the association between presenting complaints or risk factors and DD; b)correlation between DD and disease stage; c) whether DD and TTT or DD+TTT(overall delay:OD) impact on overall survival (OS); d) whether TTT or OS differs in patients followed at a third-level referral centre (3LRC) vs community hospitals (CH).

Methods: Single-centre prospective cohort of consecutive PDAC patients, recording demographics, presenting complaints, stage, imaging, endoscopic-ultrasound (EUS), cytological diagnosis, first treatment (chemotherapy/surgery), survival. DD was considered time between first symptom onset and first imaging detecting PDAC; TTT from first imaging to first treatment, overall delay (OD) as DD+TTT. Mann-Whitney test was used to compare continuous variables, Kendall tau for correlation analysis, ROC curves for defining cut-offs; survival analysis with Kaplan–Meier method, and results compared by log-rank test. Overall survival (OS) was defined as the time between diagnosis and death.

Results: 283 patients were included, mean age 66, 40 with incidental diagnosis. Patients with jaundice had a significantly shorter median DD (18 days; p=0.003), while pain (69 days; p<0.001), pancreatitis (146 days; p=0,014), new onset diabetes (66 days; p=0.015) had longer median DD. Ever smokers had borderline significantly longer DD (52 days non-smokers; p=0.07). DD correlated with disease stage (Kendall's tau=-0.167; p<0.0001). OD>92days (HR 1.73; p=0.02), DD>51days (HR 1.73; p=0.007) and TTT>49 days (HR 1.56; p=0.03) were significantly associated with shorter OS at cox regression adjusted for stage and age. Patients entirely cared in 3LRC presented a significantly shorter median TTT (49 vs 56days; p=0.048) compared to CH.

Conclusion: Presenting symptoms influence DD in PDAC patients, which in turn, when >51 days impairs survival. A TTT>49 days and an OD of >3 months also significantly impairs survival. While DD might be reduced with higher awareness for specific warning symptoms (especially in idiopathic pancreatitis), TTT might be reduced optimizing waiting time to EUS and/or first oncological evaluation through dedicated pathways for PDAC patients.

P-12-31

The prognostic impact of comprehensive histopathological disease assessment in resected pancreatic cancer

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Abstract

Background: Resection is the only potential cure for pancreatic cancer patients. Although recent advances in the histopathological assessment of pancreatic resections specimens have led to increased standardization and improved the prognostication for each patient, several disease characteristics are underreported. Thus, their prognostic impact remains uncertain to date. Here we thoroughly examined the histopathologic disease characteristics of pancreatic resection specimens and report the impact of each variable on patient outcome.

Methods: The diagnostic pathology reports of 556 pancreatic resection specimens, resected for pancreatic ductal adenocarcinoma (PDAC) between 2000 and 2016 at a large academic centre were revised and disease characteristics such as tumour diameter (three dimensions), margin involvement, lymph node status and ratio, perineural, lymphatic vessel and blood vessel invasion, as well as metastatic sites were recorded. For histologic subtype and assessment of areactive stroma invasion fronts, slides were centrally reviewed. A cohort of 126 resected PDAC cases with available digital images was used for validation. Tumour staging was updated to the currently employed UICC system. The association of disease characteristics and patient outcome was determined in univariate and multivariate analyses, with respect to adjuvant chemotherapy.

Results: Staging by tumour volume allowed for more precise prognostication compared to largest tumour diameter or UICC stage (HR 1.37, p<0.001). The number of margins involved (HR 1.32, p < 0.001), but not the site of margin involvement was associated with poor prognosis (HR 1.01, p = 0.20). Areactive stroma invasion fronts were significantly associated with worse outcome, which was confirmed in the validation cohort (HR 2.53, p<0.001). We retrospectively confirmed the CRM concept in PDAC and the advantage of the 2017 UICC classification over older versions as well as lymph node ratio as independent prognosticator. The prognostic impact of histopathological traits was independent from adjuvant therapy.

Conclusion: Thorough histopathologic assessment of PDAC resection specimens allows for more accurate prognostication. We identified tumour volume, areactive stroma invasion fronts and the number of involved margins as novel risk factors and confirmed known prognostic factors such as the CRM concept and T-stage by largest tumour diameter. We propose a novel T-stage classification based on tumour volume.

P-12-33

Pancreatic enzyme replacement therapy influences survival in patients with incurable pancreatic cancer

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Abstract

Background: The majority of patients with pancreatic cancer suffer from non-curative disease with dismal prognosis already upon diagnosis. Recent data suggests improved survival for patients who receive pancreatic enzyme replacement therapy (PERT). The aim of this study was to investigate a possible impact of PERT on overall survival in palliative pancreatic cancer patients.

Methods: All patients with incurable pancreatic cancer from 2010 to 2019 were retrieved from the National Pancreatic Cancer Registry. Data on PERT prescription and pick up as well as individual survival time were acquired from the National Medical Products Agency and the Cause of Death Registry. Only patients with a survival longer than one month were included in analysis. Survival data was analysed using cox regression models adjusted for age and sex and presented as Hazard Ratio (HR) for risk of death in the PERT group.

Results: In total 9,420 patients with non-resectable pancreatic cancer were found. Among these, 6742 (50.6% females, median age71 years) survived more than one month after diagnosis. Median overall survival was 7 months (range 3-151). PERT was picked up by 3343 patients, the medicated group was significantly younger (70 vs 72 years, p=0.001) while other basic characteristics did not differ. When dividing the patients into groups according to T-stage and PERT treatment, the number of patients given PERT was in general significantly (p<0.001) fewer compared to the non-treated group. Still, in survival analysis using Hazard Ratio (HR) describing risk of death, PERT was associated with overall prolonged survival; HR=0.72, CI 0.69-0.76, p<0.001). Except from the T1-group, results were equal when patients were partitioned according to both T-status and full TNM-status with superior overall survival for T2 (HR=0.73 (0.63-0.84), p<0.001), T3 (HR=0.70 (0.63-0.78), p<0.001) and T4 (HR=0.69 (0.63-0.75), p<0.001).

Conclusion: In this large retrospective cohort the results indicate an association between PERT treatment and improved survival in patients with incurable pancreatic cancer.

P-12-34

Fatty pancreas is a risk factor for pancreatic cancer: a systematic review and meta-analysis of 2956 patients

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Abstract

Background: Pancreatic cancer (PC) is one of the most lethal cancers in the world, and by 2050, it is expected to become the leading cause of cancer-related deaths. Fatty pancreas (FP) is defined by significant fatty infiltration of the pancreatic parenchyma in the absence of chronic, excessive alcohol intake. The link between FP and PC is not fully understood; however, as a possible modifiable risk factor, FP is suspected of contributing to PC development. The aim was to assess the association between PC and FP by conducting a systematic review and meta-analysis.

Methods: We systematically searched three databases on 21.10.2022: MEDLINE (via PubMed), Embase, and CENTRAL (PROSPERO no.: CRD42022369017). Case-control and cross-sectional studies reporting on patients where the intra-pancreatic fat deposition was determined based on modern radiology or histology were included. We investigated patients with PC and without PC. As main outcome parameters, FP in PC patients and in non-PC patients, and PC in FP and in non-FP patients were measured. Proportion and odds ratio (OR) with a 95% confidence interval (CI) was used for the effect size measure.

Results: In total, 17 articles were identified, including 2,956 patients. The possibility of having FP among patients with PC was more than six times higher (OR 6.13; 95% CI 2.61-14.42) than in patients without PC. The presence of PC among patients with FP was 32% (OR 1.32; 95% CI 0.42-4.16). The proportion of FP among PC patients was higher (0.62; 95% CI 0.42-0.79) than in non-PC patients.

Conclusion: In conclusion, FP was identified six times more in PC patients. Proper patient management can result in better survival rates among patients with identified predisposing factors for PC. (The last two authors equally contributed)

P-12-35

Chemotherapy regimens and survival in pancreatic cancer - a ten year single centre overview

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Abstract

Background: During the last decade chemotherapy recommendations for pancreatic cancer (PDAC) have changed as novel regimens have demonstrated superior survival in selected cohorts. Herein we aim to, in a local cohort, analyse therapy changes and possible survival alterations over a 10-year period.

Methods: Patients with PDAC linked to a southern region in Sweden were enrolled from the Swedish Pancreatic Cancer Registry and split into an Early (2010-2011) and Late group (2018-2019). Baseline characteristics and chemotherapy regimens were obtained from medical records. Resected and palliative patients were analysed separately. Follow-up was at least two years.

Results: In total 323 patients were enrolled: 81 resected and 242 palliative. In the resected group no differences were found for basic characteristics, in the palliative cohort patients in the Late group had more comorbidities. The use of neoadjuvant treatment appear to be more common over time, however only demonstrating a significant difference in the palliative group. Similarly, numbers for 1st and 2nd line chemotherapy increased between the time periods but the change did not prove significant. A clear shift could be seen regarding adjuvant treatment of resected patients where Gemcitabine (81 vs 23%, p=0.001) has been replaced by Gemcitabine plus Capecitabine (0 vs 50%, p=0.001) and FOLFIRINOX (0 vs 7%, p=0.25). In the palliative group 1st line regimen consisting of primarily

Gemcitabine (45 vs 17%, p<0.001) or Gemcitabine plus Capecitabine (9 vs 0 %, p<0.001) changed to FOLFIRINOX (1 vs 17%, p<0.001) and Gemcitabine plus NabPaclitaxel (1 vs 29%, p<0.001). Neoadjuvant treatment is nowadays primarily FOLFIRINOX.

The overall two year survival remained unchanged in the palliative group (7 vs 5%, p=0.65) whereas a significant increase was seen in the resected group with 82% of the patients still alive two years after diagnosis (p=0.03).

Conclusion: This retrospective observational single centre study demonstrates a shift in oncological PDAC treatment towards the use of combination therapies. The number of patients receiving chemotherapy increased between the time periods but the change was not significant. Interestingly, a distinct increase in 2-year survival was found for the resected group and further follow-up is needed to see if this trend persists.

P-12-36

Endoscopic papillectomy for ampullary lesions in patients with familial adenomatous polyposis compared to sporadic lesions in a propensity-score matched cohort

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Abstract

Background: Familial-adenomatous-polyposis (FAP) is a rare inherited cancer predisposition syndrome. The treatment for FAP-related ampullary lesions (AL) is challenging and the role of endoscopic papillectomy (EP) is not elucidated yet. Data of FAP associated AL are limited and showed, at least in part, inconclusive results. We retrospectively analysed the outcomes of EP in matched cohorts of FAP-related and sporadic ampullary lesions (SAL).

Methods: The ESAP study included 1422 EPs. A propensity-score matching (nearest-neighbour-method) including age, gender, comorbidity, histologic subtype and size was performed. Main outcomes were complete resection (R0), technical success, complications and recurrence.

Results: Propensity-score-based matching identified 202 patients (101 FAP, 101 SAL) with comparable baseline characteristics. FAP-patients were mainly asymptomatic (79.2% vs. 46.5%, p<0.001). The initial R0-rate was significantly lower in FAP-patients (63.4% [95%CI 53.8-72.9] vs. 83.2% [95%CI 75.8-90.6], p=0.001). However, after repeated (mean: 1.30 per patient) interventions, R0 was comparable (FAP 93.1% [95%CI 88.0-98.1] vs. SAL 97.0% [95%CI 93.7-100], p=0.194). The overall complication rate was 28.7%. Pancreatitis and bleeding were most common adverse events in both groups. Severe complications were very rare (3.5%). Twenty-one patients in the FAP group (20.8% [95%CI 12.7-28.8]) and sixteen patients in the SAL group (15.8% [95%CI 8.6-23.1], p=0.363) had a recurrence. Recurrences occurred later in FAP-patients (25 [95%CI 18.3-31.7] vs. 2 [95%CI CI 0.06-3.9]).

Conclusion: EP is safe and effective in FAP-related ampullary lesions Criteria for endoscopic resection of AL can be extended to FAP-patients. FAP-patients have a life-time risk to relapse even after complete resection and require long-time-surveillance.

P-12-37

Unveiling the connection: a meta-analysis of environmental pollutants and pancreatic cancer

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Abstract

Background: More and more research is being done to investigate whether or not there is a correlation between exposure to environmental pollutants and pancreatic cancer. It is believed that some of these contaminants play a role in the development of pancreatic cancer or the progression of the disease. In spite of the fact that a meta-analysis that summarises the connection between the two would be helpful for comprehending and directing continuing research, such a study has not yet been conducted. This study's goal is to provide a high-level review of the knowledge that is currently known regarding the ways in which exposure to environmental pollutants is linked to pancreatic cancer.

Methods: A protocol for conducting a meta-analysis was developed based on the MOOSE and PRISMA principles. In order to locate the protocols, a search was conducted in the PROSPERO registry. By the use of PubMed, we looked for relevant research, such as first-of-their-kind, human observational studies that had been subjected to peer review and that quantitatively investigated the link between environmental pollutants and pancreatic cancer. It was required that all publications be written in the English language. The inverse variance method was utilised to establish weighting, and SPSS Version 29.0.0.0 was utilised to calculate odds ratios (ORs) and, if necessary, other ratios. The Newcastle-Ottawa and ROBINS-I assessments were applied in order to assess the quality of the study and any potential bias.

Results: PROSPERO did not turn up any protocols that matched given search criteria. In conclusion, we found that the OR was 1.00 across the board (0.87-1.16). The odds ratios that were obtained were anywhere from 0.82 to 1.10 for pesticides, 1.42 to 4.62 for p,p'-DDT and 1.24 to 4.76 for p,p'-DDE, 1.17 to 4.63 for PCB 138, 1.27 to 5.16 for PCB 153, 1.12 to 5.44 for PCB 180, 1.09 to 0.48 for HCB, and 1.16 to 5.01 for β-HCH.

Conclusion: The results of this meta-analysis indicate that exposure to environmental toxins may play a role in the progression of pancreatic cancer; however, additional research is required to establish conclusions that can be considered more definitive

P-12-38

Diagnostic adequacy of needles used in EUS-guided tissue acquisition of solid pancreatic masses – a systematic review and network meta-analysis

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Abstract

Background: Several needle designs are available in different sizes for endoscopic ultrasound (EUS)-guided tissue acquisition (TA) of solid pancreatic masses, and they offer different efficacy and safety profiles. No clear guidelines exist for the choice of needle for TA in this context. We aimed to compare the needles in terms of efficacy (diagnostic adequacy, technical failures) and safety (adverse effects), and by means of network meta-analysis create a ranking of all available needle types.

Methods: This review was registered in Prospero (CRD42021284755). Randomised controlled trials comparing at least two needles of a specified gauge for TA of solid pancreatic masses were eligible for inclusion. MEDLINE (via PubMed), CENTRAL, Embase, Web of Science and Scopus were searched on October 15th, 2021, without filters or restrictions. Risk of bias was assessed using the Cochrane Risk of Bias Tool (RoB2).

Results: 3665 records were identified, and 35 were finally included for analysis. For the outcome of histological adequacy, Fork-tip and Franseen needle designs had the highest likelihood of being best (p-score 0.846 and 0.788 respectively), while Westcotts (forward and reverse bevel) and Menghini needles were least likely to be the best (p-score 0.365, 0.318 and 0.183 respectively). For the outcome of cytological adequacy, Fork-tip and Franseen needles were most likely to be the best (p-scores: 0.900 and 0.602 respectively) and Reverse-bevel and Menghinis the least likely (0.346 and 0.151 respectively). For technical failures, the most likely to perform best were Franseen and Menghini needles (p-scores 0.855 and 0.664 respectively), Fork-tip, Forward-bevel and Reverse-bevel the least (p-scores: 0.451, 0.412, 0.118). In avoiding adverse events, the Reverse-bevel, Forward-bevel, Fork-tip and Menghini needles performed similarly (p-scores: 0.628, 0.558, 0.518, 0.487) and Framseen needles the worst (p-score: 0.310)

Conclusion: Based on our results, fork-tip and Franseen needles can be recommended for their higher diagnostic adequacy, but with a slightly increased risk of adverse events and technical failures. Menghini needles performed worst for nearly all outcomes. Limitations of the review are large uncertainties due to low event numbers for adverse events and technical failures, and a small number of direct comparisons.

P-12-39

Impact of endoscopic ultrasound-guided tissue acquisition on prognosis in resectable or borderline resectable pancreatic body and tail cancer

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Abstract

Background: Reportedly, overall survival of patients with resectable (R) or borderline resectable (BR) pancreatic cancer undergoing neoadjuvant chemotherapy followed by surgery appears to be more favourable compared to upfront surgery. For this reason, nowadays, the preoperative pathological diagnosis of suspected R/BR pancreatic cancer is necessary. However, the indication of endoscopic ultrasound (EUS)-guided tissue acquisition (EUS-TA) for preoperative diagnosis still remains controversial, especially for patients with R/BR pancreatic boy and tail cancer, because of the possible risk of needle tract seeding (NTS) after EUS-TA. Objective: This retrospective study aimed to evaluated the effect of EUS-TA on postoperative prognosis in patients with R/BR pancreatic body and tail cancer.

Methods: we analysed data of 127 patients who underwent surgical resection for R/BR pancreatic body and tail cancer between January 2006 and December 2019. The patients were divided depending on whether EUS-TA for preoperative pathological diagnosis was performed or not (EUS-TA group and non-EUS-TA group).

Results: NTS within the gastric wall was postoperatively found in two patients (1.6%). There was no significant

difference in the overall survival between the EUS-TA group and non-EUS-TA groups (p=0.83) from analysis by the Kaplan-Meier method. In the multivariate Cox proportional hazards regression model, preoperative EUS-TA was not identified as an independent factor related to overall survival (hazard ratio [HR] 0.89, P = 0.69), whereas preoperative serum CA19-9 level ≥150 (HR 1.95, P = 0.02), positive peritoneal lavage cytology (HR 2.61, P < 0.01), histologically proven poorly differentiated adenocarcinoma (HR 3.64, P < 0.01), and histologically proven lymph node metastasis (HR 2.54, p<0.01).

Conclusion: EUS-TA have no negative impact on postoperative prognosis in patients with R/BR pancreatic cancer. However, the indication of EUS-TA should be considered carefully according to individual cases because of risk of NTS at the puncture route, a rare but serious complication.

P-12-40

Safety of multimodality treatment with a combination of intra- operative chemotherapy and surgical resection in locally confined or borderline resectable pancreatic cancer: The combiCaRe study

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Abstract

Background: Pancreatic cancer is a devastating disease with an exceptionally poor prognosis. Complete resection of the primary tumour followed by adjuvant chemotherapy is the current standard treatment for patients with resectable disease and the only curative treatment option. However, tumour cell dissemination due to manipulation during surgery may increase the rate of future metastases and local recurrence. Perioperative chemotherapy might diminish local, distant and circulating minimal residual disease. Yet, safety and feasibility of systemic chemotherapeutic treatments during pancreatic cancer resection have to be evaluated in a first instance.

Methods: In a prospective, single-centre phase I/II feasibility study (combiCaRe) the safety and tolerability of a combination of intraoperative chemotherapy and surgical resection in pancreatic cancer are investigated. Participants receive calcium folinate and 5-fluorouracil over 48 hours, started on the day before pancreatic surgery and thus continuing during surgery. The primary endpoint is the 30-day overall complication rate according to the Clavien-Dindo classification. Secondary endpoints comprise toxicity and treatment associated complications. Patients receiving perioperative chemotherapy are compared to a propensity score matched contemporary control group of pancreatic cancer patients receiving the standard treatment.

Results: Following treatment of the first 10 patients with locally confined or borderline resectable pancreatic cancer, meeting all proposed criteria, an interim analysis for safety was be performed. None of the specific stopping criteria, including unusually high numbers of patients, who developed grade B/C postoperative pancreatic fistula, insufficiency of the biliodigestive anastomosis, or died within 30 days, was reached.

Conclusion: Based on a preliminary, interim analysis of the combiCaRe study multimodality treatment with a combination of intraoperative chemotherapy and surgical resection in pancreatic cancer seems to be safe and feasible.

P-13-01

The anticancer effect of artesunate-induced ferroptosis and its role for overcoming oxaliplatin resistance in pancreatic cancer

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Abstract

Background: Pancreatic cancer (PC) remained one of the worst prognostic cancers. Overcoming resistance to cytotoxic chemotherapy are one of the most important clinical unmet needs. In this study, the effect of artesunate (ART)-induced ferroptosis on pancreatic cancer was evaluated to overcome oxaliplatin (OXA) resistance.

Methods: Five PDPCOs with OXA-resistance and 4 PC cell lines were used. The efficacy of ART for PC and ART-induced ferroptosis were evaluated in proper experimental methods. PDPCOs were established from single-pass EUS-FNA samplings, and performed whole exome sequencing, and bulk RNA sequencing. To find the molecular pathways of action of ART-induced ferroptosis, quantitative real-time PCR and western blotting were conducted. Mutational variants and differential expressed gene analysis were conducted to find underlying mechanism of ART-induced ferroptosis, and to identify core related factors to the response to ART.

Results: PDPCOs with KRAS wild type did not show effective cell death by ART. PDPCOs with KRASG12V mutation showed the most effective anti-cancer effect by ART. ART effectively induced ferroptosis even in OXA-resistant PDPCOs, and the synergistic effect of ART with OXA was shown accompanying by the enhanced level of ferroptosis. ART effectively induced ferroptosis in PC to induce an elevated level of intracellular iron level by overexpression of the iron-import metabolic pathway. According to the results from differential expressed genes analysis, gene set enrichment analysis, pathway analysis, and protein-protein interaction network analysis, upregulation of ceruloplasmin was suspected as a key biomarker for the prediction of ART unresponsiveness.

Conclusion: ART showed promising anticancer effects by ferroptosis for PC and effective cell death was also maintained even in the OXA-resistant PDPCOs, and the synergistic anticancer effect was confirmed by combinatorial treatment of OXA and ART. Further clinical trials in human subjects to overcome OXA resistance in PC using ART are needed in near future.

P-13-02

Etoposide and navitoclax as triggers of senescence and senolysis: in vitro and in vivo studies in murine pancreatic cancer models

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Abstract

Background: Chemotherapeutics and irradiation act partly by inducing the senescence of tumour and bystander cells. While senescent cells themselves are growth-arrested, they may still favour tumour progression by creating a pro-tumourigenic microenvironment, e.g., through the secretion of proteins termed senescence-associated secretory phenotype (SASP) factors. Employing experimental models of pancreatic ductal adenocarcinoma (PDAC), we have challenged the hypothesis that combining drugs triggering senescence with drugs promoting senolysis may exert potentially beneficial effects. Furthermore, we have analysed underlying molecular mechanisms.

Methods: C57BL/6J mice with orthotopic transplants of Panc02 and 6606PDA PDAC cells were treated with the cytostatic drug etoposide (Eto), the BCL-2-inhibitor navitoclax (Nav), and combinations thereof. These *in vivo* studies were accompanied by cell culture experiments. Gene expression profiles and the activity of senescence-associated βgalactosidase (SA-β-gal) were used to monitor cellular senescence. Furthermore, tumour growth and cell proliferation were assessed employing standard experimental procedures.

Results: Eto inhibited Panc02 and 6606PDA cell proliferation *in vitro* and *in vivo* and induced cellular senescence as indicated by increased expression of SA-β-gal and genes related to aging (*Cdkn1a*, *Mdm2*). Nav, applied as a single agent, stimulated Panc02 and 6606PDA cell proliferation and reduced expression of *Cdkn1a* and *Mdm2* in Panc02 cells. The combination of Eto and Nav diminished the proliferation of Panc02 but not 6606PDA cells *in vitro* and *in vivo* stronger than Eto treatment alone. In 6606PDA cells, adding Nav to Eto was associated with lower numbers of SA-β-gal^{+}-cells and senescence-associated heterochromatin foci. In both cell lines, expression levels of *Cdkn1a* and *Mdm2* were numerically lower after treatment with Eto+Nav compared to Eto alone.

Conclusion: The results of this study indicate that senescent PDAC cells can subsequently be eliminated by Nav treatment. The effects, however, depend on the cellular background and the experimental conditions, suggesting a limited efficiency of Nav. Nevertheless, the concept of combining triggers of senescence with senolytic drugs deserves further attention.

P-13-03

In vivo CRISPR/Cas screening of immune checkpoint proteins in pancreatic cancer

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Abstract

Background: Immunotherapy plays an emerging role in the fight against cancer. By dysregulating immune checkpoint signalling cancer cells are able to cleverly escape from the immune system. Despite the success stories of immune checkpoint blockade in other cancer types, pancreatic cancer remains largely resistant against any forms of checkpoint inhibitor or other immune therapies. Therefore, our aim is to perform an in vivo based CRISPR/Cas screening for immune checkpoint proteins in tumour cells to identify proteins, which inhibit the immune response and promote growth.

Methods & Results: To realize this project, we designed an immune checkpoint library containing sgRNAs against 21 genes and 96 NTCs, which cover important parts of the immune checkpoint signalling pathway. Every gene is targeted with at least 4 sgRNAs. As a first step flow cytometry on ten different human and two mouse cell lines was performed to proof if the targeted immune checkpoint proteins are expressed at the surface of the cells and can be knocked out. The results indicate that the designated proteins are expressed heterogeneously in most of the cell lines. For further evaluation organoids containing the sgRNA library from the transfected TB32047 Cas9 cell line will be produced. These organoids are going to be implanted orthotopically in C57BL/6 and NSG mice. After 35 days the mice will be killed to isolate the developed tumour and metastases. DNA will be isolated from the tumours and amplified through PCR. The specific sgRNA PCR products are going to be deep sequenced to analyse differentially sgRNAs. We focus on differentially sgRNAs from the C57BL/6 mice which are not shared with the NSG mice to find important immune checkpoint proteins and candidate genes for further evaluation of their role in pancreatic cancer.

This could unravel new therapeutic target to treat pancreatic cancer.

P-13-04

Interleukin-3 amplifies the development and progression of pancreatic ductal adenocarcinoma

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease with one of the lowest 5-year survival rates of all solid tumours. Although multiple therapeutic strategies have been explored to improve the survival of PDAC patients, the outcome is still limited. Henceforth, the exploration of a promising prognostic biomarker is very crucial. In this study, we sought to investigate the importance of interleukin-3 (IL-3), a hematopoietic growth factor, master regulator of inflammation, which is produced by T and B cells and its influence on the lymphatic microenvironment during pancreatic cancer disease.

Methods: In the period from 2020 to 2022, we removed lymph nodes (LN8a (n=53), LN12b (n=12)) and collected peripheral blood (PDAC=99, control =40) from patients who underwent PDAC surgery and cholecystectomy (control) at the University Hospital in Erlangen, Germany. IL-3 plasma level were measured using ECLipse. We performed orthotopic injection of murine pancreatic cancer cell line (TB32047). Mice were sacrificed 3 weeks post injection of tumour cells. Organs were isolated and Flow cytometry, qPCR and ELISA were performed.

Results: In Human, IL-3 serum level were significantly increased in PDAC patients than control patients. PDAC patients with perineural invasion (Pn) and higher grading (G3) had significantly increased IL-3 level than Pn0 and G2. IL-3 level in treated patients were significantly reduced than untreated patients. In the LN8a of PDAC patients, B cells (i) had significantly higher frequencies of IL-3, (ii) and expressed higher HLA DR, CD40 than LN12b of control patients. LN8a with tumour infiltration had increased proliferating B cells, and decreased expression of Blimp1 in proliferating B cells and plasmablast B cells than tumour free LN8a. Using a mouse model, we report that IL-3 potentiates the development and progression of pancreatic cancer. IL-3 deficiency resulted in better survival and protected the mice from weight loss. IL-3 increased the number of B cells, and decreased frequencies of Blimp1 in the lymphatic environment.

Conclusion: Our results identify a previously unrecognized role of IL-3 producing B cells in the development and progression of pancreatic cancer and underscore the potential significance of B cell/IL-3 axis as a therapeutic target.

P-13-05

COL8A1 promotes progression and gemcitabine resistance of pancreatic ductal adenocarcinoma through an autocrine/paracrine fashion

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Abstract

Background: The effectiveness of cytotoxic therapy for pancreatic ductal adenocarcinoma (PDAC) has been constrained by a unique microenvironment with increased desmoplastic reaction. The modification of the stroma may induce therapy responsiveness. We evaluated collagen type VIII alpha 1 chain (COL8A1), whose function in PDAC is currently unknown.

Methods: Seven PDAC and 1 patient-derived fibroblast cell lines, pancreas tissue from PDAC patients and LSL-KrasG12D/+; Pdx-1-Cre (KC) mice were used to analyse the target gene selected by bioinformatics analysis, followed by RT-qPCR, Western blotting, immunohistochemistry, machine-learning-based contextual tissue analysis, RNA interference, colony formation, transwell, wound healing, cell adhesion, EMSA and co-immunoprecipitation assays; gene array analysis; spheroid growth analysis and in vivo xenotransplantation.

Results: We identified COL8A1 expression in 7 examined PDAC cell lines by microarray analysis, western blotting, and RT–qPCR. Higher COL8A1 expression occurred in 2 gemcitabine-resistant PDAC cell lines; pancreas tissue (n=15) from LSL-KrasG12D/+; p48-Cre mice with advanced PDAC predisposition; and PDAC parenchyma and stroma of a patient tissue microarray (n=82). Bioinformatic analysis confirmed higher COL8A1 expression in PDAC patient tissue available from TCGA (n=183), GTEx (n=167), and GEO (n=261) databases. siRNA or lentiviral sh-mediated COL8A1 inhibition in PDAC cells reduced migration, invasion and gemcitabine resistance and resulted in lower cytidine deaminase and thymidine kinase 2 expression and was rescued by COL8A1-secreting cancer-associated fibroblasts (CAFs). The activation of COL8A1 expression involved cJun/AP-1, as demonstrated by CHIP assay and siRNA inhibition. Downstream of COL8A1, activation of ITGB1 and DDR1 receptors and PI3K/AKT and NF-κB signalling occurred, as detected by expression, adhesion and EMSA binding studies. Orthotopic transplantation of PDAC cells with downregulated COL8A1 expression resulted in reduced tumour xenograft growth and lower gemcitabine resistance but was prevented by co-transplantation of COL8A1-secreting CAFs. Most importantly, COL8A1 expression in PDAC patient tissues from our clinic (n=84) correlated with clinicopathological data, and we confirmed these findings by the use of patient data (n=177) from the TCGA database.

Conclusion: Both intrinsic and extrinsic COL8A1 from tumour and stroma cells, respectively, play a role in enhancing tumour progression and chemoresistance. Targeting COL8A1-DDR1/ITGB1-PI3K-AKT pathway may serve as a new strategy for overcoming drug resistance in PDAC.

P-13-07

Single-cell epigenomic analysis reveals an important role of the receptor kinase Ror2 in the erosion of cellular identity during pancreatic carcinogenesis

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Abstract

Background: The major driver for pancreatic ductal adenocarcinoma (PDAC) is oncogenic KRAS. However, adult acinar cells, a probable origin of PDAC, are largely refractory to $Kras^{G12D}$-mediated oncogenic transformation. With the concomitant loss of transcription factors that regulate acinar cell differentiation, such as Pdx1 (Pancreatic and Duodenal Homeobox 1), acinar cells undergo a rapid cell identity switch, known as acinar-to-ductal metaplasia (ADM). How loss of cell identity cooperates with oncogenic Kras to induce pancreatic transformation is largely unclear.

Methods: To elucidate mechanisms responsible for the accelerated cellular reprogramming in $Kras^{G12D}$;$Pdx1^{f/f}$ animals, single-cell ATAC-seq (Assay for Transposase-Accessible Chromatin using sequencing) from frozen pancreatic bulk tissue was performed. Chromatin accessibility states were captured at early stages of carcinogenesis and correlated to RNA-seq data. Differentially regulated genes were validated by multiplex RNAscope and immunohistochemistry staining and functionally studied in pancreatic cancer cell lines.

Results: Single-cell ATAC-seq proved a powerful tool for defining cell-type identity, cellular reprogramming and target genes in early metaplastic transformation of pancreatic tissue. Notably, acinar cells of $Kras^{G12D}$;$Pdx1^{f/f}$ animals as well as a proportion of metaplastic lesions in both, $Kras^{G12D}$ and $Kras^{G12D}$;$Pdx1^{f/f}$ mice, showed elevated accessibility and expression of the Ror2 gene. As a receptor tyrosine kinase, Ror2 controls essential signalling pathways, such as Ras-MAPK signalling. By analysing Ror2 knockout mice, we found that the receptor kinase regulates the identity of metaplastic epithelia. Moreover, Ror2 expression highly correlates with the more aggressive basal-like subtype in mouse and human PDAC. Overexpression of ROR2 in pancreatic cancer cell lines with a classical differentiation induced epithelial-to-mesenchymal transition, characterised by the downregulation of multiple epithelial markers and upregulation of mesenchymal genes. In addition, ROR2-overexpressing cells proliferated much more rapidly, while knockout of ROR2 in pancreatic cancer cells significantly decreased cell proliferation.

Conclusion: Our in-depth sequencing data revealed that expression of $Kras^{G12D}$ with the concomitant loss of Pdx1 leads to vast alterations of acinar cell identity. We identified the receptor kinase Ror2 as a regulator of pancreatic cancer initiation and driver of pancreatic cancer cell aggressiveness.

P-13-08

GARP expression in the local lymphatic microenvironment predicts the progression of pancreatic ductal adenocarcinoma

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease with one of the lowest 5-year survival rates of all tumours. It is often diagnosed only after reaching an advanced stage in which it is often metastasized and inoperable. Henceforth, the exploration of a prognostic biomarker during the development and progression of pancreatic cancer is crucial. In this study, we investigated the role of GARP, a transmembrane protein that promotes the tumour proliferation and therapeutic resistance. In addition, GARP upregulation positively correlates with Tregs and was directly proportional to the expression of CTLA-4 and PD-L1.

Methods: Lymph node (Ln) 8a (n=53) was removed from patients who underwent PDAC surgery and Ln12b (n=10) was removed from patients who underwent cholecystectomy serving as controls. Written consent forms were collected from the patients before samples were collected for research purpose at the university hospital in Erlangen, Germany, between 2020 and 2022. To investigate the importance of GARP during PDAC, immunohistochemistry (IHC), quantitative polymerase chain reaction (qPCR) and Flow Cytometry were used.

Results: We show that Ln8a of PDAC patients expressed significantly higher GARP than Ln12b of control patients. High expression of GARP in LN8a was directly proportional to positive to survival, nodal, metastatic, perineural invasion, lymph angiogenesis status of PDAC patients. Tumour positive Ln8a had significantly increased GARP expression than tumour free Ln8a of PDAC patients. We demonstrate that during tumour infiltration in the Ln8a of PDAC patients, a non-hematopoietic cell compartment expressed GARP, which has not been previously described.

Conclusion: Increased expression of GARP in the local lymphatic microenvironment could possibly predict the outcome in PDAC patients. Our results identify a previously unrecognized role of GARP in the progression of pancreatic cancer and underscores its potential role as an immunotherapeutic target.

P-13-09

Regulation of pancreatic cancer metastasis by signal conversion in the epigenome

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Abstract

Background: Most patients with pancreatic ductal adenocarcinoma (PDAC) present with unresectable or metastatic disease at the time of diagnosis. Hence, PDAC remains one of the most lethal malignancies with a 5-year survival rate below 10%. PDAC is characterised by early KRAS mutation with the hyperactivation of the mitogen-activated protein kinase (MAPK) signalling pathway. Studies in animal models determined that early KRAS mutation alone is insufficient for PDAC formation. Inflammation-induced signalling activates nuclear factor kappa-light-chain-enhancer of activated B cells (NFKB), which functions downstream of proinflammatory signalling to promote PDAC tumourigenesis. We hypothesized that MAPK and NFKB cooperate to promote PDAC aggressiveness. Hence, it is critical to investigate and delineate the transcriptomic and epigenetic landscape of KRAS/MAPK and NFKB signalling in PDAC.

Methods: We investigated the molecular crosstalk between KRAS/MAPK and NFKB signalling. We employed multiple next generation sequencing approaches to study the transcriptomic and epigenetic landscape (RNA- and ChIP-seq). We also utilised live-cell imaging analysis to study the effect of the synergistic signalling on phenotype and tumour aggressiveness.

Results: Live cell imaging analysis of PDAC cell lines after the simultaneous hyperactivation of MAPK and NFKB signalling by epidermal growth factor (EGF) and tumour necrosis factor alpha respectively (TNF alpha), showed significant increases in cell migration. The simultaneous stimulation of both pathways revealed significant increases in the occupancy of the active mark, H3K27ac, at target genes. This was observed around transcription start sites of a subset of genes involved in cell polarity, migration, and molecular subtype identity, processes known to be important for tumour aggressiveness. Analysis of the genome occupancy of FOSL1 and RELA, transcription factors that are downstream targets of the MAPK and NFKB signalling pathways, respectively, show their co-occupancy at these H3K27ac-enriched regions. Furthermore, loss-of-function approaches show the synergistic effect on the migration capacity.

Conclusion: Our results reveal a mechanism of the convergence of MAPK and NFKB on the epigenome to activate the expression of genes involved in PDAC metastasis and aggressiveness. This study will provide novel insights into the development of mechanism-based therapeutic approaches.

P-13-11

Proteomic analysis of co-cultured human pancreatic stellate cells and cancer cell-derived exosome cargo: novel insights into signalling pathways in pancreatic cancer

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Abstract

Background: Pancreatic stellate cells (PSCs) play a key role in pancreatic cancer (PC) by secreting factors that potentiate cancer progression. Exosomes (small extracellular vesicles of 40-160nm) are gaining attention as important elements in all stages of cancer. Given the known interactions between PSCs and PC cells, we hypothesised that co-culture of human PSCs and cancer cells results in secretion of exosomes containing unique proteins that specifically drive cancer progression and aimed to analyse the exosomal proteome.

Methods: Normal human PSCs (NhPSCs) and cancer-associated PSCs from PC patients (CAhPSCs) were cultured alone or with the pancreatic cancer cell line, AsPC1 (NhPSC+AsPC1 and CahPSC+AsPC1). Exosomes were isolated using ultracentrifugation and characterised by electron microscopy and immunoblotting. Proteomic profiles were determined by LC-MS/MS followed by Gene set enrichment analysis (GSEA) to identify specific pathways (FDR<0.01; n=3/group).

Results: Exosomes were within 40-160nm in size, exhibited a cup-shaped morphology and expressed exosome specific markers (ALIX/TSG101/CD9/81/Syntenin). As expected, AsPC1-exosomes expressed cancer-related proteins involved in signalling pathways (MAPK, SHH, TGFb, Wnt), cell adherence and ubiquitin-mediated proteolysis. Interestingly, in the presence of cancer-associated PSCs, co-culture (CahPSC+AsPC1) derived exosomes expressed unique proteins that mediate complement and coagulation cascades (complement 6, SERPINC1, Fibrinogen-γ, coagulation factor XI) that may be associated with hypercoagulability and thromboembolic status of PC. In the presence of normal hPSCs, co-culture derived (NhPSC+AsPC1) exosomes expressed unique proteins involved in Jak-STAT and

cytokine-cytokine receptor interaction pathways (IL-6, IL2RG), which may mediate the host's immune response to the developing cancer. When cultured alone, CAhPSC-derived exosomes exhibited upregulation of extracellular matrix proteins and stromal components (SERPINE1&2, Fibronectin and COL1A2), involved in the desmoplasia of PC, while NhPSC-derived exosomes were enriched in proteins related to the neuroactive-ligand receptor pathway and nociception (bradykinin, prostaglandin, endothelin), which may be associated with development of pain in PC.

Conclusion: We show for the first time that co-culture of human PSCs with human cancer cells (mimicking the clinical scenario of desmoplastic PC) results in the secretion of exosomes with unique protein signatures that may mediate pancreatic cancer associated complications such as coagulopathy and pain.

P-13-12

Molecular mechanisms of perineural invasion in pancreatic cancer

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Abstract

Background: Perineural invasion (PNI) is a key event for tumour dissemination, especially in pancreatic ductal adenocarcinoma (PDAC). During PNI, cancer cells invade nerves and migrate along them, establishing a microenvironment that promotes cancer growth and neural remodelling. PNI has a prevalence of up to 100% in PDAC, it is associated with early recurrence and poor prognosis, and, to date, there are no available therapies targeting it. We aim at exploring the molecular mechanisms governing PNI and at clarifying the reciprocal interactions between PDAC and nervous cells, with the purpose of developing new therapeutic approaches.

Methods: We exploited primary Schwann cells - Dorsal Root Ganglia neuronal co-cultures and K8484 PDAC cancer cells to characterize the crosstalk between nerves and pancreatic cancer cells. This model, crucial to replicate PNI *in vitro*, allowed us to characterize the reciprocal communication between PDAC cells and neurons. To evaluate these interactions and the involvement of PNI in tumour formation, we developed pancreatic spheroids from K8484 cells, orthotopically transplanted them in mice and followed tumour progression and dissemination.

Results: Our *in vitro* results showed that K8484 cells affect myelin stability both by paracrine signalling and direct interactions. We identified a cancer-derived factor as one of the molecules responsible for myelin degeneration. Indeed, both the inhibition of its downstream signalling in myelinated co-cultures and the ablation of its expression in cancer cells rescued the observed aberrations. This molecule is also expressed in human PDAC samples by cancer cells invading nerves. In addition, we performed *in vivo* experiments to characterize the role of this protein in tumour development, by deriving control and null spheroids from K8484 cells and orthotopically transplanting them in murine pancreata. Unlike mice transplanted with control spheroids, mice transplanted with null spheroids developed smaller tumours in absence of metastases. These results confirm the role of this protein in PDAC growth and spreading.

Conclusion: We analysed the interactions between PDAC cells and nerves and partially clarified the molecular mechanisms at the basis of PNI in PDAC. Moreover, we identified a promoter of tumour development and progression potentially becoming a new therapeutic target in PDAC patients.

P-13-13

Pancreatic proteases are mediators of pain in murine pancreatic cancer

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal tumours. In addition to the poor survivability, pain management predominately in later stages is often insufficient. Increased peripheral nociception is caused by classical nociceptive mediators e.g. CGRP or substance P, but also through activation of protease-activated receptors (PAR). However, the exact subtypes of proteases that mediate pancreatic pain are yet unknown.

Methods: We measured intrapancreatic protease levels to identify suitable targets for later selective inhibition to ameliorate pain. We generated tumours in mice through orthotopic transplantation of KPC cells (Ptf1a-Cre; LSL-KrasG12D/+; Trp53R172H/+) and also investigated the autochthonous KPC mouse model. We used abdominal Von-Frey Test (VFT) to detect the abdominal mechanosensitivty of the mice.

Results: Intrapancreatic protease levels in PDACs collected from orthotopic transplanted tumours and those from KPC-GEMM showed both similarly altered profiles compared to healthy controls. Cathepsin S showed a near 6-fold higher expression in tumour samples compared to healthy groups. Upon inhibition of cathepsin S using its specific inhibitor LY3000328, treated animals displayed significant lowered pain levels versus the control group. We isolated immune cells from the transplanted tumours and healthy pancreas and identified an increased number of macrophages in the tissue. Furthermore, we were able to show an elevated expression of CTSS-mRNA in sorted macrophages from tumour tissue compared to the healthy control.

Conclusion: The Inhibition of selective proteases, foremost cathepsin S, decreases significantly the pain levels of PDAC-bearing mice. This could lead to a new approach to the management of tumour-associated pain in pancreatic cancer.

P-13-15

Glutamine deficiency in pancreatic tumours confers vulnerability to ferroptosis via H3K4 trimethylation

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) characterised by poor vascularization and high interstitial pressure and has been found to be deficient in nutrients, espicially glutamine. How PDAC cells exposed to these glutamine-scarce tumour milieus exhibit metabolic flexibility to sustain growth and survival remains largely unknown.

Methods: To investigate the effects of glutamine starvation on epigenetic and transcriptional regulation, we performed RNA-seq, ATAC-seq and Cut&Tag for histone marks on PDAC under different metabolic stress conditions. Epigenetic-focused CRISPR-Cas9 screens were used to identify key epigenetic factors for metabolic stress adaption. Human PDAC cells as well as PDX tumours were used to validate our findings.

Results: Here, we showed that glutamine deprivation triggered cellular ferrous overload and lipid peroxidation, leading to ferroptosis susceptibility in PDAC cells. Mechanistically, we delineated the epigenetic redistribution and transcriptome alteration in response to glutamine restriction, and demonstrated that increased H3K4me3 in the promoter region contributed to the transcriptional activation of ferroptosis-related genes, both driver and repressor genes, implying a survival strategy for PDAC cells in the face of a glutamine-deficient tumour microenvironment. Furthermore, pharmacologic glutamine restriction could synergize with ferroptosis inducers to inhibit tumour growth both in vitro and in vivo.

Conclusion: Our findings suggest that glutamine deficiency in PDAC confers vulnerability to ferroptosis via H3K4me3 redistribution and revealed an innovative combination strategy for PDAC treatment.

P-13-16

Pancreatic cancer cells are addicted to expression of the PLAC8 mRNA, but not the encoded protein, for maintenance of genome integrity and cell viability

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Abstract

Background: We have previously shown that the *PLAC8* gene, which codes for an evolutionarily highly conserved small protein of 115 AA, is strongly ectopically expressed in pancreatic ductal adenocarcinoma (PDAC) as well as a subset of pancreatic neuroendocrine tumours (PanNET). Inhibition of *PLAC8* expression significantly impairs cell proliferation and viability in PDAC and PanNET cells. Here we show that the functional entity mediating the cell-intrinsic pro-tumourigenic effects is not the PLAC8 protein, but instead the *PLAC8* mRNA itself.

Results: CRISPR/Cas genome editing approaches aimed at complete abrogation of *PLAC8* mRNA expression (homologous repair templates with transcription termination elements) consistently failed to inactivate all *PLAC8* alleles in cancer cells, even in repeat rounds using different selectable markers. Clones deficient in producing the PLAC8 protein, however, were readily obtained (random indel mutations disrupting the *PLAC8* ORF following non-homologous end joining). Moreover, PLAC8 protein-deficient clones showed no differences in growth rates compared to parental cell lines, but strongly reacted to *PLAC8* mRNA knockdown, in particular to LNA GapmeR-mediated knockdown of nuclear-located *PLAC8* mRNA, with induction of massive DNA damage and growth inhibition. Nanopore sequencing identified several novel *PLAC8* splice isoforms, but recombinant expression of none of these isoforms was able to rescue the knockdown phenotype.

Conclusion: Our results strongly imply that the *PLAC8* mRNA i) functions similarly to a cis-acting long non-coding RNA; ii) has an important and non-redundant role in maintaining genomic integrity in pancreas cancer cells; and iii) functions completely independently of the encoded protein. To the best of our knowledge, both aspects (separate functions of mRNA and encoded protein, and a central role of an mRNA in maintaining genome stability) have not previously been described in any cellular context.

P-13-17

Sodium butyrate induces cell senescence in murine pancreatic intraepithelial neoplasia cells

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer-related death. Recent studies have shown that microbiota and their metabolites may alter PDAC progression. Preliminary data demonstrated a decrease of *Clostridiales_IS_XIII* and other genera during pancreatic carcinogenesis in K-Ras overexpressing mice with pancreatic intraepithelial neoplasia (PanIN) lesions (KC) and in mice with additional p53 inactivation developing invasive PDAC (KPC) compared to wild-type (Cre) mice. *Clostridiales_IS_XIII* are known to produce short-chain fatty acids (SCFAs), which may modulate tumourigenesis by inhibiting histone deacetylases, leading to cell cycle arrest, and apoptosis in various tumour cell types. However, little is known about the effects of SCFAs on early PDAC stages.

Methods: In this study, we investigated how SCFAs (particularly propionate, butyrate, and pentanoate) influence early pancreatic tumour development using two different murine PanIN cell lines, PanIN4994 and PanIN6585. We performed CellTiter-Glo® Cell Viability Assays (Promega, Germany), analysed morphological alterations and assessed different marker proteins by Western blot analysis.

Results: We observed a significant inhibitory effect of SCFAs on cell viability. In this regard, sodium butyrate (NaBut) showed the greatest effect on PanIN cell lines compared to the other two SCFAs tested. However, a pro-apoptotic effect via upregulation of cleaved PARP-1 signals was cell line-dependent. Furthermore, we demonstrated that NaBut treatment caused increased histone H3 acetylation and distinct morphological changes with increased cellular size, suggesting that NaBut induces senescence in both PanIN cell lines.

Conclusion: Our results indicate that microbiota-derived SCFAs might affect pancreatic cancer development through their growth-inhibitory and senescence-inducing effect. However, further studies need to be conducted to verify the findings.

P-13-18

Immune disbalance in peripheral blood mononuclear cells of pancreatic ductal adenocarcinoma patients is related to low expression of AhR

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Abstract

Background: PD-1/PD-L1 related immunotherapy in different cancers has shown unprecedented response rates, however it demonstrates failure in pancreatic ductal adenocarcinoma (PDAC). Post-transcriptional regulation may allow tumour cells to avoid immunosurveillance. We hypothesized that aryl hydrocarbon receptor (AhR) expression in pancreatic cancer patients could affect and/or reflect anticancer immunity functions. The aim of study was to identify the relation of AhR expression and immune response in peripheral blood mononuclear cells (PBMC) of

PDAC patients.

Methods: PBMCs from 20 patients with histologically confirmed diagnosis of PDAC and 20 healthy controls (HC) were obtained from venous blood and isolated by Ficoll-Paque gradient centrifugation. Expression of AhR, PD1, IL1b, IL4, IL6, IL10 genes mRNA was evaluated by qRT-PCR. Phagocytosis was measured after induced activation. Monocytes differentiation was evaluated by FACS analysis. Patients were divided into 3 groups according by AhR expression. Expression of AhR in High and Medium AhR groups did not differ significantly from HC. However, Low AhR group was significantly different.

Results: The expression of AhR strongly correlated with the expression of measured cytokines and PD1 receptor in PBMCs' from PDAC patients. AhR expression in PBMC's of PDAC patients was lower than in healthy controls. As well as expression of evaluated cytokines and PD1. The subgroup of PDAC patients with significantly lower AhR expression in PBMC's was identified. This Low AhR group of patients was further characterised by significantly lower expression of cytokines (IL1b, IL4, IL6, IL10) in PBMC's as well as low levels of PD1 expression. Moreover, Low AhR group demonstrated lower levels of relative monocyte count. In addition, the phagocytosis function of monocytes was significantly diminished in this particular subgroup of patients.

Conclusion: The immune response disbalance with regards of cytokine production, monocyte count and function as well as PD1 expression in PBMC's is related to low AhR gene expression. This might explain the checkpoint inhibitor treatment failure in particular subset of patients (low AhR expression group).

P-13-19

Metabolic characterisation of pancreatic juice in pancreatic cancer: a novel prognostic tool?

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Abstract

Background: Analysis of metabolites in body fluids revealed disease specific profiles in the context of different malignancies. Pancreatic Cancer (PC) cells undergo extensive metabolic rearrangement during the process of tumour progression. Previously we demonstrated how metabolomic analysis of pancreatic juice discriminated between PC and other pancreatic pathologies. The current analysis aims at identifying distinct metabolic profiles in pancreatic juice of PC associated to a distinct clinical behaviour.

Methods: All patients that underwent a surgical resection for PC at Humanitas Research Hospital were registered in a prospectively collected database. For scientific purpose, pancreatic Juice (PJ) was collected at time of surgery in a subgroup of patients between 2015-2019 included in the present study. PJ was analysed with high-resolution mass spectrometry. Pre-elaboration of raw mass data was conducted using MATLAB, including metabolic cluster analysis.

Results: Fifty-eight patients were included in the analysis. Three distinct metabolic clusters have been identified: Cluster 1 (C1), 2 (C2) and 3 (C3) including 22 (37.9%), 30 (51.7%) and 6 (10.3%) cases, respectively. Patients from the three different clusters were homogeneous in term of age (p=0.808), sex (p=0.750), BMI (p=0.828), preoperative Ca19.9 (p=0.458). Six (10%) of PC progressed from IPMN and 11(19.0%) patients underwent neoadjuvant therapy

(NAT), no difference was observed in metabolic profile between the groups (p=0.540 and p=0.510, respectively). C2 was associated to a lower rate of T3-4 tumours (C1: 50.0%, C2: 20.0%, C3:50.0%, p=0.056) and a lower rate of nodal metastases (C1: 90.9%, C2: 63.3%, C3:83.3%, p=0.065). No difference in prevalence of R1 margins (p=0.673), G3-4 tumours (p=0.642), perineural (p=0.226) and lymphovascular (p=0.258) invasion was observed. Regression analysis confirmed that C2 associates to a lower prevalence of T3-4 tumours (OR 0.17(0.03-0.88),p=0.035) and of nodal metastases (OR 0.25(0.07-0.85),p=0.026).

Conclusion: Metabolic clusters identified in pancreatic juice of PC patients are associated to well-known prognostic factors as T stage and nodal metastases. Further investigations are ongoing on PJ collected pre-operatively. Metabolic characterisation of PJ may help in the future prognostic stratification of pancreatic cancer.

P-13-20

Prognostic significance of AXL and role of the associated pathways in modulating proliferation and migration in pancreatic ductal adenocarcinoma (PDAC)

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Abstract

Background: PDAC remains one of the deadliest malignancies with an overall 5-year survival rate of only 10%. New biomarkers for early diagnosis and strategies to fight metastasis spreading are warranted. Although not implicated as an oncogenic driver itself, AXL upregulation has been linked to tumour proliferation, invasion and chemoresistance. In this context, we used warfarin, which blocks Gas6-mediated Axl activation and MYD1-72Fc, a decoy receptor with sub-picomolar affinity to GAS6, in *in vitro* and *in vivo* models of PDAC.

Methods: AXL prognostic value was first assessed in publicly available databases and then validated by immunohistochemistry (IHC) in tissue microarrays (TMAs) of two cohorts of radically-resected and liver-metastatic patients. The impact of warfarin and MYD1-72Fc on inhibition of cell growth and migration was studied with SRB, wound-healing and invasion assays. To evaluate the role of AXL on PDAC growth and liver metastases we used mouse orthotopic models of Firefly-transduced primary human PDAC cultures with differential AXL expression and metastatic behaviour.

Results: In PDAC tissues AXL levels are significantly higher than in normal pancreas and across several databases high AXL expression was associated with significantly shorter survival. This prognostic role was confirmed by the IHC performed in TMAs, showing a correlation between high levels of AXL expression and worse clinical outcome. Warfarin and MYD1-72Fc had limited cytotoxic activity but inhibited migration and invasion. The orthotopic models showed in vivo metastatic potential through lymph nodes and liver, as observed in patients. However, the PDAC1 primary culture, harbouring low levels of AXL-expression, had only limited metastases to the liver, while PDAC3 cells, which have high levels of AXL, created both large primary tumours, and numerous liver metastases. Treatment with MYD1-72Fc reduced the number of metastases, inducing tumour necrosis.

Conclusion: Through -omics and IHC, we identified the tyrosine-kinase receptor AXL as an enriched component in PDAC samples, with a prognostic role. We showed that AXL expression correlated with migration/invasion and metastasis in PDAC primary cultures and can be targeted by agents that act on the GAS6/AXL pathway. Collectively,

these findings suggest that AXL could constitute a future biomarker and target to be exploited in PDAC.

P-13-21

HFE H63D variant promotes epithelial to mesenchymal transition of pancreatic cancer in cell-cycle dependent manner

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) retains an unmodified ominous prognosis further darkened by its rising incidence. Although genetic background of PDAC has been increasingly elucidated, the actionability runs short.The common germ-line variant H63D, member of major histocompatibility complex, has been associated with an increased risk of PDAC, yet its role in disease development and progression is unexplored.

Methods: *HFE* genotyping of PDAC patients (trial set, 389; replication, 171; validation, 163; total, 723) plus interrogation of TCGA (110); genotype-phenotype correlations with clinical-pathological features and outcome. Functional studies of cellular and animal models obtained crossing PDAC-prone mice (with tissue-specific expression of mutated Kras) with hfe h67d (homolog) ones. Expression of mRNAs and proteins investigated in cellular models were validated in human PDAC specimens by immune -histochemistry or -fluorescence and Opal Multiplex Staining.

Results: *HFE* H63D was enriched in PDAC patients (29.4% vs 15% in population; p <0.001), due to its clustering in those with local disease, suit for surgery (38%). Such high prevalence was confirmed in replication (37.4%), validation (35%) and TCGA (29.1%) sets of resected PDAC. H63D patients had worse post-surgical survival than wild-type ones in trial (HR 1.7; p=0.03, and p=0.02 at multivariable), validation and TCGA dataset (all p<.05). PDAC mice bearing h67d had as well significantly shorter survival than hfe WT mice (p<0.004). Both human H63Dand animal h67d cancer cells showed superior invasiveness and extended lifecycle, sustained by increased expression of genes mastering epithelial to mesenchymal transition (EMT) and regulating G1-rest. Consistently, enhanced expression of EMT factors in G1-synchronized cells occurred only in H63D/h67d background. Back to human PDAC, the expression of EMT factor TWIST1 and of CyclinD1 was increased in H63D specimens, in which they co-localized in cancer glands.

Conclusion: Data unveil the role of H63D as disease modifier of PDAC progression. High chance of early diagnosis and surgery of H63D patients are compatible with elongated cell-cycle rest, sustaining local growth. In parallel, EMT enhancement plus unrecognized invasiveness would lead to the spread of cancer cells, their seeding explaining later progression. The capability to interfere with these mechanisms might alter the prognosis of a fraction of cases amenable of surgery, otherwise unsuccessful.

P-13-22

Impact of G9a and DNMT1 expression in pancreatic cancer survival: new potential epigenetic therapeutic strategy

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Abstract

Background: Pancreatic cancer (PC) is a devastating disease often detected at advanced stages when surgery cannot be performed. Conventional and targeted systemic therapies perform poorly, therefore effective drugs are urgently needed. Different epigenetic modifications occur in PC and contribute to malignancy, opening new therapeutic opportunities. In the present work we have evaluated the functional relevance of the epigenetic complex constituted by DNA methyltransferase 1 (DNMT1) and the histone methyltransferase G9a in PC, its implication in patient prognosis, and the in vitro and in vivo therapeutic efficacy of a first-in-class substrate-competitive dual G9a-DNMT1 inhibitor.

Methods: Expression of G9a and DNMT1 was determined by immunohistochemistry in ninety-one patients' surgical PC tissue samples. Correlations between expression levels and clinicopathological features and survival were analysed. Antitumoural efficacy of our dual G9a/DNMT1 inhibitor lead compound, CM272, was tested in human and mouse PC cell lines, alone and in combination with current standard chemotherapy. Transcriptomic studies on PC cells treated with CM272 were performed. Antitumoural activity and safety of CM272 were also evaluated in an orthotopic tumour model using murine DT6606 PC cells.

Results: G9a and DNMT1 proteins were significantly overexpressed in PC tissues compared to normal pancreatic tissues. There was a significant association of concomitant of DNMT1 and G9a expression with poor disease free and overall survival. All human and mouse PC cell lines showed high sensitivity to CM272. The epigenetic inhibitor significantly blunted neoplastic behaviour and sensitized PC cells to chemotherapy. Mechanistically, G9a/DNMT1 inhibition resulted in an enhanced antigen presentation, a significant upregulation of MHC class I expression and Th1-attracting chemokines, such as CXCL9, CXCL10 and CCL5, and a significant tumour cell cytotoxicity. CM272 treatment induced significant tumour regression in the orthotopic syngenic tumour model with increased apoptosis and infiltration of cytotoxic T lymphocytes.

Conclusion: All these data suggest that the epigenetic modifiers DNMT1 and G9a play an important role in PC aggressiveness. Their combined targeting with compounds such as CM272 can emerge as a promising strategy for PC treatment. Our findings also underscore the potential of CM272 in enhancing the efficacy of other systemic therapies, particularly in combination with immune checkpoint inhibitors.

P-13-23

Molecular characterisation of precursor lesions of pancreatic cancer and their microenvironment in KC and KPC mice

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is characterised by poor prognosis due to advanced disease at diagnosis. Pancreatic intraepithelial neoplasia (PanIN) is considered the most common PDAC precursor with ductal origin. Moreover, acinar-ductal metaplasia (ADM) and atypical flat lesions (AFL) have been suggested as alternative precursor lesions of acinar lineage. In order to improve clinical outcome, further characterisation of precursor lesions is crucial.

Methods: Cohorts of 15 KC and 15 KPC mice ranging from 1 to 7 months of age were used for the analyses. AFL, ADM, PanIN and PDAC areas were annotated and laser-microdissected by the Zeiss Palm MicroBeam Microdissection System. Next generation sequencing (NGS) was performed on the IonTorrent platform using a customized gene panel including 20 genes and the snakemake varlociraptor workflow for variant calling (https://doi.org/10.5281/zenodo.4675661).

Multiplex immunofluorescence according to the Opal Multiplex method was employed to characterize the microenvironment using the following markers: αSMA (activated stromal cells), CD8 (cytotoxic T-cells), F4/80 (macrophages) and FoxP3 (regulatory T-cells). Images were analysed using ImageJ. Statistical analysis was done with one-way ANOVA in GraphPad PRISM.

Micro-RNA expression for miRNA 21-5p was visualized by the miRNAScope Kit.

Results: In preliminary NGS results, AFLs had most frequently PTEN, ARID1a, RNF43 and SMAD4 mutated genes. AFL were surrounded by the highest amount of αSMA-positive fibrous tissue with significant differences ($p<0.05$) to normal tissue, ADM, PanIN and central PDAC areas in KC and KPC mice. Comparing immune cells per area, all analysed lesions showed significantly higher immune cell infiltration compared to the normal tissue.

AFL showed the highest proportion of immune cells normalized to area and whole cell count, with significant differences for CD8-positive cytotoxic T cells and F4/80-positive macrophages compared to normal tissue, ADM, PanIN, peripheral and central PDAC. This also applies for FoxP3-positive cells in KPC mice.

Lastly, all analysed lesions including AFLs and ADMs showed higher expression of miRNA21-5p compared to normal tissue.

Conclusion: Our study supports the thesis that AFL are unique PDAC precursor lesions of acinar lineage in KC and KPC mice, showing a distinctive microenvironment with higher levels of immune cell infiltration and stromal remodelling.

P-13-24

Expression of lysine demethylase 5a (Kdm5a) influences tumour aggressiveness in murine pancreatic cancer cells

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Abstract

Background: Lysine demethylase 5a (KDM5A) is a histone demethylase that specifically eliminates transcriptionally activating tri-methylation of lysine 4 of histone 3 (H3K4me3). KDM5A coordinates many crucial cell events, such as cellular senescence, cell cycle, cell motility and epithelial-to-mesenchymal transition (EMT), which are often deregulated in cancer. In own previous studies, we detected a loss of H3K4me3 modifications at pancreas differentiation genes with a concomitant increased expression of Kdm5a in murine pancreatic tumour lesions, indicating an oncogenic role for Kdm5a. Hence, we suppose that Kdm5a-driven removal of H3K4me3 at pancreas differentiation genes during tumour progression results in an undifferentiated, more aggressive phenotype.

Methods: The role of KDM5A in human pancreatic cancer was determined using in silico analysis. A knockout of *Kdm5a* (Kdm5a-KO) was generated in murine pancreatic tumour cells using the CRISPR/Cas9 system. The Kdm5a-KO was confirmed by sanger sequencing and immunoblot analysis. The Kdm5a-KO tumour cells were characterised phenotypically by cell assays determining colony formation, proliferation, migration, cell cycle and cancer stem cell potential. Transcriptional changes in Kdm5a-KO tumour cells were analysed by RNA sequencing.

Results: High expression of KDM5A in pancreatic cancer patient tissue was associated with shorter progression free intervals and worse overall survival. The top 100 positively correlated genes of KDM5A were linked with 'signalling pathways regulating pluripotency of stem cells', whereas negatively correlated genes were related to mitochondrial and respiratory regulations. Upon Kdm5a-KO, overall H3K4me3 levels were increased and Kdm5a-KO tumour cells showed significant reduction in proliferation, migration, colony formation and the expression of cancer stem cell markers CD24 and CD44 in comparison to control cells. Furthermore, Kdm5a-KO cells demonstrated a delayed escape from the G0 cell cycle phase after medium starvation.

Conclusion: Our data suppose that KDM5A induces cancer stem cell signalling pathways, while a loss of Kdm5a caused reduced abundance of cancer stem cell markers and a less aggressive phenotype of the murine pancreatic tumour cells. An overall enrichment of the activating histone modification H3K4me3 upon Kdm5a deletion suggests an epigenetic reprogramming towards a more differentiated phenotype.

P-13-25

Feedback inhibition relationship between AHR and ELAVL1 in pancreatic cancer in vitro

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Abstract

Background: The aryl hydrocarbon receptor (AHR) is a transcription factor that is commonly upregulated in pancreatic ductal adenocarcinoma (PDAC). AHR can block Human antigen R (ELAVL1) from shuttling from nucleus to cytoplasm where it stabilizes its target messenger RNAs (mRNAs) and increases protein expression of said mRNAs.

Among those target mRNAs are those induced by gemcitabine treatment. Frequently with upregulated AHR expression, ELAVL1 would be sequestered in the nucleus which would lead to increased chemoresistance, however the relationship between AHR and ELAVL1 in pancreatic cancer (PC) is still poorly understood. The aim of the study was to investigate the interaction of AHR and ELAVL1 genes and proteins in pathogenesis of PDAC.

Methods: Two PDAC cell lines were used (BxPC-3, Su.86.86). AHR and ELAVL1 genes were silenced for 24-hours by lipofectamine mediated siRNA transfection. After RNA and protein extraction, real-time polymerase chain reaction (RT-PCR) and Western Blot (WB) analysis were performed. Direct binding between ELAVL1 protein and AHR mRNA or protein was analysed by immunoprecipitation assay, RT-PCR and WB and template based protein-protein docking software - HDOCK.

Results: The results of immunoprecipitation assay showed that ELAVL1 protein binds AHR mRNA resulting in mRNA stabilization. Lipofectamine mediated small interfering RNA transfection showed that by silencing ELAVL1 expression, AHR mRNA and protein expression decreases proving that ELAVL1 modulates AHR expression through stabilizing its mRNA. That shows a direct link between these two molecules. Moreover, silencing of AHR resulted in the increase of ELAVL1 mRNA and protein expression. It indicates that AHR blocks ELAVL1 expression. Investigating protein-protein interaction of AHR and ELAVL1, HDOCK docking software with template-based modelling showed that the two proteins are likely to bind. Alternatively, our co-immunoprecipitation assay did not show direct binding of AHR and ELAVL1, leaving the question of protein-protein interaction unanswered.

Conclusion: Both AHR and ELAVL1 can modulate each other's expression and by inhibiting AHR expression it is possible to increase ELAVL1 expression which in turn might contribute to PC cells responding better to chemotherapy.

P-13-26

Pathological assessment of tertiary lymphoid structures in pancreatic cancer: development and validation of a novel haematoxylin-eosin based classification

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Abstract

Background: Although TNM staging is a well-established system, improvements to guide individualized patient care, especially in regards to immunotherapy, are sought. Recent studies pointed out tertiary lymphoid structures (TLS) to be a predictive biomarker for immunotherapy efficacy in many solid tumours; however, its role in pancreatic cancer (PCa) is still unknown. Our aim was to develop and validate a standardised scoring system for the quantification of TLS in PCa.

Methods: For validation purposes, we analysed the presence of TLS in a total of 114 patients with PCa from our institution (M-Cohort) and 151 patients from the publicly available TCGA database. Multiplex immunofluorescence was used to quantify the expression of the classical TLS-morphology markers (CD8, CD4, CD20, Ki67, PGP9.5 and PNAd) in 52 PCa patients in which TLS were analysed using our newly developed HE-based TLS-classification. Differential gene expression in patients with high numbers of late-stage TLS was analysed using bulk RNA sequencing in fresh frozen PCa samples (n=24).

Results: TLS maturation stages are characterised based on morphological criteria: (i) round dense lymphocytic aggregation and (ii) sharp delineation edges for early TLS (E-TLS); primary follicular TLS (PF-TLS) present in addition high endothelial venules and/or a nerve in the immediate vicinity. Secondary follicular TLS (SF-TLS) contain B-cell follicles with actively replicating B-cell germinal centres (GCs) surrounded by a T-cell region. SF-TLS were present in 41% of primary resected patients and correlated with improved survival (M-Cohort: 22 vs. 10 months, p=0.001; TCGA Cohort: 19 vs. 10 months, p=0.043). In the tumour microenvironment, the presence of late-stage TLS correlated with increased numbers of B cells and massively reduced amounts of M2 macrophages. Lastly, bulk RNA-seq analysis of PCa samples demonstrated an upregulation of antigen presentation and pathways related to immune responses in patients with high numbers of SF-TLS in the tumour microenvironment.

Conclusion: Late-stage TLS are associated with prolonged survival in PCa patients and might serve as a potential predictor for immune activity within the pancreatic tumour microenvironment.

P-13-27

Stratification of PDAC patients based on their tumoural multiomics prognostic profiles

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Abstract

Background: During the last years, a plethora of cancer-specific data were generated by high-throughput biotechnological platforms, facilitating the investigation of cancer biology and classification of patients. Pancreatic ductal adenocarcinoma (PDAC), a low incident tumour with a high mortality rate, mainly due to late detection, would benefit greatly from data resources. Although great efforts have been done in defining PDAC prognosis, the majority of the studies have used unimodal data approaches, missing the opportunity of integrating data of different nature. Here we show a multimodal data integration of tumour gene expression (mRNAcount), mutation (DNAmut), and microbiome (TMic) to stratify patients based on their overall survival (OS).

Methods: We used the resources of TCGA study, including 138 PDAC cases with mRNAcount and DNAmut data. TMic at the order level was obtained with the bioinformatics tool kraken2. Pre-processing procedures including filtering out the low prevalence features, batch effect correction and normalization when needed, were performed for each omics type. After computing a separate similarity matrix for each omics data, a Bayesian multikernel based regression was applied to integrate the three omics data as predictors of OS.

Results: The three omics explained >50% of the total variance of OS. In particular, mRNAcount and DNAmut explained the largest percentage of variance (~21% each) and TMic explained the lowest proportion (~8%). Scores based on mRNAcount and DNAmut or TMic were positively correlated (ρ=0.43 and 0.28), whereas no correlation between DNAmut and TMic based scores was observed. After applying a backsolving strategy to rank the omics features based on the scaled absolute value of their effect estimates, we observed that 14/20 first twenty features were mRNAcount and the rest were DNAmut. Six out of 42 GO biological processes enriched with the top mRNAcount were related to the immune response. Three of the top genes (LYZ, OLFM4 and DMBT1) were markers of the classical subtype, and others such as PRSS1 and REG1A, had a role in the exocrine pancreas or have been previously identified as a contributor in PDAC pathology (i.e., MUC5AC).

We plan to validate these findings with other PDAC studies including ICGC and PanGenEU.

P-13-28

The PSCA-rs2976395 functional variant is associated with pancreatic cancer development

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Abstract

Background: Only a very limited proportion of pancreatic ductal adenocarcinoma (PDAC) heritability has been determined, indicating that many more loci need to be discovered. Functional annotation of Genome wide association studies (GWAS) polymorphisms is a proven strategy to identify additional loci. In addition to environmental and genetic components, also epigenetics plays a role in PDAC development. However, DNA methylation is tissue- specific and changes over time, which makes impractical to analyse it in an epidemiologic setting. Correlated Regions of Systemic Interindividual Variation (CoRSIV) represent a small proportion of the human genome, showing methylation patterns that are the same in all human tissues and are different among individuals. In this study we aimed at investigating single nucleotide polymorphisms (SNPs) within CoRSIVs and their involvement with PDAC risk.

Methods: We analysed 29,099 SNPs in 12,355 cases and 214,430 controls of European descent. In particular, we used the Pancreatic Cancer Cohort Consortium (PanScan) I-III and the Pancreatic Cancer Case-Control Consortium (PanC4) GWAS data (8738 cases and 7034 controls) and the FinnGen project (881 cases and 204,070 controls) as discovery phase and the PANcreatic Disease ReseArch (PANDoRA) consortium as replication phase (2,736 cases and 3135 controls). The rs2976395 SNP was selected for the replication. Furthermore, a meta-analysis was performed between the two phases.

Results: We observed that the A allele of the rs2976395 SNP was associated with increased PDAC risk in Europeans ($p=2.81x10^{-5}$). This SNP is located in the Prostate Stem Cell Antigen (PSCA) gene and is in perfect linkage disequilibrium with a variant (rs2294008) that has been reported to be associated with risk of many other cancer types. The A allele increases the methylation level of the gene, the expression of which is been observed to be deregulated in many tumours of the gastrointestinal tract.

Conclusion: In conclusion, we propose a novel association for PDACC through a functional SNP that regulates the methylation in a CoRSIV region.

P-13-29

Expression of Irf3 and Irf7 in tumour cells drives pancreatic cancer development and progression

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Abstract

Background: The interferon regulatory factors 3 and 7 (Irf3 and Irf7) are transcription factors downstream of the Toll-like receptor 3 (Tlr3) signalling pathway. Tlr3 signalling is stimulated by double-stranded RNAs, which are generated during viral infections but also during tissue stress and cell injury. In previous studies, we found Tlr3, Irf3, and Irf7 to be overexpressed in metaplastic acinar cells and pancreatic tumour cells. The purpose of this project is to investigate the functional role of Irf3 and Irf7 in pancreatic carcinogenesis, particularly in non-immune cells.

Methods: Pancreatic tumourigenesis was examined at various time points in caerulein-treated Irf3/Irf7 knockout mice with inducible Kras mutation. Furthermore, we generated Tlr3-hyperactivated and Irf3/Irf7 double knockout murine pancreatic tumour cells. These tumour cells were phenotypically characterised in vitro and further used in orthotopic and metastatic mouse models. Additionally, we identified transcriptional alterations in Irf3/Irf7 knockout tumour cells by RNA-Seq.

Results: Global loss of Irf3/Irf7 prevents the formation of precursor lesions and pancreatic cancer in caerulein-treated Kras mutant mice. Consequently, depletion of Irf3 and Irf7 in tumour cells leads to reduced invasive capacity and decreased colony formation in vitro. In the orthotopic and metastatic mouse models, injection of Irf3/Irf7 knockout cells markedly impaired tumour and metastasis formation, whereas Tlr3-hyperactivated cells led to increased tumour and metastasis volumes. Our in vivo and in vitro experiments confirmed an immune-independent function of the Tlr3/Irf3/Irf7 signalling pathway in pancreatic tumour cells that is crucial for tumour progression.

Conclusion: Our findings suggest that Irf3 and Irf7 expression in tumour cells is required for the development of pancreatic cancer. Moreover, activated Tlr3/Irf3/Irf7 signalling enhances tumour cell aggressiveness in pancreatic cancer cells.

P-13-30

Physical activity and pancreatic cancer risk: a Mendelian randomization study

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Abstract

Background: Understanding whether modifiable factors increase or decrease the risk of developing pancreatic ductal adenocarcinoma (PDAC) is central for disease prevention. Several epidemiological studies have described the benefits of physical activity and the risks associated with sedentary behaviour, in relation to cancer. However, observational studies may be affected by confounding or other types of bias, thus preventing the identification of true causal relationships. Mendelian randomization is a technique for inferring causal relationships between variables using genetic data.

The aim of this work was to identify the potential causal effects of physical activity and sedentary behaviour on PDAC risk, and the possible involvement of BMI as a mediating factor, by using Mendelian randomization.

Methods: A two-sample Mendelian randomization approach was applied using publicly available data for genetic

variants associated with physical activity and sedentary behaviour traits, and genetic data on 8,769 PDAC cases and 7,055 controls from the Pancreatic Cancer Cohort Consortium (PanScan) and the Pancreatic Cancer Case-Control Consortium (PanC4), and on 1,249 cases and 259,583 controls from the FinnGen study. Summary-level genetic data for BMI were obtained from the GIANT consortium.

Results: An association between genetically determined hours spent watching television and an increased risk of developing PDAC was observed in both study samples (PanScan-PanC4 OR = 1.52, 95% CI = 1.17-1.98, p = 0.002 and FinnGen OR = 1.84, 95% CI = 1.19-2.85, p = 0.006). In addition, mediation analyses using PanScan-PC4 provided evidence for a role of BMI in mediating an estimated 54% (95% CI 36%-71%) of the effect of television watching time on pancreatic cancer risk.

Conclusion: This is the first Mendelian randomization-based evidence for an association between a measure of sedentary behaviour (television watching time) and the risk of developing PDAC. However, such association was substantially mediated by the indirect increase in BMI, which is a well-known PDAC risk factor. In terms of prevention, these results clearly suggest that interventions on television watching time may be effective in reducing PDAC risk only if reducing also BMI.

P-13-31

Biological role of acid sphingomyelinase for pancreatic carcinogenesis

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Abstract

Background: Sphingolipids, including the two central bioactive lipids, ceramide, and sphingosine-1-phosphate (S1P), have opposing roles in regulating cancer cell death and survival. Acid sphingomyelinase (Smpd1) is the key enzyme that hydrolyses sphingomyelin to ceramide and is responsible for more than 50% of the cellular ceramide pool affecting carcinogenesis. Here, we studied the role of SMPD1 in different cellular compartments during pancreatic ductal adenocarcinoma (PDAC) carcinogenesis.

Methods: We performed targeted quantitative plasma metabolite analysis from 637 patients (PDAC, 356; non-pancreatic disease, 281). We completed IHC multiplex staining in TMAs of 124 PDAC patients. Using CRISPR-Cas9 gene editing *SMPD1* was deleted in PDAC cell lines. The influence of *SMPD1*-KO was studied for proliferation, colony formation and migration. Tumour progression and carcinogenesis was monitored in an orthotopic PDAC model employing SMPD1 null cells as well as in KC and KPC mice.

Results: Plasma metabolite analysis from 637 patients (PDAC, 356; non-pancreatic disease, 281) revealed most pronounced changes in the group of complex lipids with the highest prevalence of sphingomyelins and ceramides. Overall survival correlated significantly with high SMPD1 expression in tumour tissue in two independent cohorts. Interestingly, IHC multiplex analysis SMPD1 “high expression” in cancer cells was associated with poorer survival, while SMPD1 “high expression” in immune cells was associated with longer overall survival. Smpd1 expression level differed from preneoplastic to neoplastic lesions in PDAC mouse tissue. *Smpd1*-KO in PDAC cell lines resulted in decreased proliferation, colony formation and migration. In an orthotopic mouse model, *Smpd1*-KO clones resulted in significantly lower tumour weight and size in comparison with WT-clones. Additionally, injecting WT-clones in global *Smpd1*^{het}-KO mice resulted in a significant increase in tumour weight in comparison with injecting WT-clones in WT

mice. In a tail vein injection model, injecting *Smpd1*-KO led to significantly reduced metastasis formation in the lung in comparison with WT-clones. Overall, we show a significant increase in survival in an orthotopic PDAC model using PDAC *Smpd1*-KO cells.

Conclusion: SMPD1 acts as a tumour suppressor in pancreatic carcinogenesis in the cellular context. Inhibiting SMPD1 specifically in cancer cells is a viable therapeutic option, which should be explored in future studies.

P-13-33

Results of the first investigation about the understanding and engagement at time of diagnosis of patients with pancreatic cancer: the Communi.CARE study

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Abstract

Background: Pancreatic adenocarcinoma (PDAC) is an aggressive disease. Communication and understanding of treatment plan are of paramount importance. This is the first attempt to measure clarity of communication and understanding at time of PDAC diagnosis and whether they can influence patients' engagement and compliance.

Methods: Consecutive PDAC patients were enrolled at diagnosis upon informed consent in a single-centre study. During the visit conducted by a physician, patients filled-in a validated scale (Patient Health Engagement Scale; PHE-s®, 7 items, score 1-4; score≥3 considered high engagement). The visit audio was recorded and evaluated to assess understanding rate. Patients were proposed appropriate standard treatments and defined compliant if accepted. Within three days from visit, patients were interviewed to correlate results of the analysis with patients' own perception. Finally, the correlation between PHE-s® and understanding and compliance was calculated.

Results: Thirty patients were enrolled (15 female, mean age 64.4, 13 metastatic, 22 from north of Italy, 8 from centre/south, 14 by an oncologist, 14 by a gastroenterologist, and 2 by a surgeon). The mean recording time was 31 minutes (95%CI 26.9-35.4); mean duration longer in oncology visits vs gastroenterology or surgery (39 vs 25; p=0.002). The mean engagement level was 2.93/4. The qualitative analysis of the doctor-patient interactions showed limited questions (total 320; most (215) from doctors, 79 from patients and 26 of caregivers). Most questions from patients and caregivers occurred during the discussion of future treatment (59/105); there were 19 questions related to misunderstandings by doctors, 25 by patients and 7 by caregivers. Only 1 patient declared to be aware of the occurred misunderstandings and all but 2 were compliant, thus the correlation between compliance and PHE-s® was unfeasible. In a multivariate logistic regression analysis, sex, age, educational status, doctors' specialty, visit duration, number of questions and misunderstandings were not associated with high engagement, but only origin from south of Italy was (OR=18; p=0.0087). Visit duration, number of questions and misunderstanding episodes were not correlated with PHE-s® (Rank correlation test ns).

Conclusion: None of the investigated variables explained the variability in engagement but for origin of the patient.

P-13-34

An in ovo model to study tumour morphogenesis and metastatic dissemination of PDAC

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is expected to be the second most common cause of cancer related deaths in the United States by the year 2040. Despite extensive progress in understanding the genetic and molecular mechanisms of the disease, the clinical outcome has not improved in the last decade demanding the search for novel prognostic markers and therapeutic strategies. For such studies, scalable, cost-effective model systems that mimic the complex tumour biology harbor predictive value for the clinic.

Methods: We employed chick embryo chorioallantoic membrane (CAM) to study PDAC biology using murine PDAC cells and patient-derived organoids (PDOs). We performed histological analyses to characterize tumour engraftment, growth and histology, including characterisation of the tumour stroma, on CAM xenografts. In addition, we performed tumour bud quantification on CAM xenografts to determine the invasiveness of the PDAC tumour cells. Spontaneous metastatic dissemination to the chick embryo organs were quantified by species specific quantitative PCR (qPCR).

Results: We successfully developed CAM xenografts of phenotypically and genetically diverse murine PDAC cell lines and PDOs. CAM xenografts recapitulated the histomorphological features of the primary tumours. Importantly, quantification of invasion and metastases of murine cells and PDOs is highly reproducible and, at the same time, displays significant differences between the lines indicating heterogeneous metastatic capabilities. In addition, extra-cellular matrix deposition and the stromal recruitment was observed in the primary tumours which correlated to the invasiveness and metastatic potential of the murine PDAC cell lines and PDOs.

Conclusion: CAM model provides a scalable personalised oncology platform to study functionally PDAC tumour biology. In the future, we will further exploit this model to study the subpopulations of the stroma and its influence in invasion and metastatic dissemination. We will also use the model to study the impact of PDAC driver gene mutations in recruiting CAF subpopulations and early metastatic dissemination. In summary, with the CAM assay, we aim to answer fundamental questions in the metastatic cascade of PDAC to improve patient outcomes.

P-13-35

Splicing regulation as a new potential prognostic tool for personalised medicine in PDAC

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Abstract

Background: Late diagnosis, high genetic and phenotypic heterogeneity and lack of efficacious targeted therapies contribute to the extremely poor prognosis of pancreatic ductal adenocarcinoma (PDAC). To date, surgical resection remains the most curative approach for PDAC. Whole genome transcriptomic studies have uncovered the existence of distinct PDAC subtypes, which were shown to display different prognosis and response to treatments, but unfortunately this classification has not led to proportional improvement in the development of targeted therapies. A recent improvement in oncological research has been provided by the development of Patient-Derived Organoids (PDO), 3D primary cultures that maintain most of the genotypic and phenotypic features of the original tumour and represent a valuable tool for drug screening. Furthermore, it was demonstrated how the reduced efficiency and fidelity of the splicing process in cancer cells is an interesting and targetable vulnerability. Our aim is to identify splicing-related targets in basal-like and classical PDAC patients that affect the responsiveness to existing and novel therapies.

Methods: The current project employed bioinformatic analyses of public datasets and RT-PCR analyses of RNA extracted from Endoscopic Ultrasound (EUS) guided tissue acquisition (TA) diagnostic PDAC biopsies, and Rna-seq analysis on PDAC cell lines.

Results: We identified a pattern of splicing isoforms that is able to discriminate the two canonical Classical and Basal-like PDAC subtypes. Interestingly, some of these splicing isoforms displayed high prognostic value in the whole cohort of PDAC patients. RT-PCR analyses of EUS-TA biopsies and PDOs of PDAC patients with a follow-up > 12 months confirmed their prognostic value in an independent cohort. Next, among the RNA Binding Proteins (RBPs) involved in the regulation of the subtype-specific splicing we identify QUAKING as a main determinant (with high prognostic value) of the basal-like splicing signature in both unselected PDAC patients and in PDAC cell lines, by controlling a pro-mesenchymal splicing program in basal-like PDAC.

Conclusion: Our data suggest that splicing isoforms represent new biomarkers of PDAC subtypes with potential prognostic value and indicates that splicing regulation is a key hallmark of PDAC, with potential implications for disease outcome.

P-13-36

Inverse correlation of abundance of sphingomyelins with length of associated N-acyl fatty acid chain contributes to pathogenesis of pancreatic cancer

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Abstract

Background: We recently conducted employing metabolomics, a large study to identify a biomarker signature distinguishing PDAC from chronic pancreatitis and identified 9 metabolites, which was used in conjunction with CA19-9 to detect PDAC with a much higher diagnostic accuracy than CA19-9 alone. This targeted unsupervised analysis suggested sphingolipids independent of tumour burden to be the best discriminating group of metabolites. Plasma membrane levels of Sphingolipids maintain the intricate balance between signal transduction and membrane biophysics through the changes in lipid membrane composition as a result of the sphingomyelins (SM) pathway. Though there is considerable research progress on sphingolipid physiology, there is little to no evidence on the role of sphingolipids during carcinogenesis.

Methods: We performed sub-analysis on patients with PDAC, chronic pancreatitis, liver cirrhosis, healthy blood donors and pre-operative patients with non-pancreatic diseases (n=914). Total lipids were extracted from plasma by liquid/liquid extraction using chloroform/methanol. The lipid extracts were subsequently fractionated by normal phase liquid chromatography into 11 different lipid groups using Gas chromatography-mass spectrometry (GC-MS), liquid chromatography–MS/MS (LC–MS/MS), and solid-phase extraction-LC-MS/MS (SPE-LC–MS/MS).

Results: Metabolome analysis focusing on SMs revealed an inverse correlation of fatty acid chain length of SMs within each sphingosine base moiety comparing PDAC patients and blood donors. This correlation was only apparent in saturated fatty acid chains while mono-and polyunsaturated fatty acids failed to show a correlation. Interestingly, fatty acids derived from fatty acid synthase (FASN) in cytoplasm or taken up by through diet were not affected, whereas endoplasmic reticulum localized Fatty acid Elongases (ELOVLs) derived fatty acids showed inverse correlation. When compared to chronic pancreatitis, we observed no statistically significant correlation with regard to chain length.

Conclusion: This points towards the crucial influence of de novo synthesis of SMs taking place in the ER and driven by ELOVLs, as a driving force in carcinogenesis. Comparison of chronic pancreatitis, as a benign systemic inflammatory condition, revealed tumour dependent effect, excluding inflammation as the cause of dysregulated SM metabolism.

P-13-37

Understanding the cellular mechanisms of cell death in pancreatic cancer models following irreversible electroporation and calcium combination therapy

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is an aggressive cancer with a 5-year survival of 9%. Irreversible Electroporation (IRE) is a novel, non-thermal ablative therapy thought to cause cell death by increasing cell membrane potential and forming nanopores. Prior studies suggest mitochondrial changes drive apoptosis with calcium being implicated. Preliminary evidence supports apoptosis as the mechanism of IRE-induced cell death, though this is unclear. We aimed to investigate the impact of combining IRE and calcium on pancreatic cancer in 2D and 3D models of pancreatic cancer cell lines and the underlying molecular mechanisms.

Methods: PANC-1 and PDX 185 (patient-derived xenograft) cells were exposed to calcium, IRE or both. Cells were electroporated in 4mm cuvettes with a BTX generator (Harvard Apparatus). The effects of the treatment on cell viability, cell proliferation, cell death and mitochondrial membrane potential were evaluated by flow cytometry (treated with TMRE staining) and Western blotting at 6-hours and 24-hours post-treatment. Results were validated using 3D models, where PDX 185 cells were grown as spheroids and electroporated as above.

Results: IRE combined with calcium was more cytotoxic than monotherapy with cell proliferation assays demonstrating a statistically significant reduction in proliferation ($p<0.0001$) across both models of pancreatic cancer. Interestingly, only cells exposed to both IRE and calcium showed depolarisation of mitochondria and loss of mitochondrial membrane potential. There was a higher expression of pro-apoptotic proteins in the combination therapy group compared to monotherapies at both time points.

Conclusion: Combining calcium with IRE appears to potentiate cell death in pancreatic cancer models through depolarising the mitochondrial membrane. The observed higher expression of apoptotic proteins in combination therapy suggests a beneficial synergistic effect. The immediate treatment effect is evident by markedly higher protein levels at 6-hours than 24-hours post-treatment. These results support the potential of the combination therapy in inducing apoptosis in pancreatic cancer cell lines. Further investigations will analyse additional pro- and anti-apoptotic proteins to investigate the pathways inducing sensitivity to this therapy.

P-13-38

Inflammatory landscape after neoadjuvant chemotherapy in pancreatic ductal adenocarcinoma

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Abstract

Background: Pancreatic Ductal Adenocarcinomas (PDACs) are characterised by a high mortality rate and a lack of effectiveness of therapies. The tumour microenvironment (TME) is believed to be responsible, at least in part, for the resistance to conventional therapies, like chemotherapy. Thus, an accurate assessment of TME could be useful for the development of effective therapeutic strategies.

The aim of the study is to investigate the immune landscape of PDACs and the composition and distribution of the immune and inflammatory infiltrate in PDACs, comparing patients who received neoadjuvant chemotherapy followed by resection and patients who underwent upfront surgery at first.

Methods: A total of 81 cases were analysed: 65 cases of patients who underwent upfront surgery and 16 cases who received chemotherapy as a first line treatment, instead. The specimens underwent a histopathologic, immunohistochemical (IHC) and molecular characterisation to evaluate: grading, Tumour Infiltrating Lymphocytes (TILs), Tumour Associated Macrophages (TAMs), extracellular matrix and PD-L1 expression.

Results: The majority of the infiltrate was concentrated in the intra and peritumoural area, therefore it was the most inflamed compartment. The analysis found out that the majority (45.5%) were PD-L1+/TILs+ in both groups and no statistically relevant differences were pointed out concerning the inflammatory infiltrate, the extracellular matrix and PD-L1 expression.

Conclusion: Chemotherapy does not seem to impact on PD-L1 status and inflammatory infiltrate, which could play a predictive role in the response to immunotherapy. Considering that biopsy is performed only in third level structures and that the majority of our cases were “hot” in terms of infiltrate (PD-L1+/TILs+), a possible therapeutic strategy could be immunotherapy in doublets or in addition to chemotherapy as a first line treatment in patients with locally advanced or metastatic PDACs.

P-13-39

PLAC8 is associated with the classical subtype and regulates EMT in pancreatic ductal adenocarcinoma

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Abstract

Background: Placenta-associated 8 (PLAC8) is a small protein initially described as a ‘cooperation response gene’ for mutant p53 and Ras proteins. Although previous studies described a role in epithelial tumourigenesis, its function seems to be variable and context-dependent. Here, we studied its role in PDAC tumourigenesis.

Methods: We analysed its expression in different stages of pancreatic ductal adenocarcinoma (PDAC) development and found that PLAC8 exhibited a low expression in normal pancreas, moderate in preneoplastic lesions and high in PDAC suggesting a prominent role in PDAC formation.

Results: We found that in PDAC, PLAC8 expression is significantly associated with the "classical" subtype (p=8.3e-09) and correlated with the classical biomarker GATA6 (r=0.34; p=5.3e-08) and GATA4 (r=0.24; p=0.00011), linked to a better prognosis.

Interestingly, PLAC8 expression was significantly lower in PDAC metastasis vs primary tumour (p=0.0092) in a similar fashion than the classical surrogates GATA6 or GATA4. In the metastatic setting, PLAC8 exhibited a higher correlation with classical surrogates than in primary tumour GATA6 (r= 0.57; p = 9.4e-07 vs r = 0.23; p = 0.0021) or GATA4 (r = 0.31, p = 0.013 vs r = 0.22, p = 0.0036).

Importantly, GSEA analysis showed that epithelial-mesenchymal transition (EMT) signature associated with oncogenesis is significantly enriched in low vs high PLAC8 expression (Norm p-value<0.05, FDR<0.25).

To study the direct role of PLAC8 in EMT, we generated PLAC8 knock-out by 2 sgRNA CRISPR/Cas9 in a panel of human pancreatic cancer cell lines. We performed functional migration studies by analysing Transwell™ cell migration. We found that PLAC8 loss-of-function significantly promoted cell migration (p<0.001) and EMT markers ZEB-1 and N-cadherin were upregulated in KO cell lines. Importantly, these effects were rescued by ectopically expressing CRISPR-resistant GFP-fused versions of the protein on the KO cell lines.

Interestingly, PLAC8 loss-of-function increased the resistance to state-of-the-art adjuvant therapies FOLFIRINOX and Gemcitabine in accordance with published data.

When analysing the regulation of PLAC8 expression, ATAC-seq data showed that Krüppel-like factor 4 (KLF4) was a prospective target significantly correlated with PLAC8 (r=0.37, p=2.4e-09).

Conclusion: PLAC8 expression is associated with the classical subtype program and its downregulation is linked with PDAC metastatic features.

P-13-40

Do surgical tumour resection and chemotherapy lead to liver inflammation and outgrowth of liver metastases? Insights from a clinically adapted pancreatic cancer mouse model

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is an aggressive disease with a poor prognosis. Surgery is the only curative treatment option. However, even patients with surgical removal of the primary tumour followed by adjuvant chemotherapy (e.g. Gemcitabine) often relapse with liver metastases. Elevated blood levels of inflammatory mediators were already detected in PDAC patients after tumour resection. However, whether surgery and chemotherapy directly impact the liver microenvironment thereby promoting outgrowth of liver metastases is still poorly understood. Therefore, this study aimed to investigate the therapy induced effects on inflammation and metastases formation in the liver using a clinically adapted PDAC mouse model.

Methods: C57Bl6 mice were orthotopically inoculated with R252 pancreatic cancer cells. After two weeks, animals were randomised and underwent the following treatment: NaCl/-, NaCl/surgery of primary tumour, Gemcitabine/- or Gemcitabine/surgery of primary tumour. As control, pancreatic surgery was performed in non-tumour bearing animals. Liver and lungs were taken at an early and late treatment time point. Additionally, inflammatory mediators were determined in liver and lungs of healthy mice. The inflammatory status of the liver was assessed by a multiparameter analysis and ELISA using homogenized liver tissue samples.

Results: Basal levels of several inflammatory cytokines such as IL-6, IL-10 and TNF-α were higher in the liver than in the lungs of healthy animals, while VEGF levels were lower in the liver than in the lungs.

Surgery particularly increased VEGF levels in the liver but not in the lung of tumour resected mice compared to control treated tumour bearing mice. This effect was not further increased by adjuvant Gemcitabine treatment and was also observed after surgery in the absence of a tumour. In contrast, Gemcitabine alone did not cause elevation of VEGF in the liver.

Conclusion: Our findings suggest that surgery leads to elevation of inflammatory mediators and VEGF in the liver but not in the lung providing an explanation for the frequent outgrowth of liver metastases after surgery of primary PDAC. Ongoing studies use mass spectrometry and qPCR analysis to substantiate these findings and correlate inflammatory mediators with the extent of liver metastasis.

P-13-41

The role of platelet-induced LGALS1 expression of pancreatic cancer cells in anoikis resistance

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Abstract

Background: Thrombocytosis is present in more than 30% of patients with solid malignancies and correlates with worsened patient survival. In addition, occurrence of distant metastases reduce pancreatic cancer patient survival significantly. A prerequisite for circulating tumour cells (CTC) to ultimately contribute to haematogenous dissemination and to survive in the blood stream is anoikis resistance. It has been shown that platelets interact with CTCs to protect them from cytokine and immune cell-mediated cell death. However, little is known about the transcriptional and post-transcriptional changes in detached pancreatic cancer cells upon platelet co-incubation.

Methods: In this study, we cultured pancreatic cancer cells in adherent and non-adherent conditions with or without platelets *in vitro* and measured anoikis rates using flow cytometry. In addition, we analysed transcriptional changes of attached and detached cells using RNASeq and compared gene expression changes to detached cells co-cultured with platelets

Results: As expected, detached human pancreatic cancer cells showed significantly higher anoikis rates compared to cells that grow under attached conditions. Interestingly, this high cellular apoptosis rate was strongly reduced by platelet co-culture. We identified galectin-1 (LGALS1) as an important differentially regulated gene between attached and detached human pancreatic cancer cells. Specifically, LGALS1 was downregulated in cancer cells under detached conditions, however, was strongly increased by platelet co-culture. Preliminary experiments show that a reduction of LGALS1 in cancer cells using siRNAs alleviates platelet-mediated anoikis resistance

Conclusion: Collectively, our results indicate that cancer cells depend on platelets to avoid anoikis-mediated cell death, which is crucial to succeed in the metastatic process. Upregulation of LGALS1 by platelets might be an important cell-intrinsic mechanism to control anoikis resistance. In addition, LGALS1 can also be secreted by cancer cells and thereby influence other components of the tumour microenvironment, including immune cells, that can contribute to tumour progression and metastasis.

P-13-42

Examining the effects of cytidine deaminase in pancreatic ductal adenocarcinoma cell lines and relation to gemcitabine and capecitabine efficacy

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Abstract

Background: Combination chemotherapy with Gemcitabine and Capecitabine (GemCap) is commonly used in both adjuvant and palliative settings. Cytidine deaminase (CDA) is involved in the metabolism of both gemcitabine and capecitabine. We have previously shown that the human equilibrative nucleoside transporter (hENT1) is only predictive of gemcitabine benefit in cells with low levels of CDA RNA (Aughton. Cancers. 2021. 13(22):5758). It is unclear what regulates CDA RNA and protein levels within cells.

Methods: CDA expression in pancreas cancer cell lines was analysed using Western blotting and quantitative Reverse-Transcription PCR. Inducibility was assessed after gemcitabine and cytidine treatment of cell lines. MTS assay analysis was used to assess dose responses and synergy between gemcitabine and dFUR using R. siRNA transfection was used to knockdown CDA. CDA expression in ESPAC-4 trial samples were analysed using immunohistochemistry and RNAScope.

Results: CDA protein and RNA expression is highly variable across cell lines. In cell lines expressing CDA, it is further inducible with gemcitabine or cytidine. Cell lines with low baseline protein had low RNA levels. In clinical samples, there was weak or no relationship between RNA and protein levels. In cell lines where CDA was knocked down, dFUR was antagonistic compared to wild-type cell lines. Some evidence of synergy at higher concentrations of gemcitabine was seen in wild-type cell lines. Variation in dose responses exists between wild-type and CDA knockdown.

Conclusion: CDA levels are determined by genetic background and protein is proportional to RNA levels at baseline, but levels can be induced by external nucleosides giving protein levels that are not proportional to RNA. In clinical samples RNA levels but not protein levels determine response to adjuvant gemcitabine. From cell line work we assume RNA represents genetically determined baseline expression. Knocking down CDA in cell lines increases the benefit of capecitabine in the presence of gemcitabine, we propose that as gemcitabine dependent hENT1 prognostic value is only seen in patients with low baseline CDA that capecitabine will offer the greatest benefit in patients with low CDA and low hENT1.

P-13-43

Pembrolizumab combined with IL6R-inhibition leads to tumour regression in murine pancreatic cancer

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Abstract

Background: Targeting the immune compartment in pancreatic cancer (PDAC) holds promise for prognostic improvement, yet our knowledge on the spatial and temporal dynamics, and on the molecular modulators of the PDAC-associated immunophenotype is scarce.

Methods: Using flow cytometry and immunohistochemistry, we quantified markers of several major immune cell subclasses longitudinally in the life span in the primary tumour tissue of oncogenic Kras-driven murine (n=19) and human PDAC (n=36), and in mice with conditional ablation of interleukin-6 (KC;IL6-/-) or CXCL12/SDF1-alpha (KC;Cxcl12+/fl) signalling (n=11). Using a murine tumour transplantation model (n=36), tumour size and survival was quantified after a combination treatment with IL6R-inhibitor and pembrolizumab.

Results: We demonstrate that tumour progression is associated with a parallel drop in the CD8+:CD11b+ ratio. Mice with ablation of IL6 (KC;IL6-/-) or CXCL12/SDF1-alpha (KC;Cxcl12+/fl) exhibited a higher CD8+:CD11b+ ratio and slower tumour progression than KC mice. The systemic treatment of KPC mice with an IL6 receptor (IL6R)- blocking antibody was sufficient to increase the CD8+:CD11b+ ratio and to dampen PanIN development in the pancreas. In harmony, treatment with IL6R-antibody sensitized pancreatic cancer to immunotherapy with pembrolizumab in our murine transplantation model. This resulted in a smaller tumour size as well as in higher survival rate.

Conclusion: Perturbation of selected cytokines can be sufficient for attaining an increased, favourable, intratumoural CD8+:CD11b+ ratio in PDAC. These observations have implications for future immunotherapy approaches that consider combining inhibitors of IL6R or other cytokine receptors for enhancing therapy response. The combination of IL6R-antibody with the PD-1-inhibitor pembrolizumab could lead to a higher rate of operable pancreatic cancers in clinical use.

P-13-44

Applying an automated image-based algorithm for phenotypical characterisation of cancer cell spheroids

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Abstract

Background: Pancreatic cancer remains a particularly lethal type of cancer despite growing efforts in medical research in the past decades. Research focus expanded from targeting cancer cells exclusively to cancer cells and stroma. This shift delivered new potential targets for new treatments, since previously proposed treatments have repeatedly failed to reach clinical practice. In part this is due to many drug screens being carried out with too simple cell models unfit to represent this type of cancer adequately. We therefore developed a 3D tumour-stromal-model. We will focus on the altered metabolic mode of PDAC tumours which consume high amounts of glucose and pro-

duce lactate, part of the syndrome known as Warburg effect. We theorize that interfering with this wasteful mode of metabolism will leave cancer cells more vulnerable. The use of established viability markers using ATP as a readout seemed potentially compromised to us, because the ATP amount per cell might not be constant after treatment. Instead, we developed an image-based algorithm using bright-field images to deduce the viability of spheroids.

Methods & Results: We use a reproducible, high-throughput-screen-ready 3D-coculture-cell model: heterospheroids of Panc1 and human pancreatic stellate cells (hPSCs) which enables modeling the crosstalk between both cell types. The phenotypic analysis parameters are spheroid size and shape, optical tissue density and the degree of tissue integrity. Segmentation is fully automated, using contrast and shape filtering functions and separately recognizing (and excluding) noise and commonly found artifacts.

Conclusion: We show this algorithm can detect changes in cell viability with different types of spheroids responding to treatment and conclude that this image-based classification of spheroids is a valid alternative for cell viability measurements.

P-13-45

The role of CCN1 in the crosstalk between pancreatic stellate cells and Panc1 cancers cells in 3D spheroids

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Abstract

Background: Pancreatic ductal adenocarcinoma is a deadly disease that is almost completely resistant to conventional chemo- and radiation therapy. A major reason for this resistance seems to lie in the dense desmoplastic stroma, which includes abundant heterogeneous cancer-associated fibroblast (CAF) populations. Previously, we used a 3D heterospecies heterospheroid co-culture model to examine the crosstalk between human pancreatic tumour Panc1 and mouse pancreatic stellate cells (mPSCs) by global expression profiling. Since we found CCN1 strongly upregulated in Panc1 cells by coculture, we decided to study the role of CCN1 by CRISPR-Cas9 knockout technology.

Methods & Results: CCN1-KO cell lines were generated by CRISPRCas9 and verified with western blot. Viability of cells grown in 2D and 3D to gemcitabine, paclitaxel and SN38 was measured with CelltiterGlo3D and Apoptosense CK18. RT-PCR and Western blotting was performed on selected genes and proteins for phenotypical characterisation of the cells.

Panc1 cells lacking CCN1 were more de-differentiated and less sensitive to gemcitabine, the latter due to the lower expression of gemcitabine transporting and metabolizing genes.

Based on the previous observation of increased mRNA expression of TGFB and the LPA generating enzyme (Enpp2) in heterospheroids, we treated cells with TGFB1 and lysophosphatidic acid. These stimuli not only upregulated the CCN1 expression in Panc1 cells but also shifted mPSCs to a more myCAF-like phenotype.

Conclusion: We conclude that CCN1 renders cancer cells more sensitive to gemcitabine. The identification of pathways shifting CAFs from immunosuppressive iCAFs to more tumour suppressive myofibroblastic myCAFs may represent a new therapeutic opportunity for PDAC intervention.

P-13-46

Influence of cancer associated fibroblasts (CAFs) heterogeneity on shaping immunosuppressive tumour microenvironment in PDAC

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is a very desmoplastic tumour, believed to influence its behaviour in terms of aggressiveness and resistance. Cancer-associated fibroblasts (CAF) are responsible for the desmoplastic stroma, and it is now known that CAFs are dynamic and heterogeneous cells that contribute to disease progression. Although CAFs contribute to the immunosuppressive tumour microenvironment (TME), their influence on survival and cell dynamics is poorly understood. In the present study, we aim to delineate unbiased CAFs subtyping and explore its functional relevance and cellular dynamics in chronic pancreatitis (CP) and PDAC.

Methods: We performed single-cell RNA-sequencing (scRNA-seq) of forty thousand myofibroblasts isolated from resected human PDAC and CP. For validation of our subtypes, we performed immunohistochemistry (IHC) multiplexing on a human PDAC and CP- tissue microarray (TMA) of 126 and 66 patients, respectively. Subsequently, we analysed spatial distributions of the fibroblasts between tumour and adjacent normal regions.

Results: We delineated by unbiased clustering 11 independent CAF subtypes. To systematically isolate and target these the subtypes, we identified and validated the surface receptor signature of the enriched subtypes. The IHC-Multiplexing using the surface receptor markers validated the scRNAseq results and showed the corroborating our finding. The most dominant subtypes both in PDAC and CP were End Stage iCAFs (inflammatory CAFs) (35.7% vs 56.6%), End Stage myCAFs (myofibroblastic CAFs) (35.3% vs 25.6%). While early myCAFs2 were abundant in cancerous area, we observed that early myCAFs1 were more abundant in normal area.

Conclusion: The CAF subtypes identified by the single cell RNA sequence are validated by IHC-multiplexing. Our future goal is to classify FACS/MACS subtypes using surface receptors and characterised these subtypes at the cell level in order to understand the relationship between CAF subtypes and cancer cells and immune cells.

P-13-47

Small extracellular vesicles-mediated crosstalk between pancreatic cancer cells and neurons

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Abstract

Background: The mechanisms behind the development of neural invasion in Pancreatic ductal adenocarcinoma (PDAC) remain unclear. Several studies showed that small extracellular vesicles (sEVs) are crucial in the communi-

cation of cellular components of the PDAC microenvironment. We intended to investigate whether PDAC cells and DRG neurons communicate via sEVs secreted from neurons toward PDAC cells and vice versa and whether the communication can promote Neural invasion (NI).

Methods: We isolated sEVs from murine and human neuro-invasive/non-neuro-invasive PDAC cell lines, and dorsal root ganglion (DRG) neurons. After performing sEVs characterisation, RNA-sequencing of the long-non coding RNA (lncRNA) in purified sEVs was conducted. The total RNA of PDAC cell lines was sequenced after the DRG-derived sEVs treatment. Uptake of the CFSE labelled-sEVs in co-culture (DRG neuron and PDAC cell lines) was checked under a fluorescence microscope. We next treat the culture DRG neurons with the PDAC cell (neuroinvasive and non-neuroinvasive)-derived sEVs, and the neurogenesis was following quantified.

Results: Electron microscopy, nanoparticle tracking analysis and western blot showed that the purified sEVs conformed to the known sEVs characteristics. The PDAC cells and DRG neurons can internalize the sEVs from each other under the co-culture. The RNA-sequencing confirmed: the existence of snhg8 in DRG derived-sEVs; the amount of the lncRNA snhg8 in KPC cell lines increased after DRG-derived sEVs treatment; the expression level of the snhg8 in TPAC cell lines derived-sEVs was significantly higher than KPC cell lines-derived sEvs; the expression level of several lncRNAs was significantly increased in the TPAC cell lines derived-sEVs compared with the KPC cell lines-derived sEVs.

Conclusion: The DRG neurons and PDAC cells can internalize the sEV from each other, and lncRNA carried by the DRG derived-sEVs can be transferred to the PDAC cells. This communication mediated by the sEVs may promote the NI.

P-13-48

Investigating the synergistic effects of irreversible electroporation and cisplatin on patient-derived pancreatic cancer models

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Abstract

Background: Pancreatic cancer (PC) is a deadly disease, with a 5-year survival of <6% despite recent therapeutic advances. Surgery remains the only curative option, however, only ~20% of patients are eligible. The poor prognosis of PC is multi-factorial and includes insidious disease progression, vague symptomatology, a complex tumour microenvironment, and the predilection for early metastatic spread[1]. There is an unmet need for more effective treatment options for PC patients. Irreversible electroporation (IRE) is a non-thermal, loco-regional ablative therapy that uses high-voltage electric currents to induce membrane destabilisation, enhancing drug influx into cells and cell death[1]. Cisplatin is a widely used chemotherapeutic agent that causes DNA damage, but is often rendered ineffective due to increasing tumour resistance. This study explores the effects of combining cisplatin and IRE on patient-derived pancreatic cancer models.

Methods: Patient-derived pancreatic cancer cells (PDX185) were treated with increasing concentrations of cisplatin and IRE, alone and in combination, for 24 hours. For optimisation, assays were performed at different time points post-treatment to obtain optimal time point for treatment outcome analysis. Effects of the combination treatment on cell proliferation and viability were measured using MTT (soluble 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) and Live/Dead assays, as well as flow cytometry. Changes in mitochondrial membrane potential were evaluated by flow cytometry and fluorescence microscopy using the dye TMRE (tetramethylrhodamine ethyl ester). Protein expression of γ-H2AX, a marker of DNA damage, was measured by Western Blot to assess DNA dam-

age induction.

Results: Cisplatin and IRE combination induced greater cytotoxicity and growth suppression than both monotherapies, with decreasing metabolic activity at later time points post-treatment. The combination group showed a decrease in mitochondrial membrane potential, not observed in the monotherapy groups, and an increase in γ-H2AX protein expression in comparison to cisplatin and IRE alone.

Conclusion: This study demonstrates an enhanced tumouricidal effect achieved with cisplatin and IRE combination in comparison to the treatments alone, highlighting a potential novel therapeutic approach for pancreatic ductal adenocarcinoma.

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P-13-49

Metabolomics of duodenal juice for differentiating pancreatic cancer from benign disease

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) has extremely poor prognosis. As early diagnosis of PDAC is difficult, many PDACs are diagnosed at advanced stages. Although cytology and histology via endoscopic retrograde cholangiopancreatography (ERCP) are standard methods for diagnosing pancreatic diseases, those sensitivities and accuracies are low. Furthermore, ERCP can cause complications such as pancreatitis. Meanwhile, duodenal juice includes pancreatic juice in contact with the tumour and can be easily collected and analysed by genomics, proteomics and metabolomics. Therefore, we focused on metabolomics of duodenal juice as a more effective and minimally invasive alternative diagnostic method.

Methods: From October 2021 to January 2023, duodenal juice was obtained from 102 patients with suspected pancreatic diseases who required endoscopic ultrasonography and endoscopic retrograde cholangiography for treatment/diagnosis. Metabolomes in the samples were analysed by nuclear magnet resonance spectroscopy using 800MHz spectrometer. The metabolomes were compared between pancreatic cancer-derived and benign disease-derived, and multivariate analysis was performed.

Results: The male to female ratio was 52:50, median age was 70 years (27-86), and the ratio of malignant to benign cases was 49 to 53. The number of metabolites that could be detected was averaging 18. Acetone was significantly more abundant in malignant group. Phenylalanine was significantly higher in the pancreatic benign group. Regarding ROC curve analysis of a diagnosis of PDAC, acetone was superior to serum CA19-9 (AUC: 0.847 vs 0.733, P = 0.0757).

Conclusion: Acetone, in the metabolic map of the ketone body, is an end product of pyruvate metabolism. The Warburg effect, which suppresses the TCA cycle in cancer cells resulting in an increase of pyruvate would increase acetone in duodenal juice of the malignant group. In conclusion, metabolomics of duodenal juice is feasible and available for differential diagnosis of malignant and benign disease in the pancreatic field.

P-13-50

Location of tissue associated macrophages M2 in pancreatic cancer

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Abstract

Background: Neoadjuvant chemotherapy (NCTx) has become an essential component in the treatment of borderline and locally advanced pancreatic ductal adenocarcinoma (PDAC), however, its impact on the tumour microenvironment (TME) is incompletely understood. We investigated the impact of neoadjuvant chemotherapy on the immune TME of PDAC patients by analysing bulk RNAseq data and immunofluorescence (IF) from chemo-naïve and post-chemotherapy (post-CTx) samples.

Methods: RNAseq was conducted on 97 fresh frozen samples (chemo-naïve and post-CTx) as described in a previously reported study. A further spatial analysis was performed, using IF on FFPE tissue samples (n=14): in 9 chemo-naïve samples from patients who received adjuvant chemotherapy and in 5 post-CTx samples in patients who received neoadjuvant treatment. M2 macrophages were identified using CD68 (a transmembrane protein that is expressed on the lysosomal membrane of macrophages) and CD163, a scavenger receptor that is expressed by in response to anti-inflammatory stimuli) and cancer cells were identified using pancytokeratin (PanCK). Quantitative analysis of IF-staining was performed using TissueFAXS software, and statistical analyses were conducted to investigate the density of M2 macrophages in tumour-adjacent and distal areas.

Results: RNAseq showed that neoadjuvant chemotherapy reprograms the TME by significantly enriching immune cell types, including M2 macrophages. Patients with tumours containing high M2 enrichment values had a significantly worse overall survival outcome. TissueFAXS analysis showed a significant difference in the density of M2 macrophages, CD68 cells, and CD163 positive cells between regions adjacent to the tumour and regions distal from the tumour, with a higher cell density in the regions distal from the tumour ($p<0.05$).

Conclusion: Neoadjuvant chemotherapy reprograms significantly enriches TME M2 macrophages. Higher M2 marker expression levels were located distant from the tumour cells. This suggests that M2 macrophages play a role in establishing an immunosuppressive environment throughout the tumour microenvironment, not just in direct proximity to cancer cells, warranting further mechanistic investigation.

P-13-51

Pancreatic cancer related diabetes: impaired glucose tolerance and insulin signalling may drive progression of pancreatic intraepithelial neoplasms (PanINs)

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Abstract

Background: Pancreatic cancer-related diabetes (PCRD), a paraneoplastic phenomenon possibly driven by the developing cancer, could be a harbinger of pancreatic cancer (PC). Pancreatic stellate cells (PSCs, which produce the collagenous stroma of PC) can be activated by hyperglycaemia and facilitate PC progression. We hypothesised that exosomes secreted by activated PSCs and cancer cells impair glucose tolerance and insulin signalling leading to hyperglycaemia, accelerating cancer progression. Our aim was to assess effects of exosomes derived from mouse PSCs+cancer (KPC) cell co-cultures, on insulin signalling in hepatocytes; and high fructose diet (HFrD) on glucose metabolism and cancer progression in transgenic KC mice.

Methods: Exosomes isolated from PSC+KPC and acinar cells (controls) by ultracentrifugation and characterised. 10µg exosomes incubated with mouse hepatocytes (AML12;100,000 cells) for 24 hours; expression of insulin signalling factors [insulin receptor (IR) and GLUT-2] assessed by immunoblotting (n=4 separate exosome preparations).

10-week-old KC mice pair-fed HFrD (14% fructose) or isocaloric control diet (n=10-12 mice/group). At 8 and 16 weeks, glucose tolerance, fasting glucose and insulin measured. Pancreatic sections assessed for PSC marker, α-SMA; PanIN marker, MUC1; PanIN grades and area occupied by PanIN lesions.

Results: Isolated exosomes were of expected size (40-160nm) and expressed specific markers (CD9/ALIX/TSG101). Compared to acinar cell-derived exosomes, PSC+KPC co-culture-derived exosomes decreased IR and GLUT 2 expression (by 87.03% and 95.8% respectively; $p<0.05$) in AML12 cells.

Compared to KC controls, KC-HFrD mice showed i) glucose intolerance [(Integrated AUC of plasma glucose levels at 8 weeks (562.2±77.3 vs 901.9±75.3, $p<0.001$) and 16 weeks (592.1±127.4 vs 843.2±135.5, $p<0.01$)]; ii) increased PanIN area (8.8±3.3 vs 30.4±8.4% square pixels/section, $p<0.05$); iii) advanced PanINs/overt cancer foci; iv) 2.3-fold increased MUC1 expression ($p<0.05$); v) 3.5-fold increased PSC activation ($p<0.05$). No significant differences between KC and KC-HFrD for fasting glucose or insulin levels.

Conclusion: This novel study shows that in mice with a genetic predisposition to PC, HFrD impairs glucose tolerance, increases PSC activation and induces progression of early PanINs to advanced PanINs/overt cancer. PSC+KPC-derived exosomes inhibit expression of insulin signalling factors in hepatocytes, providing new insights into PCRD and PC progression.

P-13-52

The protective effect of atopic diseases against pancreatic cancer is not driven by Th2-biomarkers

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Abstract

Background: Pancreatic cancer (PC) is an aggressive malignancy with a dismal prognosis, <10% of patients survive >5 years due to limited diagnostic approaches, rapid progression, and poor treatment responses. Although studies have found atopic individuals have reduced PC risk by almost 40%, the underlying molecular mechanisms remain unclear. Given the complexity of atopic conditions, this study examined their protective effects on PC according to different biomarkers of atopic disease endotype.

Methods: The study utilised 688 cases and 558 controls from the PanGenEU study. Self-reported information on asthma and rhinitis was obtained using the European Community Respiratory Health Survey questionnaire. PC status was obtained from hospital registries and measurements of serum total and specific IgE-antibodies were performed by the ImmunoCAP™ test platform following WHO standards. "High-IgE" was defined as having >100kU/L total IgE and being sensitized to at least one of the food or aeroallergens. An additional of 544 cases and 92,038 controls from the UK Biobank (UKB) cohort were considered to examine the effect of blood eosinophil levels on PC risk. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated using multivariable logistic regression models. Restricted cubic spline models were applied to examine the nonlinear relationship between IgE and PC risk among atopic individuals.

Results: Within PanGenEU study, atopic individuals with low-IgE were associated with reduced PC risk (OR:0.56, 95%CI: 0.39-0.80) compared to the non-atopic and low-IgE population. Specifically, patients with asthma or rhinitis had a 44% and 40% lower PC risk, respectively (OR range: 0.56-0.60, 95%CI:0.39-0.90). Similarly, results from the UKB revealed that atopic individuals with below 0.15 x109 cells/L eosinophils were significantly less likely to develop PC (OR:0.67, 95%CI: 0.47-0.95).

Conclusion: The two population-based studies showed that atopic diseases protect against PC risk independent of Th2 biomarkers. Individuals with low levels of IgE and eosinophils present the lowest risk, indicating non-Th2 mechanisms underlying the protective effect. Future studies should incorporate other immune effectors and longitudinal data to identify the genetic pathway driving PC protection to benefit the prevention, diagnosis, and treatment of this disease.

P-13-53

Importance of MUC17 in the bile-induced pancreatic cancer progression

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Abstract

Background: We have previously shown that bile acids (BAs) accelerate carcinogenic processes in pancreatic cancer

(PC) in which mucin 4 (MUC4) expression has a central role. However, the role of other mucins in PC are less clear, especially in bile-induced cancer progression. The study aim was to investigate expression of MUC17 in BAs- or human serum-treated pancreatic ductal adenocarcinoma (PDAC) cell lines.

Methods: We used different assays with RNA silencing to study the role of MUC17 in cancer progression. Protein expression of MUC17 was evaluated in 52 human pancreatic samples by immunohistochemistry, and Kaplan–Meier survival analysis was used to compare survival curves.

Results: Expression of MUC17 increased in PDAC patients, especially in obstructive jaundice (OJ) and the elevated MUC17 expression associated with poorer overall survival. Treatment of Capan-1 and AsPC-1 cells with BAs or with human serum obtained from PDAC + OJ patients enhanced the expression of MUC17, as well as the proliferative potential of the cells, whereas knockdown of MUC17 alone or in combination with MUC4 decreased BAs-induced carcinogenic processes.

Conclusion: Our results demonstrated that MUC17 has a central role in bile-induced PC progression, and in addition to MUC4, this isoform also can be used as a novel prognostic biomarker.

P-13-54

Role of myeloid cell population in pancreatic cancer progression and targeting of myeloid subpopulations

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Abstract

Background: Pancreatic cancer is characterised by a pronounced stromal reaction and an immune-suppressive micro milieu. Although abundant myeloid cell populations in the pancreatic ductal adenocarcinoma (PDAC) microenvironment have been postulated to enhance tumour progression and suppress antitumour activity, the composition of these populations in comparison to early and late stage, their spatial localisation in the tumour tissue and how they interact with each other is poorly understood. With this study, we aim to identify the spatial landscape of myeloid cell subtypes and their cellular network, which could be used as a biomarker for targeted therapy for pancreatic cancer patients.

Methods: We have developed a quantitative multiplex immunofluorescence assay panel to understand the spatial landscape of immune cell subpopulations at single-cell resolution in pancreatic cancer development using Opal Polaris kit, and automated multispectral imaging system (Vectra 3.0, Akoya Biosciences). We have used KPC (LSL-KrasG12D/+; LSL-Trp53R172H/+; Ptf1a-1-Cre) and KC (LSL-KrasG12D/+; Ptf1a-1-Cre) mice pancreas tissue at different time points to characterize the immune cell population.

Results: From the preliminary results of our ongoing project, we observed that myeloid cells are enriched within the tumour stroma, and macrophages are the most abundant cells among the other myeloid cell population. In addition, the M2 macrophage population significantly increases in the tumour stroma during the late stage of pancreatic cancer.

Conclusion: It has been observed that a broad range of immune cells is present in the tumour microenvironment, however, direct comparative analysis of immune cell subpopulations in early and late stages is lacking, and here our study will provide a wide immune cells spatial landscape in pancreatic cancer development. Furthermore, we aim to perform our analysis in human tissue samples to correlate our findings.

P-13-55

Correlation analysis of the relationship between the level of apoptosis markers and the severity of liver failure

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Abstract

Background: Apoptosis is biological programmed cell death. Massive hepatocytes apoptosis leads to acute liver failure (LF). The development of cholestasis causes the development of pathological necroptosis, with an increase the level of caspase-3 - the main marker of early liver parenchyma damage. Bcl-2 is one of the most important anti-apoptotic proteins. The severity of LF may be the result of imbalance between these factors. We aimed to assess the correlation of apoptosis markers level with LF in patients with malignant obstructive jaundice (MOJ).

Methods: The study included 84 patients with MOJ who underwent preoperative biliary drainage (PBD). All patients had LF: moderate LF was diagnosed in 52 (61.9%), severe one in 32 (38.1%). The levels of CASP3 and Bcl-2 were determined in blood serum during PBD and the main surgical intervention, using the Sandwich-ELISA method.

Results: The average values of apoptosis markers levels at the time of PDB depending on the severity of LF did not statistically differ, $p>0.05$. The markers values in patients with LF at the time of PBD and the main surgical intervention were difference CASP3 (13.46 (11.61-19.96) vs. 4.26 (2.62-9 ,40), Bcl-2= 4.19 (1.21-6.18) vs. 10.0 (7.31-13.15), $p<0.001$. A correlation was established between levels of CASP3 ($r =0.812$, $p<0.001$), Bcl-2 ($r=0.753$, $p<0.001$) in patients with moderate LF and severe LF: CASP3 ($r=0.732$, $p <0.001$), Bcl-2 ($r=0.613$, $p<0.001$). Binary logistic regression analysis established correlation between CASP3 and Bcl-2 levels at the time of PBD with the presence of LF (R2(Nagelkerke)=0.327, $p=0.003$).

Conclusion: The imbalance of pro- and anti-apoptotic markers in patients with MOJ associated with LF, however, for the implementation of these laboratory indicators in practice, further observations on a larger patients sample are necessary to validate the data.

P-13-56

Neural invasion in pancreatic cancer is characterised by beta-1-integrin- and N-cadherin-dependent heterotypic cell adhesion between pancreatic cancer cells and neural Schwann cells

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Abstract

Background: Perineural invasion is the main mode of invasion in pancreatic cancer, with a prevalence of up to

100%. Therefore, it is often associated with local recurrence and neuropathic pain sensation. The progression of this pathogenesis involves the continued dissemination of cancer cells via intrapancreatic nerve fibres to the extrapancreatic plexus. Given this phenomenon, it was necessary to ask whether pancreatic cancer cells anchor themselves to the Schwann cells that wrap axons in inner nerves. Furthermore, we investigated the molecular mechanisms underlying this heterogeneous intercellular adhesion.

Methods: The analysis of adhesion molecule expression in PCa tissues, human Schwann cells (hSC), and normal human pancreas (NP) was conducted using immunohistochemistry, QRT-PCR, and immunoblotting techniques. We created a novel assay for heterotypic cell-cell adhesion. To investigate alterations in phosphorylation levels and metabolic activity following the co-culture of Schwann and cancer cells, we employ a phosphorylation array and metabolic assays with the MxP® Quant 500 kit.

Results: The analysis of the expression of adhesion molecules on PCa cells and human Schwann cells (hSC) revealed that integrin beta 1 exhibits high expression levels in human PCa cells, whereas n-cadherin was strongly present on hSC. Our newly developed in vitro adhesion assay demonstrated the adhesion capacity between PCa cells and hSC. Our investigation into blocking the adhesion molecules on hSC revealed that the blockade of n-cadherin on hSC reduced the heterotypic PCa-hSC adhesion. Also, inhibition of beta-1-Integrin on tumour cells resulted in significant adhesion reduction. Immunoprecipitation experiments showed that b1-integrin is capable of binding to N-cadherin on hSC. Regarding metabolic testing, Schwann cells were found to exhibit strong glutamine synthetase (GS) activity. Phosphorylation arrays revealed that P-p38 in co-cultured cells was enhanced in comparison to mono-cultured hSC, while P-AKT and P-Erk in co-cultured cells were upregulated in co-cultured tumour cells when compared to mono-culture.

Conclusion: During the neural invasion, pancreatic cancer cells (PCa) can establish adhesion with Schwann cells. This adhesion is facilitated by Beta-1-Integrin expressed on PCa cells, and by n-cadherin on hSC. It is worth exploring the activation of the p38 pathway as a means of modulating the efficacy of neural invasion.

P-13-57

Phenotype screens of genetically engineered mouse models of pancreatic cancer identify a Tgfa-Ccl2-paxillin axis driving human-like perineural invasion

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Abstract

Background: Solid cancers like pancreatic cancer (PDAC) frequently exploit nerves for rapid dissemination. This

neural invasion (NI) is an independent prognostic factor in PDAC, and the foremost inducer of local recurrence and severe pain. Therefore, understanding the mechanisms of NI is of major translational relevance in oncology.

Methods: We systematically screened for human-like NI in a repository of genetically engineered mouse models (GEMM) of PDAC comprising 295 different allele combinations of oncogenes and tumour suppressors. We used the genotype information of the GEMM that phenocopy human NI to functionally study the mechanisms that give rise to human-like NI. We correlated the identified mediators to the clinical characteristics in human PDAC.

Results: Our phenotype screens uncovered two GEMM of PDAC with human-like NI, i.e., engulfment of nerves by perineurally aligned cancer cells. Both GEMM are characterised by pancreas-specific overexpression of transforming growth factor alpha (TGFa) and conditional depletion of p53. Mechanistically, cancer-cell-derived TGFa upregulates CCL2 secretion from sensory neurons which induced hyperphosphorylation of the cytoskeletal protein paxillin viaC-CR4 on PDAC cancer cells. This activated the cancer migration machinery and filopodia formation toward neurons. Disrupting CCR4 or paxillin activity limits NI, decreases tumour size, and dampens tumour innervation. In human PDAC, phospho-paxillin and TGFa expression constitute strong prognostic factors.

Conclusion: Phenotype screens of PDAC GEMM unveiled the TGFa-CCL2-CCR4-p-paxillin axis as a clinically actionable target for constraining NI and tumour progression. The herein reported GEMM with human-like NI represent novel and potent tools for studying the mechanisms of neuron-cancer crosstalk.

P-13-58

The tumour biology of early onset pancreatic cancer – a matched case study

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Abstract

Background: Pancreatic cancer (PDAC) is a highly aggressive malignancy with a dismal prognosis. While average pancreatic cancer mainly occurs at higher patient age, early onset pancreatic cancer (EOPC) is defined as diagnosis before the age of 50. EOPC is a rare, but aggressive form of the disease. In this study, we aimed to compare the biology of EOPC patients with matched average onset pancreatic cancer (AOPC) patients on the genomic, transcriptional and epigenomic level and in the composition of their tumour microenvironment (TME).

Methods: This retrospective study included 50 PDAC patients resected between 2000 and 2016. To 25 EOPC patients, 25 AOPC patients were propensity score matched by UICC-stage, differentiation grade, R-status, sex, localisation and adjuvant therapy. Clinicopathological data and FFPE samples were obtained from the institutes archive and the hospitals database. Nucleic acids from FFPE samples were extracted using the truXTrac Kit. For 50 cases, NGS analysis was performed using the Oncomine Comprehensive Assay v3. For 48 cases RNA expression was assessed using the nanostring nCounter Tumour Signalling 360 panel. Methylation profiles were assessed using Illumina EPIC arrays. The TME composition was assessed by multiplexed immunohistochemistry on a Vectra Polaris platform and metagenomic 16s-rRNA-Sequencing.

Results: Mean patient age for EOPC was 43.4 years and 74.1 years for AOPC. There were no significant differences between the groups in sex distribution, tumour size, histology, stage, perioperative chemotherapy, and tumour lo-

calisation. EOPC patients showed significantly longer overall survival (OS) than AOPC patients (28.6 vs 22.4 months, p=0.034) and a trend towards longer disease-free survival (DFS, 11.9 vs. 9.5 months, p=0.08). In preliminary NGS analysis, CDKN2A and MIR6795 mutations were significantly more abundant in EOPC tumours (p=0.037) and there was a non-significant higher frequency of KRAS and TP53 alterations. The initial gene expression analysis indicated several differentially expressed genes. Methylation profiles differed significantly between cohorts whereas the TME composition did not.

Conclusion: The preliminary findings of our matched case study suggest that EOPC and AOPC possess distinct molecular characteristics, which could have substantial implications for treatment and prognosis. Further studies are needed to validate these findings.

P-13-59

Indoleamine-2,3-dioxygenase as therapy target in pancreatic cancer

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Abstract

Background: Indoleamine-2,3-dioxyenase 1 (IDO1) was described as immunosuppressor in solid malignancies including pancreatic cancer (PDAC). Clinical trials of IDO1 inhibitors to restore tumour immune responses failed thus far. We examined the prognostic impact of IDO1 expression in advanced PDAC patients treated with or without EGFR-targeting agents and tested the effect of IDO1 expression and activity on sensitivity to EGFR inhibition in vitro.

Methods: The expression of IDO, pERK, CD8 and FoxP3 in the tumour tissue of advanced PDAC patients treated within the AIO-PK0104 trial (n=143) and translational trials (n=63) was examined immunohistochemically. IDO expression was assessed in PDAC cell lines and modulated by siRNA-mediated knockdown or lentiviral transduction and its activity was inhibited by 1-methyltryptophane (1-MT). The impact of IDO expression or activity on chemosensitivity in vitro was assessed by resazurine assays. Kynurenine levels were measured photometrically.

Results: IDO expression was a negative prognosticator for progression-free survival (PFS, 2.8 vs 1.4 months, p=0.01) and overall survival (OS, 6.8 vs 1.4 months, p<0.001) restricted to erlotinib-treated patients. Significantly less patients with IDO+ tumours developed skin rash, a sign of response to EGFR-inhibition (p=0.02). IDO expression correlated inversely with phospho-ERK expression, a hallmark of MAPK activity (p=0.008) but not with CD8+ or FoxP3+ infiltration. IDO knockdown or inhibition lowered kynurenine levels, increased erlotinib-sensitivity in vitro, increased phosphoERK-levels and MAPK-target gene expression, whereas its overexpression had a contrary effect (p<0.001 each). IDO-inhibition or knockdown did not affect response to gemcitabine or 5-FU.

Conclusion: IDO seems to suppress MAPK activity. Conversely, IDO-inhibition increases the tumours´ dependency on MAPK-activity, rendering them more sensitive to EGFR-targeting agents. We propose IDO-inhibition combined with EGFR-blockage as promising therapy strategy in IDO+ PDAC.

P-13-60

CD24 and EpCAM expression on endoscopic ultrasound fine needle biopsy pancreatic ductal adenocarcinoma samples

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is characterised by intense fibrosis which enhances the tumour growth and drives an epithelial-mesenchymal transition. The consequence is the uncontrolled proliferation of cancer cells, including pancreatic cancer stem cells (PCSC), which may enhance the metastatic potential. The aim of this study is to assess the expression of CD24 and EpCAM, on pancreatic endoscopic ultrasound-guided fine-needle biopsy (EUS-FNB) specimens.

Methods: A total of 35 patients diagnosed with PDAC after EUS-FNB within the Research Centre of Gastroenterology and Hepatology of Craiova, were included in the study, and the samples were sent for immunohistochemical assessment. Anti-Human CD 24 (policlonal, Abcam, ab 199140) and EpCAm (Epr 20532-225, Rb monoclonal, Abcam, ab 223582) were used.

Results: All cases were positive for CD24 and EpCAM. In NOS ductal adenocarcinomas, CD24 immunomarking was heterogeneous, with variable intensity and a variable number of positive cells within the same case. Well and moderately differentiated adenocarcinomas that formed tubular or papillary structures showed a higher intensity CD24 expression compared to poorly differentiated or undifferentiated adenocarcinomas. EpCam showed a stronger immunolabelling intensity in the analysed samples. PDAC EpCam expression was of moderate and high intensity and with a heterogeneous appearance in NOS G1 adenocarcinomas, but the intensity of the immunomarking tended to decrease with increasing histological grade.

Conclusion: EUS-FNB of CD24 and EpCAM immunohistochemistry is feasible. At the subcellular level, the basolateral membranous and cytoplasmic staining of EpCam in PDAC could be correlated with tumour invasion and possibly with the unfavourable evolution of this type of carcinoma, while CD24 frequently presents an apical immunostaining pattern and could suggest the presence of an epithelial-type phenotype of tumour cells, with a lower potential for invasiveness and metastasis.

P-13-62

In-situ-characterisation of the tumour microbiome in pancreatic cancer

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is an aggressive disease with dismal prognosis, also in the minority of primarily resectable patients, resulting in mortality rates almost equal to incidence rates. Adjuvant gemcitabine-based chemotherapy remains a therapeutic mainstay, but responses are heterogeneous and its toxicity

limits treatment duration. Increasing evidence indicates a crucial impact of the tumour microbiome on patient outcome by influencing the immune system, promoting cancer-associated inflammation, and potentially affecting the tumours response to therapy.

Methods: We developed a novel multicolor 16s-rRNA flourescence in-situ hybdridization (16s-mFISH) approach targeting the five most relevant bacterial phyla and classes in PDAC and assessed their composition, abundance, and spatial distribution in the resection specimens of 326 patients. A supervised machine learning image analysis algorithm enabled a simultaneous quantification of the tumour microbiome and the precise identification of each bacteria's location. In exploratory analyses, we investigated the prognostic significance of the microbiome composition, its spatial characteristics and developed a novel tumour-microbiota based classification model predicting patient outcome according to the applied adjuvant chemotherapy regimen.

Results: Multispectral imaging followed by spectral unmixing of n= 326 samples revealed a complex and heterogenous tumour microbiome with varying abundance and distribution. The phylum of proteobacteria with its dominant classes gammaproteobacteria and betaproteobacteria were the most enriched intratumoural bacteria, followed by the phyla of actinobacteria, firmicutes and bacteriodetes. The tumour microbiome composition and abundance correlated with common risk factors, such as hypercholesterolemia, diabetes and alcohol consumption as well as transcriptional subtype and CD8+ T-cell infiltration. Importantly, it was associated with response to adjuvant therapy. A tumour-microbiota based classification model identifies a distinct microbiome signature outperforming common clinical prognosis scores.

Conclusion: Using a novel 16s-mFISH approach, we characterised the abundance, composition, and co-localisation of intratumoural bacteria in PDAC. Importantly, we show that these characteristics significantly affect patient outcome and response to adjuvant chemotherapy. We propose a microbiome-based risk assessment model. Our findings may be used to inform adjuvant therapy and identify the tumour microbiome as potential treatment target in PDAC.

P-13-63

Neuropeptide Y silencing negatively impacts the invasion capacity of pancreatic cancer cells

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Abstract

Background: Pancreatic adenocarcinoma (PCa) with a 5-year survival rate <5%, is the third leading cause of cancer-related death. Neural invasion (NI), an independent prognostic factor for survival, is a hallmark of PCa. Recently, our group performed a transcriptome analysis of genetically engineered mouse models, and Neuropeptide Y (NPY) was found to be one of the most upregulated molecules especially in neuro-invasive mouse model compared to non-neuro-invasive mouse models. So far, the role of NPY in PCa aggressiveness remains unclear. Therefore, this study focuses on understanding the potential role of NPY PCa.

Methods: NPY expression profiles were analysed in human pancreatic epithelial and PCa cells at both RNA and protein levels. The highest and the lowest NPY-expressing cell lines with invasive characteristics were selected to be

subjected to *in vitro* functional assays including proliferation, motility, migration, and matrigel-based neural-invasion assays. Gene silencing at transcriptome level was obatined through small interfering RNA (siRNA). Cell toxicity of siRNA transfection was measured by Cell Counting Kit-8 (CCK-8). Then, colony formation, scratch, and trans-well invasion assays were performed. Immunostaining on paraffin-embedded pancreatic tissue sections of the normal pancreas (NP) and PCa against NPY was performed and analysed via QuPath.

Results: Based on NPY expression profile, SU.86.86 and T3M4 cell lines were found to have the highest and lowest NPY transcript, respectively. NPY silencing did not cause a difference in viability as obtained in CCK-8 assay results. While NPY knockdown did not affect colony forming and wound healing capacity, it significantly reduced the invasion ability of SU.86.86 cells in Matrigel-coated transwells (*P=0.0029). NPY-treated T3M4 cells showed significantly less invasiveness (*P=0.0014). Average tissue immunoreactivity against NPY in PCa tissue was 24.6% (±3.4 SEM), while this percentage was found at 5.7(±1.2 SEM) in NP, indicating that NPY is expressed more than four times in cancer tissue compared to normal pancreas tissue (*P=0.0029).

Conclusion: NPY expression and immunoreactivity in human PCa are significantly higher than in the normal pancreas. NPY silencing does not change cells' proliferation and mobility but affects the invasion capacity of PCa cells. Further analysis is needed to examine the exact mechanisms of NPY on PCa aggressiveness.

P-13-64

Precision therapy for pancreatic cancer; the role of patient derived cancer avatars

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Abstract

Background: Systemic therapy serves as an essential component of pancreatic cancer management. Current guidelines advocate that chemotherapy regimes should be selected based on the patient's performance status. Such an approach to treatment fails to acknowledge the variability in treatment response rates between patients and the individual's tumour biology. Our aim was to evaluate whether patient derived cancer avatars can be utilised to deliver precision therapy.

Methods: Following pancreatectomy, avatars were created from each patient's tumour. Avatars were cultured with novel perfusion culture technology in order to re-establish in vivo physiological conditions. Avatars underwent daily assessment to evaluate viability and proliferative capacity. Ex vivo treatment with gemcitabine monotherapy was performed and the avatar response was correlated with the patient's outcome.

Results: Thirteen patients were recruited to this study. Under perfusion culture conditions, avatars were successfully cultured to 12 days ex vivo. Perfusion culture was associated with a significantly higher rate of metabolic function ($p < 0.01$), proliferative capacity ($p < 0.01$) and a reduction in apoptosis rates ($p < 0.05$). Gemcitabine treatment displayed variable response across avatars. When compared to the patient, the avatars correlated with treatment response.

Conclusion: Patient derived cancer avatars represent a versatile model that provides both an insight into the individual's tumour biology and an opportunity to conduct a personalised drug screen. Such an approach can be used by clinicians in order to select the most effective chemotherapeutic treatment regime for each individual patient with pancreatic cancer.

P-13-65

Innervation at acinar-to-ductal metaplasia stage of pancreatic cancer

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease that is often diagnosed at advanced stages, limiting treatment options and leading to poor patient outcomes. Early detection and intervention are crucial for improving survival rates, but the pathogenesis of PDAC remains poorly understood. Acinar-to-ductal metaplasia (ADM) is an early precursor of PDAC. While it is known that hyperinnervation and neural hypertrophy occurs early in pancreatic carcinogenesis, it is unclear whether this occur at the ADM stage. The aim of this study is to investigate whether hyperinnervation and neural hypertrophy are present at ADM stage of pancreatic carcinogenesis.

Methods: C57BL/6 wild-type (WT) mice and Ptf1a-Cre; LSL-Kras+/G12D[KC] mice were subjected to caerulein-induced acute pancreatitis(AP) via eight hourly injections on two consecutive days. The mice were euthanised 72 hours after the first injection, and their pancreatic tissues were collected, formalin-fixed, and paraffin-embedded. Four slides per mice were subjected to immunohistochemical stainings using either anti-PGP 9.5 or anti-Beta 3 tubulin antibody. Histological analysis and measurements were performed to compare the nerve densities and sizes between caerulein-induced KC and WT mice tissues.

Results: Microscopically, no obvious pathological changes were detected in the tissues of caerulein-induced WT mice. In contrast, numerous ADM lesions were observed in the tissues of caerulein-induced KC mice. Histological analysis showed no significant difference in nerve densities and sizes between the caerulein-induced KC and WT tissues.

Conclusion: This study provides preliminary evidence suggesting that hyperinnervation and neural hypertrophy may not be present at the ADM stage of pancreatic carcinogenesis. The lack of significant difference in nerve densities and sizes between the caerulein-induced KC and WT tissues could indicate that hyperinnervation occurs later in the progression of PDAC. One possible explanation for these results is that we only stained and analysed 4 randomly selected sections per tissue sample, rather than the entire tissues. Another possible explanation is that the model used in this study does not fully cover the natural progression of PDAC. Further studies are needed to confirm and extend these findings.

P-13-66

The roles of GalNT2 and St3Gal6 genes on neural invasion

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Abstract

Background: Neural invasion is a histopathological hallmark of pancreatic ductal adenocarcinoma (PDAC) and significant predictor of poor prognosis. Despite extensive research efforts, the mechanisms underlying neural invasion in PDAC remain elusive. Our previous findings suggested a potential association between neural invasion and glycosylation genes GalNT2 and St3Gal6 [1], which are involved in mucin O-glycosylation and glycoprotein sialylation, respectively. In this study, we aimed to further investigate this association, providing novel insights into the neural invasion and tumourigenesis of PDAC.

Methods: To evaluate the neuroaffinity of murine PDAC cell lines, we performed 3D migration assay comparing cells with down-regulated expression of GalNT2 or St3Gal6 to control cells, all of which were isolated from a PiggyBac transposon mutagenesis mouse model [2]. Immunohistochemical staining was conducted on human PDAC specimens to investigate the protein expression of GalNT2 and St3Gal6 in cancer cells that had invaded nerves. Orthotopic transplantation of PDAC cells with down-regulated expression of GalNT2 or St3Gal6, as well as control cells, was performed on wild-type C57BL/6 mice (n=12) to assess the potential role of these genes in PDAC tumourigenesis.

Results: Our 3D migration assay showed that cells with down-regulated expression of GalNT2 or St3Gal6 exhibited increased neuroaffinity compared to control cells. Immunohistochemical staining revealed that the protein expression of both GalNT2 and St3Gal6 was significantly lower in cancer cells exhibiting neural invasion. All mice implanted with cells down-regulated for GalNT2 or St3Gal6 developed tumours, whereas only half of the mice implanted with control cells developed tumours.

Conclusion: Our study suggests that GalNT2 and St3Gal6 may play a role in the neural invasion and tumourigenesis of PDAC. Our findings indicate that down-regulation of GalNT2 and St3Gal6 may enhance the neuroaffinity of PDAC cells. The lower expression of GalNT2 and St3Gal6 in cancer cells exhibiting neural invasion suggests that these genes may be involved in regulating the invasive phenotype of PDAC cells. Further investigation is required to elucidate the underlying mechanisms and clinical implications of targeting these glycosylation genes in the management of PDAC.

P-13-67

Exosome-mediated communication between pancreatic cancer cells and Schwann cells promotes aggressiveness of pancreatic cancer

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Abstract

Pancreatic cancer (PCa) is characterised by prominent intrapancreatic neuropathic alterations such as increased neural density and hypertrophy. PCa cells closely interact with nerves, and they can invade the perineurium and become associated with Schwann cells (SCs) and axons of neurons. This vicious interaction between cancer cells and nerves is closely associated with increased pain and poor prognosis. Although some mechanisms have been identified, the role of exosomes in cancer-nerve interaction still remains unclear. Therefore, we investigated the effect of exosomal communication between the PCa cells and neurons/SCs on the aggressiveness of PCa.

SH-SY5Y neuroblastoma cells were differentiated into neurons and differentiation efficiency was confirmed via im-

munofluorescent staining and western blot. The exosomes were obtained from three cell sources; neurons, SCs, and PCa cell lines (PANC-1 and BxPC-3). SCs and neurons were treated with either PANC-1 or BxPC-3 cell-derived exosomes and the changes in cell migration, invasion, and proliferation were evaluated. Similarly, PCa cells were exposed to exosomes derived from SCs or neurons, and the changes in cell migration, invasion, proliferation, and the expression of metastasis-related proteins were evaluated. In addition, PCa patient tissues were stained with S100A and GFAP antibodies for the nerves, and CD9 or CD81 antibodies for the exosomes. Besides, expression levels of 84 exosomal miRNAs were assessed by miRNA array, and the effect of one of the overexpressed miRNAs on PCa cell aggressive behaviours was investigated.

Results: As a result, we showed that PCa cell-derived exosomes promote the migration and invasion ability of SCs. Excitingly, PCa exosomes drastically induced the expression of the dedifferentiation marker, glial fibrillary acidic protein (GFAP), in SCs indicating the stimulation of their cancer-promoting phenotype. Similarly, exosomes derived from SCs favoured the aggressive behaviours of PCa cells by increasing cell proliferation, migration, invasion, and the expression of EMT-related proteins. The exosomal miRNA-array profiling revealed that miR-125b-5p, one of the miRNAs overexpressed in SCs, induced migration but not the invasion ability of PCa cells.

Conclusion: Briefly, these results suggest that exosomes may play a messenger role in cancer-SCs interaction which in turn accelerate tumour aggressiveness, however, further research is needed to reveal this mutual communication.

P-13-68

K-Ras independence due to N-Ras expression in cancer cell lines giving resistance to K-Ras specific inhibitors

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Abstract

Background: Most pancreatic cancers have a mutation in the gene that produces the protein K-Ras. The mutation allows the cancer cells to divide out of control and so the theory is that if we can stop the mutant protein working we will kill or at least stop the cancer growing. However, to date this has proved ineffective. This may be explained by the previous observation that pancreatic cancers can become independent of K-Ras (not needing the mutation to survive). We show that cells which are independent of K-Ras have switched on another form of Ras protein and that this protein has taken on some (but not all) functions of K-Ras. Based on the pattern of functions replaced and not replaced we have developed a model for how pancreatic cells evolve into cancer cells using Ras proteins which may allow more effective targeting of Ras related pathways to overcome the disease.

Methods: Cell lines (SUIT-2, MiaPaca, BxPC3, Panc-1, Primary mouse pancreatic cancer cell lines from KPC mice and HeLa) were cultured in RPMI with knockdown of K-Ras or N-Ras by SiRNA. Western blot and real time PCR were used to measure levels of Ras proteins and their targets. Pull down with RAF was used to determine levels of active Ras.

Results: Mutant K-Ras causes reduced mitochondrial activity, apparently by reducing the number of mitochondria and promotes the production of G2 cyclins by inhibition of the proteolysis. N-Ras or mutant K-Ras increase transcription of G2 cyclins via G1 cyclins in a cell cycle-dependent fashion. Based on results from N-Ras knockdown , it increases glycolysis and the efficiency of respiration. G2 cyclins will be degraded via the APC/c complex, therefore, in the absence of mutant Ras, the level of the G2 cyclins will be limited by the proportion of cells in G2. Bortezomib inhibits the proteasome, causing stabilisation of ubiquitinated G2 cyclins, reducing the production of ubiquitinated protein by restricting entry to (and exit from) G2.

Conclusion: N-Ras induction is a common event in pancreatic cancer, which impacts on metabolism. N-Ras acts as an antagonistic to mutant K-Ras regulating oxidative phosphorylation.

P-13-69

State-of-the-art tissue clearing and 3D imaging and its application in understanding neural invasion in pancreatic cancer

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Abstract

Background: Neural invasion is an inherent feature of pancreatic ductal adenocarcinoma and one of the reasons for poor patient survival after tumour resection. Understanding the mechanism behind the crosstalk of neural cells and cancer cells is essential to identify new treatment approaches. Therefore, neural invasion has been intensively studied using human or mouse cancer tissue with 2 dimensions (2D) microscopy. Recent technological advantages in microscopy and imaging of whole organs provide more precise visualisation of neural invasion in pancreatic cancer.

Methods: We used an easy-to-implement ethyl cinnamate (ECi) based technique (EMOVI) to clear and stain whole pancreas tissue of genetically engineered mouse models of pancreatic cancer for intrapancreatic nerve fibres, cancer cells, and blood vessels. The commonly used KPC ($Ptf1a^{+/Cre}$; $Kras^{+/LSL\text{-}G12D}$; $Trp53^{+/fl}$) mouse model was compared to the recently generated neuroinvasive TPAC (Ela1-TGFa; $Ptf1a^{+/Cre}$; $Trp53^{fl/fl}$; $p65^{fl/fl}$) mouse model and healthy pancreas tissue. 3D reconstruction images were compared to standard 2D immunohistochemistry staining. Immunolabelled and cleared pancreatic tissue was visualized using confocal laser scanning microscopy.

Results: 3D reconstruction of cleared and immunostained pancreatic tumours of KPC and TPAC mice reveals the distinct dense neural network in and around neoplastic cancer cell sides that cannot be observed with 2D histology techniques. The fine branches of nerve fibres can only be displayed in imaging of whole tissue samples. The specific differences of both genetically engineered mouse models in the aspect of neural invasion will be presented at the European Pancreas Club.

Conclusion: The application of tissue-clearing methods in pancreatic cancer mouse models will help to characterize the 3D architecture of neural invasion. This easy-to-implement visualization technique can be applied to all different cell types in the tumour microenvironment and has the potential to contribute a significant step toward understanding this complex disease.

P-13-70

Simultaneous inhibition of GSK3β and HDACs improves chemotherapeutic efficacy in pancreatic cancer cells and human pancreatic ductal adenocarcinoma organoids

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Abstract

Background: Glycogen synthase kinase 3 (GSK3) and histone deacetylases (HDACs) are both crucial for the development of pancreatic ductal adenocarcinoma (PDAC), and Metavert is a potent dual inhibitor of both of these enzymes. Recent in vitro and in vivo studies have shown that Metavert monotherapy slows PDAC tumour growth, while the exact mechanisms remain unclear.

Methods: Cell viability and rescue assays, WB, IF, and IF analyses were used to evaluate metavert-induced cell death. Using five PDAC cell lines and 36 patient-derived PDAC organoids (hPDOs), all of which were characterised by genomic, transcriptomic, and therapeutic response analyses, the interaction between Metavert and the currently used chemotherapeutic agents (gemcitabine, paclitaxel, 5FU, irinotecan, oxaliplatin) was determined using the classified synergy score (strong and weak synergistic, additive, and strong and weak antagonistic). A potential Metavert therapeutic response biomarker was found using correlation analysis of the transcriptome, proteomic, and drug sensitivity data.

Results: Clinically relevant heterogeneity was found during the therapeutic testing of hPDOs. In all five PDAC cell lines and 36 hPDOs, Metavert showed a rather high synergistic impact (synergistic score greater than 10) by triggering autophagy and apoptosis when coupled with cytotoxic chemotherapies. The combination of Metavert plus irinotecan demonstrated the most impressive outcomes and revealed a significant synergistic anti-tumour impact. For Metavert, the most accurate therapy response biomarker was found to be the protein PRELP.

Conclusion: Along with a potential biomarker for the therapeutic response, we have discovered synergistic anti-tumour effects of Metavert coupled with currently utilised cytotoxics. The continuous development of Metavert-based medicines should result in more efficient therapeutic approaches for patients with pancreatic ductal adenocarcinoma, improving patient survival.

P-13-71

Target structure in pancreatic ductal adenocarcinoma: changes in heat shock protein 90

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest cancers for which few curative therapies are available to date. Acute pancreatitis (AP) is a rare manifestation of PDAC causing high morbidity and mortality dependent on the variable severity of the disease course. Heat shock proteins (HSP) are important for protection against cell stress and inflammation. The inducible heat shock proteins-90 are anti-oxidative, anti-inflammatory, and cytoprotective enzymes, however, their upregulating role remains unknown in PDAC and AP. We aim to determine, whether HSP-90 elevation lead to the development of PDAC.

Methods: Patients with acute pancreatitis (n=50) and PDAC (n=48) were evaluated in an IRB-based study. Peripheral blood samples from AP and PDAC patients were collected on admission. Plasma samples were stored at -80 °C. Commercially available ELISA kits were used. Sandwich ELISA assays were performed in 96-well plates, using 100 µL peripheral blood plasma per well. When required, plasma was diluted in blocking buffer, in which case the concentration read from the standard curve was multiplied by the dilution factor. Statistical analysis was performed by

using SAS 9.4 program.

Results: The subjects were categorized into 2 groups based on HSP-90 levels results. For the AP group high HSP-90 was defined as adjusted HSP-90 > 26.5 ng/ml and low HSP-90 as adjusted HSP-90 <= 26.5 ng/ml. For the PDAC group, high HSP-90 as adjusted HSP-90 > 14.25 ng/ml and low HSP-90 as adjusted HSP90 <= 14.25 ng/ml. Furthermore, univariable and multivariable hazard model analysis revealed that high HSP-90 levels implied the probability of death significant increase by about three times (P-value = 0.0445) by adjusting with covariates of gender, age, race, ethnicity, marital status, BMI, pancreatitis, treatment, and max tumour size.

Conclusion: High serum levels of HSP-90 may be a risk factor and independent prognostic indicator for tumourigenesis in pancreatic ductal adenocarcinoma.

P-13-72

Profiling immuno-inflammatory and serum biomarkers for the early detection of pancreatic cancer

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Abstract

Background: Pancreatic cancer is associated with a particularly poor prognosis. Currently, pancreatic ductal adenocarcinoma (PDAC) has a median survival from the time of diagnosis of 3 to 6 months. A main reason for such poor outcomes is a lack of early detection, partly because of non-specific symptoms in early stages of the disease. Efficient strategies for the screening and surveillance of patients at risk of pancreatic cancer have not been established. Given the dismal prognosis of advanced stage disease, the development of highly sensitive and specific laboratory tests is pivotal to identify patients at risk and to improve early detection of this lethal disease.

Methods: Over the last years, we have developed a prospectively-collected biobank of pre-diagnosis samples from patients with non-specific symptoms (including chronic pancreatitis cases) and patients diagnosed with pancreatic cancer. All samples were annotated with clinical and demographic information. Our biobank contains blood, urine and tissue samples that could be of interest to other members of the research community. Protein biomarkers were quantified using ELISA, Luminex multiplex assays (MAGPIX), Olink's multiplex immunoassays as well as mass spectrometry-based approaches. An ensemble learning model was applied. Receiver operating characteristic (ROC) curves were constructed for each model to assess diagnostic accuracy. The AUC for the ROC curves was used as the performance metric.

Results: Our previously published work described a combination of inflammatory and cancer-specific biomarker signatures in blood that differentiate benign and malignant pancreaticobiliary disease. Now, even though the results are preliminary, by analysing samples from symptomatic patients, chronic pancreatic cases and PDAC, we observed that CA19-9 in combination with markers identified in our cohort and their use in multi-marker longitudinal algorithms, may improve test performances and lead time to enable early detection of PDAC. We also incorporated symptoms (QCancer) and clinical information (diabetes status, BMI, full blood count) in our studies.

Conclusion: Our data have the potential to improve the diagnosis of patients with pancreatic cancer and to be incorporated into diagnostic pathways but need improvement through the incorporation of additional biomarkers and validation to support the development of targeted high-throughput assays.

P-13-73

The role of GSK3β in DNA repair mechanisms and resistance in PDAC

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Abstract

Background: Late diagnosis, chemoresistance, high recurrence rate determines the aggressiveness of pancreatic cancer (PC). The subgroup PDAC shows a high intra- and intertumoural heterogeneity. Molecular subtypes display different tumour biology, therapy response, prognosis. The minor PDAC-subtype with gBRCA1/2 mutation characterised by insufficient DNA repair qualifies for platin-based therapy and PARP-inhibitor. Still, major subtypes require clinical implementation. GSK3β promotes proliferation, DNA repair, therapy resistance and is highly expressed especially in the infaust basal subtype. Interestingly, GSK3β-inhibition (GSK3βi) resensitises PDAC to gemcitabine.

Methods: We stained 221 patient samples for GSK3β and NFATc1. Established murine and human PDAC cell lines, patient-derived-cell lines (CDX) and -organoids (PDO) were used for experiments with GSK3βi, siRNA knock-down (KD). NFATc1 CRIPR/Cas9 knock-out (KO) was established with KPCbl6-cells. Chemotherapeutics Cisplatin and Irinotecan were applied to cells and PDO. RNA-seq, Western-blot (WB), qPCR, flow-cytometry, IHC, IF, live-cell imaging, DNA damage repair assay, BrdU, MTT were used to study effects of GSK3β and NFATc1.

Results: RNA-seq analyses exhibited a regulation of DNA damage response following GSK3βi and -KD. qPCR and WB analyses confirmed this effect showing a downregulation of DNA repair by BRCA1, BRCA2, Rad51 and an increase in DNA damage indicated by γH2AX. Combinational treatment with chemotherapeutics disclosed additional antiproliferative effects and DNA damage. ATAC-seq data revealed the NFAT binding motif in genes with altering expression following GSK3βi. Furthermore, GSK3βi reduced NFATc1 levels in WB. Following NFATc1-KD RAD51 levels were reduced and γH2AX level increased especially if combined with Cisplatin. NFATc1-KO sensitized cells to chemotherapy. Reduction of viability by GSK3βi in NFATc1-KO cells was impaired such as combination with chemotherapy had no additional effect. Resectates of PC patients showed different clustering of GSK3β- and NFATc1-level in IHC according to resectability.

Conclusion: GSK3β-NFATc1-signalling pathway regulates DNA damage response and repair in PDAC. GSK3βi induces a BRCAness phenotype and increases chemosensitivity. Furthermore, we hypothesize that GSK3β determines therapy response and stratification for therapy. Therefore, we are correlating the GSK3β-levels of patients with clinical data and investigating the role of NFATc1 in treatment with GSK3βi and chemotherapy in an animal trial.

P-13-74

Multiplex analysis of pancreatic, oesophageal and rectal adenocarcinoma – a cross-cancer approach on the impact of neoadjuvant therapy on the tumour microenvironment

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Abstract

Background: The prognosis of gastrointestinal malignancies has improved significantly with the introduction of neoadjuvant therapy (neoTx). For rectal (RCa) and oesophageal adenocarcinoma (OCa), neoTx has become the standard of care, resulting in tumour-downsizing and significantly prolonged patient survival. However, the effects of neoTx on the topographical interactions between different populations of tumour-infiltrating immune cells, the degree of intratumoural immune infiltration, the distance to tumour cells, as well as their spatial interactions with other important features of the tumour microenvironment (TME), are still unknown. In this cross-cancer histopathological profiling of the microenvironment of rectal and oesophageal tumours, we aim to investigate the local effects of cytotoxic agents and determine whether these correspond to the pathological changes observed in pancreatic cancer (PCa).

Methods: In this study, we employed multiplex immunohistochemistry (mIHC) based on tyramide signal amplification (TSA) using OPAL® dyes and a customized 7-plex approach to characterize tumour-associated stromal features (CD11c, CD34, NCAM, PGP9.5, aSMA, PanCK) as well as tumour-infiltrating lymphoid (CD3, CD4, CD8, CD20, FOXP3, PanCK) and myeloid cell subsets (CD11b, CD33, CD68, CD208, HLA-DR, PanCK). FFPE samples from 60 neoadjuvantly treated RCa and 40 OCa patients and a matched cohort of primary resected patients were included in the analysis.

Results: In PCa, neoTx alters the TME by depleting pro-tumourigenic immune cells, such as myeloid-derived suppressor cells (MDSC) and regulatory T cells, and suppressing tumour-associated stromal activation, neural invasion, and microangiogenesis. In our current study, we generated three standardised 7-plex panels for comprehensive histopathologic analysis of the immune architecture and associated stromal features of neoadjuvantly treated RCa and OCa patients compared with primary resected patients. Lymphoid subpopulations included Th-cells, cytotoxic T-cells, regulatory T-cells, and B-cells, while MDSC, dendritic cells, M1- and M2-macrophages were analysed in the myeloid panel within the same FFPE slide.

Conclusion: Our findings highlight new differential cell identities in neoTx-treated PCa patients and confirm their suitability for optimizing future clinical immunotherapy trials. Our current approach validates multiplex-IHC approaches for histological profiling of FFPE tumour samples in RCa and OCa and demonstrates the importance of a deep topographic characterisation to understand the TME composition of gastrointestinal malignancies after neoTx.

P-13-75

High pyroptosis activity in pancreatic adenocarcinoma: poor prognosis and oxaliplatin resistance

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Abstract

Background: Pyroptosis, as a type of inflammatory programmed cell death, has been studied in inflammatory diseases and numerous cancers but its role in pancreatic ductal adenocarcinoma (PDAC) remains unknown.

Methods: A TCGA-PDAC cohort was enrolled for bioinformatics analysis to investigate the effect of pyroptosis on the prognosis and drug sensitivity of patients. PA-TU-8988T and CFPAC-1 cells were selected for investigating the role of pyroptosis in PDAC.

Results: A distinct classification pattern of PDAC mediated by 21 pyroptosis-related genes (PRGs) was identified. It was suggested that higher pyroptosis activity was associated with poor prognosis of patients and higher tumour proliferation rates. We further established a prognostic model based on three PRGs (GSDMC, CASP4 and NLRP1) and the TCGA-PDAC cohort was classified into low and high-risk subgroups. It is noteworthy that the high-risk group showed significantly higher tumour proliferation rates and was proved to be highly correlated with oxaliplatin resistance. Further experiments suggested that overexpression of GSDMC promoted the proliferation and oxaliplatin resistance of PA-TU-8988T cells, while downregulation of GSDMC showed opposite effects in CFPAC-1 cells. Finally, we found that the activation of pentose phosphate pathway (PPP) was the mechanism by which GSDMC overexpression promoted the proliferation and oxaliplatin resistance of pancreatic cancer cells.

Conclusion: In this study, we found that higher pyroptosis activity is associated with worse prognosis and oxaliplatin resistance of PDAC patients. In addition, as a core effector of pyroptosis, GSDMC promoted proliferation and oxaliplatin resistance of pancreatic cancer cells, which will provide new therapeutic target for PDAC patients.

P-13-76

Allelic regulation of Keratin 19 gene expression during pancreatic development and carcinogenesis

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Abstract

Background: Within the pancreas, Keratin 19 (KRT19) labels the ductal lineage and is a diagnostic marker for pancreatic ductal adenocarcinoma (PDAC), however it's role in development and disease remains poorly understood.

Methods: In order to investigate KRT19 expression dynamics during pancreatic duct formation and carcinogenesis, we developed a human pluripotent stem cell (PSC)-based KRT19 reporter system. In a HUES8 background, an mCherry reporter sequence was inserted heterozygously into the 3' end of the endogenous KRT19 locus to monitor KRT19 expression. Employing a genuine differentiation protocol, high yields of first pancreatic progenitors (PPs) and then mature pancreatic duct-like organoids (PDLO) were generated from KRT19 reporter PSCs.

Results: While KRT19/mCherry expression was initiated at early endoderm stage, mCherry signal was present in nearly all cells at pancreatic endoderm (PE) and PP stage. Interestingly, despite all cells expressing KRT19, the mCherry positivity dropped to 50% after ductal maturation, indicating a permanent switch from biallelic to monoallelic expression. DNA methylation profiling separated the distinct differentiation intermediates with site specific

DNA methylation patterns occurring at the KRT19 locus during ductal maturation. Accordingly, the monoallelic switch was reverted upon treatment with a DNA-methyltransferase inhibitor. In human PDAC cohorts, high KRT19 expression and low DNA methylation correlate with decreased survival. At the same time, activation of oncogenic KRASG12D signalling in our reporter system reversed monoallelic back to biallelic KRT19 expression in PDLOs. Furthermore, KRT19 positivity correlated with KRAS expression in single PDAC cells KRAS WT tumours harbour decreased KRT19 expression and increased DNA methylation. When elucidating KRT19 as a potential biomarker for PDAC, elevated KRT19 protein was detected in patient plasma compared to control groups. Interestingly, higher concentrations correlated with shorter progression free survival in Gemcitabine/nabPaclitaxel treated patients, while the opposing trend was observed for FOLFIRINOX treated ones.

Conclusion: Apart of being an important pancreatic ductal lineage marker, KRT19 expression is tightly controlled via a switch from biallelic to monoallelic expression upon during ductal lineage entry and is aberrantly expressed after oncogenic KRASG12D-expression, indicating a role in PDAC development and malignancy. Soluble KRT19 might be a relevant biomarker to stratify treatment in metastatic PDAC.

P-13-77

Loss of ATM facilitates nutrient stress-induced metabolic reprogramming supporting pancreatic cancer aggressiveness

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Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is expected to be the 2nd leading cause of cancer-related death by 2030. A major hallmark of pancreatic cancer is a strong desmoplastic reaction associated to a reduced nutrient perfusion. Although previous studies have demonstrated how the mutational landscape impacts the metabolic phenotype, assigning specific metabolic patterns to a given genotype is still of high interest for tailored therapies. Homologous recombination deficiency (HRD), caused by mutations such as ATM, fosters PDAC aggressiveness, a mesenchymal phenotype and a desmoplastic reaction.

Methods: To delineate the impact of ATM deficiency-driven HRD on PDAC metabolism, we investigated mouse ATM-KO PDAC cell lines. We performed a wide range of in vitro experiments to evaluate cell viability, apoptosis, and functionality of PDAC cells, as well as ATP production rates under nutrient stress. To dissect the underlying mechanisms of metabolic reprogramming in Atm-deficient cells, an individualized drug library targeting the main metabolic pathways for energy and macromolecule production was designed.

Results: We show that ATM loss facilitates PDAC cell adaptation to nutrient scarcity, evading metabolic stress-induced apoptosis. Mechanistically, adaptation to nutrient stress was accompanied by higher vulnerability to inhibitors targeting ATP-generating pathways oxidative phosphorylation (OxPhos) and glycolysis, as well as pentose phosphate pathway branching from glycolysis. Atm-deficient cells also revealed acetate metabolism dependency, channelled into fatty acid synthesis and TCA cycle. In line, ATM loss correlated with increased ATP production. These results are supported by human PDAC protein expression data showing a negative correlation between expression of ATM and OxPhos, glycolysis and acetate metabolism-related enzymes. Finally, ATM loss promoted PDAC aggressive features maintenance under nutrient starvation, including mesenchymal phenotype and DNA damage accumulation.

Conclusion: Our results indicate that specific metabolic reprogramming, affecting ATP generation and macromolecule biosynthesis pathways and occurring in ATM-deficient cancer HRD cells upon nutrient stress promotes cell

survival and aggressiveness, which may ultimately contribute to tumour progression. Overall, we demonstrate how PDAC biology is impacted by genotype-specific metabolic remodelling, enabling exploitation of HRDness metabolic vulnerabilities by interference strategies.

P-13-78

Protein expression mapping reveals molecular mechanisms in pancreatic cancer-related diabetes

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Abstract

Background: In up to 10% of individuals newly diagnosed with type 2 diabetes (T2DM), diabetes is secondary to pancreatic disease, of which 10% is pancreatic cancer-related. Individuals over the age of 50 years with new-onset diabetes are considered to be the highest risk group for pancreatic cancer, with diabetes presenting as a paraneoplastic symptom. The mechanisms underlying the onset of diabetes in pancreatic cancer and its implications in disease development, detection and treatment remain poorly understood.

Proteome research has traditionally focused on the discovery of biomarkers and drug targets. However, modern proteomics technologies present opportunities for increasingly deep quantitative analysis of the proteome. In-depth proteome profiling is affording new insights into biological processes, including disease mechanisms.

Methods: Mass spectrometry (SWATH)- and aptamer-based proteomics workflows were employed for the analysis of 210 plasma samples, comprising seven case and control groups, stratified according to diabetes status. Groups included pancreatic cancer with/without diabetes, chronic pancreatitis with/without diabetes, new-onset diabetes (<3 years post-diagnosis), long-standing diabetes (>3 years post-diagnosis) and healthy controls. Raw SWATH data was processed using three peptide libraries with outputs evaluated against those obtained from the aptamer-based analysis.

Results: Over 7,500 proteins, from >6,500 genes, were identified per sample. A significant overlap in the genes identified from SWATH- and aptamer-based analyses was observed, with further overlap seen in the number of biological pathways represented in each data set. Comprehensive bioinformatics is ongoing to align proteomics and clinical data.

Conclusion: Using highly multiplexed proteomics platforms, work is underway to interrogate the molecular pathways contributing to the pathophysiology of diabetes in pancreatic cancer. This knowledge will support the discovery of new biomarkers for earlier detection and will inform future treatment strategies for early disease.