PANKREAS

Gastrohighlights 2019

Rainer Schöfl
Linz, A
Interessenskonflikte

• persönlich:
  – Vortragshonorare Boston Scientific, Medtronic
  – Advisory Boards Norgine, Falk, Grünenthal

• Abteilung:
  – Fortbildungsunterstützung
  – Kongressunterstützung
Chronic Asymptomatic Pancreatic Hyperenzymemia: A Long-term Follow-up.
Amodio A, De Marchi G, Granato A et al. (Rom, Verona)

- chronic asymptomatic pancreatic hyperenzymemia - a benign disease?
- first phase 2005 to 2010, reinvestigated from 2013 to 2017 with a phone call ± MRCP with secretin stimulation
- 133 subjects, mean follow-up of 9.3+/−5.2 years

- no episode of acute pancreatitis or abdominal pain
- 60 of 109 underwent second MRCP with secretin stimulation: results unchanged in 54 (90%), worsened in 3 (5%) and improved in 3 (5%)

- excluding subjects with a pancreatic disease at index magnetic resonance imaging, asymptomatic hyperenzymia is a benign condition
Combination of Diclofenac and Sublingual Nitrates Is Superior to Diclofenac Alone in Preventing Pancreatitis After Endoscopic Retrograde Cholangiopancreatography.
Tomoda T, Kato H, Ueki T et al. (Okayama/J)

- 12 endoscopic units in Japan
- diclofenac suppositories (50 mg) within 15 minutes after the endoscopic procedure alone (n = 442) or in combination with sublingual ISDN (5 mg) 5 minutes before the endoscopic procedure (n = 444)

- PEP: 25 in the combination group (5.6%), and 42 in the diclofenac-alone group (9.5%) (relative risk 0.59; 95% CI 0.37-0.95; p = 0.03)

- moderate to severe pancreatitis: 4 patients (0.9%) in the combination group and 10 patients (2.3%) in the diclofenac-alone group (relative risk 0.12; 95% CI 0.13-1.26; p = 0.12)
Enhanced Recovery in Mild Acute Pancreatitis: A Randomized Controlled Trial.
Dong E, Chang JI, Verma D, Butler RK, Villarin CK, Kwok KK, Chen W, Wu BU

- non-opioid analgesia, patient-directed oral intake and early ambulation versus opioid analgesia and physician-directed diet

- 46 participants (53.1 years, 54.3% female)

- time to successful oral refeeding: 13.8h vs. 124.8h, p < 0.001

- pancreatitis activity scores trended lower at 48 to 96h

- earlier time to refeeding in patients with AP safe and effective
Cholecystectomy during Index Admission for Acute Biliary Pancreatitis lowers 30-Day Readmission Rates.


- 180.480 pts. with AP, 23% biliary AP
- same-admission cholecystectomy in 55% (n = 19.274) of pts. without severe AP

- 10.5% unplanned readmitted within 30d:

  - pts. who underwent same-admission cholecystectomy 6.5% compared with 15.1% in those who did not (p<0.001) - OR 2.27 (CI 2.04-2.56)

- severe AP, sepsis, 3 or more comorbidities and admissions to small or rural hospitals were less likely to undergo same-admission CCY
Pancreas 2019 Apr; 48(4): 537-543
Impact of Antimicrobial Prophylaxis for Severe Acute Pancreatitis on the Development of Invasive Candidiasis: A Large Retrospective Multicenter Cohort Study.
Horibe M, Sanui M, Sasaki M et al. (Japan)

• multicentric (n = 44), retrospective, consecutive patients with severe acute pancreatitis 2009 - 2013

• 1097 patients with SAP, 850 (77.5%) received antimicrobial prophylaxis and 21 (1.9%) developed invasive pancreatic candidiasis.

• multivariable logistic regression analysis: antimicrobial prophylaxis was significantly associated with the development of invasive pancreatic candidiasis, OR 4.23 (95% CI 1.14-27.6, p = 0.029)
Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis.
Schepers NJ, Bakker OJ, Besselink MG et al., Dutch Pancreatitis Study Group

DESIGN:
We performed a post hoc analysis of a prospective database of 639 patients with necrotising pancreatitis from 21 hospitals. We evaluated the onset, duration and type of organ failure ...

CONCLUSION:
In patients with necrotising pancreatitis, early persistent organ failure is not associated with increased mortality when compared with persistent organ failure which develops further on during the disease course. Furthermore, no association was found between the duration of organ failure and mortality.
Trikudanathan G, Tawfik P, Amateau SK et al. (USA)

• delay in drainage until 4 or more weeks to allow collections to wall off vs. clinical deterioration mandating earlier intervention

• 76 early and 117 standard interventions, 75% included drainage ± necrosectomy

• organ failure improved significantly in both groups
• difference in mortality (13% vs. 4%, p=0.02)
• need for rescue open necrosectomy (7% vs. 1%, p=0.03)

• no difference in complications
Increased Incidence of Pseudoaneurysm Bleeding With Lumen-Apposing Metal Stents Compared to Double-Pigtail Plastic Stents in Patients With Peripancreatic Fluid Collections.
Brimon B, Han S, Tatman PD et al. (USA)

- significant stent-related adverse events were observed ≥3 weeks post intervention in LAMS cohort. Interim audit resulted in protocol amendment where CT scan was obtained at 3 weeks post intervention followed by LAMS removal if WON had resolved. After protocol amendment, there was no significant difference in adverse events between cohorts.

Gut 2019; 68(7): 1200-1209
Non-superiority of lumen-apposing metal stents over plastic stents for drainage of walled-off necrosis in a randomized trial.

- Drainage of walled-off necrosis or pancreatic pseudocysts using DPS was associated with fewer bleeding events overall, including pseudoaneurysm bleeding, but bleeding risk with LAMS should be weighed against the trend to higher infection rates with DPS.
An Endoscopic Transluminal Approach, Compared With Minimally Invasive Surgery, Reduces Complications and Costs for Patients With Necrotizing Pancreatitis.

Bang JY, Arnoletti JP, Holt BA et al. (USA)

- RCT of infected necrotizing pancreatitis requiring intervention
- minimally invasive surgery (laparoscopic or retroperitoneal, n = 32) or endoscopic drainage +/- necrosectomy, (n = 34)

<table>
<thead>
<tr>
<th></th>
<th>endoskopische Drainage +/- Nekrosektomie</th>
<th>laparoskopische o. retroperitoneale minimal invasive Chirurgie</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Majorkomplikation o. Tod</td>
<td>11,8%</td>
<td>40,6%</td>
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<tr>
<td>Mortalität</td>
<td>8,8%</td>
<td>6,3%</td>
<td>0,999</td>
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<tr>
<td>Fisteln</td>
<td>0%</td>
<td>28,1%</td>
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<tr>
<td>Majorkomplikationen</td>
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<td>0,69 +/- 1,03</td>
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<tr>
<td>Lebensqualität (3mo)</td>
<td>besser</td>
<td>schlechter</td>
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<tr>
<td>mittlere Kosten</td>
<td>$ 75.830</td>
<td>$ 117.492</td>
<td>0,039</td>
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</table>
• 217 PRSS1 carriers
• most frequently detected mutations: p.R122H (83.9%) and p.N29I (11.5%)

• 37 PRSS1 carriers were deceased at conclusion of the study, 5 from pancreatic cancer

• median overall survival was 79.3 years

• risk of pancreatic cancer was significantly greater than age- and sex-matched SEER data, cumulative risk was 7.2% at 70 years.

• risk of pancreatic cancer was much lower than in previous reports
Fazit Pankreatitis 1

• asymptomatische Enzymerhöhung mit unauffälliger S-MRCP scheint harmlos
• ISDN zusätzlich zu Diclofenac ist günstig in der Prophylaxe von PEP sein (s. ESGE-Guideline-Update)
• (bei milder akuter Pankreatitis kann die natürliche Ernährung rasch wieder begonnen werden und ist sicher)
• bei biliärer Pankreatitis kann die Cholezystektomie während des Erst-Aufenthalts die 30-Tage-Wiederaufnahmen halbieren
• Hereditäre Pankreatitis hat ein niedrigeres Karzinomrisiko als bisher angenommen
Fazit Pankreatitis 2

• prophylaktische Antibiotika bei schwerer Pankreatitis scheinen gefährlich (Candidiasis)
• (Zeitpunkt und Dauer eines Organversagens bei schwerer akuter Pankreatitis ohne prognostische Relevanz)
• die Drainage peripankreatischer Flüssigkeitsansammlungen kann vor 4 Wochen riskiert werden, ist aber etwas komplikativer
• für die Drainage peripankreatischer Flüssigkeitsansammlungen haben LAMS gegenüber DPS Vor- und Nachteile
• bei Patienten mit infizierter Pankreasnekrose und Drainagebedarf hat der endoskopisch-transluminale Zugang im Vergleich zu minimalinvasiver Chirurgie weniger Komplikationen und ist billiger
Risk of Neoplastic Progression in Individuals at High Risk for Pancreatic Cancer Undergoing Long-term Surveillance.
Canto MI, Almario JA, Schulick RD et al. (USA)

- 354 at high risk for PDAC (genetics, family history), follow-up 5.6a
- EUS, then surveillance with EUS, MRI and/or CT
- incidence of PDAC, PANIN3 or IPMN with HGD?

- worrisome features or rapid cyst growth detected in 68 (19%)
- neoplastic progression: 24 (14 PDAC, 10 HGD) (7%) = 1.6%/a
- worrisome features before diagnosis of PDAC or HGD: 93%

- 85% PDACs detected during surveillance were resectable and survived >3a
- median time from baseline until PDAC diagnosis 4.8a
Results of First-Round of Surveillance in Individuals at High-Risk of Pancreatic Cancer from the AISP (Italian Association for the Study of the Pancreas) Registry.

Paiella S, Capurso G, Cavestro GM et al.

- asymptomatic individuals with familial (FPC) or genetic frailty (BRCA1/2, p16/CDKN2A, STK11/LKB1 or PRSS1)
- annual MRCP; EUS proposed to patients who refused or could not be submitted to MRCP
- 187 underwent a first-round screening examination with MRCP (174; 93.1%) or EUS (13; 6.9%) from 2015 to 2018, mean age 51 years (range 21-80)
- 165 (88.2%) FPC and 22 (11.8%) genetic risk individuals

- MRCP detected 28 (14.9%) IPMN and 1 invasive carcinoma
- EUS detected 4 pancreatic cancers (2.1%): 1 resected, 1 locally advanced, 2 metastatic
- Age > 50, smoking and having >2 relatives with PC were independently associated with detection of pre-malignant and malignant lesions
- rate of malignancies found in this cohort was high (2.6%)
Diagnostic Yield From Screening Asymptomatic Individuals at High Risk for Pancreatic Cancer: A Meta-analysis of Cohort Studies.
Corral JE, Mareth KF, Riegert-Johnson DL, Das A, Wallace MB (USA)

- meta-analysis: prospective cohort studies (>20 patients) of asymptomatic adults (lifetime risk >5%), screened by EUS and/or MRI, 19 studies with 1660 patients
- primary outcome: identification of high-grade PANIN or PDAC at initial screening and incidence during follow up

- 59 high-risk lesions identified (43 PDACs, 28 during the initial exam and 15 during follow-up) and 257 patients underwent surgery

- 135 patients at high-risk for pancreatic cancer must be screened to identify 1 patient with a high-risk pancreatic lesion
Retrospective study:
- Cystic lesions and first-degree relative (group 1, n = 269)
- Cystic lesions but no first-degree relative (group 2, n = 1195)
- No cystic lesions but first-degree relative (group 3, n = 720)

Among patients with Fukuoka-negative cysts, a significantly higher proportion underwent surgery in group 1 than in group 2 (10.90% vs. 5.90%; p = 0.03)
Higher Growth Rate of Branch Duct Intraductal Papillary Mucinous Neoplasms Associates With Worrisome Features.
Kolb JM, Argiriadi P, Lee K et al.

• retrospective analysis of images from 189 patients with BD-IPMN

• low-risk BD-IPMNs grow at an extremely low rate (less than 0.3 mm/year)

• BD-IPMNs in only about 6% of patients developed worrisome features and none developed high-risk features or invasive cancers

• BD-IPMNs that developed worrisome features were associated with a significantly higher rate of growth than lesions with low-risk features.

• low risk BD-IPMNs that grow more than 2.5 mm/year might require surveillance
49,749 Swedish individuals with acute pancreatitis and 138,750 controls, f/u median 5.3 years

769 developed pancreatic cancer, of whom 536 (69.7%) had a history of acute pancreatitis

Risk of pancreatic cancer was substantially increased during the first few years after acute pancreatitis but declined gradually over time, comparable to the pancreatitis-free population after >10 years.

Increasing number of recurrent episodes of acute pancreatitis was associated with increased risk of pancreatic cancer.

Delay in diagnosis of preexisting pancreatic cancer, if clinically presented as acute pancreatitis.
Resection of pancreatic cancer in Europe and USA: an international large-scale study highlighting large variations.
Huang L, Jansen L, Balavarca Y et al.

- resection rates ranged
  - from 13.2% (Estonia) to 21.2% (Slovenia) overall
  - from 34.8% (Norway) to 68.7% (Denmark) for stage I-II

- 2003-2016 resection rates only increased in the USA, the Netherlands and Denmark

- Schweiz, Österreich ?
RCT, performed in 4 centres in NL that each do 20 or more PDE/a

- Phase 1: 3 of 20 patients died within 90 days after laparoscopic PDE, compared with 0 of 20 patients after open PDE
- Phase 2: 63 additional patients randomised
- the trial was prematurely terminated by Safety Monitoring Board because of a difference in 90-day mortality

<table>
<thead>
<tr>
<th>n=105</th>
<th>laparoskopische PDE</th>
<th>offene PDE</th>
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<tr>
<td>90d-Mortalität</td>
<td>5</td>
<td>1</td>
<td>n.s.</td>
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<td>funktionelle Erholung</td>
<td>10d</td>
<td>8d</td>
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<td>Komplikationen Clavien-Dindo &gt;= III</td>
<td>25</td>
<td>19</td>
<td></td>
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<tr>
<td>Fisteln B/C</td>
<td>14</td>
<td>12</td>
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</tbody>
</table>
in patients with metastatic pancreatic cancer combination chemotherapy with FOLFIRINOX leads to longer overall survival than gemcitabine – adjuvant setting?

493 patients with resected pancreatic ductal adenocarcinoma received a modified FOLFIRINOX regimen or gemcitabine for 24 weeks.
A Multicenter Open-Label Randomized Controlled Trial of Pancreatic Enzyme Replacement Therapy in Unresectable Pancreatic Cancer.
Saito T, Nakai Y, Isayama H et al.

- in this RCT pancreatic lipase failed to improve BMI at 8 weeks in PDAC patients receiving chemotherapy
Preoperative next-generation sequencing of pancreatic cyst fluid is highly accurate in cyst classification and detection of advanced neoplasia.

Singhi AD, McGrath K, Brand RE et al.

- mutations in \textit{KRAS/GNAS} are highly specific for IPMNs and mucinous cystic neoplasms (MCNs), while \textit{TP53/PIK3CA/PTEN} alterations are associated with advanced neoplasia.

- 102 (17%) patients with surgical follow-up
- \textit{KRAS/GNAS} mutations were detected in 56 (100%) IPMNs and 3 (30%) MCNs and associated with 89% sensitivity and 100% specificity for a mucinous PC

- combination of \textit{KRAS/GNAS} mutations and alterations in \textit{TP53/PIK3CA/PTEN} had a 89% sensitivity and 100% specificity for advanced neoplasia

- patients with solid pancreatic lesions ≤ 15 mm in size
- stiffness was retrospectively compared with final diagnosis by FNA/FNB or surgical resection
- 218 patients, average size 11±3mm
- 23% PDAC, 52% NET, 8% metastases, and 17% others, 66% benign
- elastography: 50% stiff lesions and 50% soft lesions

**High Stiffness** had a sensitivity of 84%, specificity of 67%, PPV 56%, NPV **89%** for diagnosis of malignancy, for diagnosis of PDAC 96%, 64%, 45% and **98%**

- in patients with small solid pancreatic lesions EUS elastography can rule out malignancy with a high level of certainty if the lesion appears soft. A stiff lesion can be either benign or malignant.
Prediagnosis Use of Statins Associates With Increased Survival Times of Patients With Pancreatic Cancer.
Hamada T, Khalaf N, Yuan C et al.

- regular statin use before diagnosis was similarly associated with survival in the Nurses' Health Study (HR 0.79; 95% CI, 0.64-0.97) and Health Professionals Follow-up Study (HR 0.86; 95% CI, 0.63-1.15)

Metformin Use Is Associated With Longer Progression-Free Survival of Patients With Diabetes and Pancreatic Neuroendocrine Tumors Receiving Everolimus and/or Somatostatin Analogues.
Pusceddu S, Vernieri C, Di Maio M et al.

- a retrospective study of patients with pNETs found a significant association between metformin use and longer PFS

Increased levels of Branched-Chain Amino Acid associated with Increased risk of Pancreatic Cancer in a prospective Case-Control Study of a Large Cohort.
Katagiri R, Goto A, Nakagawa T et al.

- Japan Public Health Center-based prospective study showed association between increased plasma BCAA level and increased risk of pancreatic cancer - particularly when the increase in BCAAs was observed at least 10 years before diagnosis
Fazit Pankreastumore 1

- die meisten in Screening-Programmen entdeckten Pankreaskarzinome sind operabel und überleben länger als 3a
- ob Pankreas-Screening-Programme die Mortalität reduzieren und kosteneffizient sind, ist noch unbewiesen
- (Zystenwachstumsgeschwindigkeit, aber nicht eine familiäre Belastung erhöhen das Risiko beim IPMN)
- akute Pankreatitis als erstes Symptom eines Pankreaskarzinoms verzögert die Diagnose des Karzinoms
- (Resektionsraten des Pankreaskarzinoms in Europa sind generell niedrig und zwischen den Staaten sehr variabel)
Fazit Pankreastumore 2

- die laparoskopische Pankreaskopfresektion scheint gestorben
- FOLFIRINOX ist effektiver als Gemcitabine im adjuvanten Setting, aber toxischer
- (Pankreasenzymsubstition kann den Substanzverlust während Chemotherapie nicht aufhalten)
- Next Genome Sequencing verbessert pankreatische Zystensaftanalyse (so wie biliäre Histo und Zyto)
- (EUS-Elastographie bringt am Pankreas wenig)
- (Ätiologie: Assoziationen, aber Kausalität ?)