1. **Title:** Contemporary outcomes after pancreatoduodenectomy in a complete national cohort: Short-term morbidity and mortality within a universal health care system

**Presenter:** Linn Såve Nymo, Tromsø

**Background and aims:** High-volume series and RCTs excluding the old and frail can underestimate the real burden of complications after pancreatoduodenectomies. The aim of this study was to describe the short-term outcomes after PD in a complete, unselected national cohort and to assess possible regional divergence in activity or outcome.

**Study design:** An observational, national cohort study from the National Patient Registry (NPR) for the five-year period of 2012-2016. Outcome measures were mortality within 30 and 90 days and rate of reoperations and readmissions within 30 days. Age- and gender-adjusted resection rates were compared combining with data from Statistics Norway.

**Results:** Some 930 patients underwent pancreatoduodenectomy during the study period. Mortality was 1.5% (n=14) at 30 days and 3.7% (n=34) at 90 days. Reoperation rate was 14.1% and readmission rate 12.4%. Male patients had significantly higher 90-day mortality (OR 3.0 (CI 1.3-7.2) p=0.013) and reoperation rate (OR 1.9 (CI 1.3-2.8) p<0.001) compared to women. Mortality rates increased significantly for age ≥65 years, with an OR of 5.3 (CI 1.5-18.2) p=0.009 for those aged 65-74 years and OR 9.9 (CI 2.8-35.3) p<0.001) for those ≥75 years. There were no significant differences between the four RHAs in any clinical outcome or resection rate.

**Discussion:** Contemporary short-term outcomes after pancreatoduodenectomies in a national health care system with universal coverage demonstrate low 30- and 90-day mortality in an unselected population with negligible regional differences. **Conclusion:** The practice of pancreatoduodenectomies in Norway demonstrates favourable short-term outcomes on a national level with insignificant regional differences.

2. **Title:** The possibilities for prehabilitation in patients scheduled for liver or pancreatic tumour resection

**Presenter:** Laura van Wijk, Groningen

**Background:** Morbidity and mortality rates after resection of hepatic and pancreatic tumors are relatively high. Unfit patients, are more prone to complications. Preoperative risk stratification with subsequent necessary interventions (prehabilitation) can improve the overall condition of these patients and reduce perioperative complications. Prehabilitation focuses at different levels such as exercise, hemoglobin level, nutrition and psychosocial approaches. In this study, we aimed to gain more insight in the possibilities for prehabilitation in hepato pancreato biliary (HPB) cancer patients.

**Methods:** Cardiopulmonary fitness was measured by the Veterans Specific Activity Questionnaire (VSAQ) for all HPB patients for two consecutive months. If the score was <7 metabolic equivalent (MET), they performed a Cardio Pulmonary Exercise Test (CPET). Secondly, we retrospectively analyzed hemoglobin level, nutritional status, and postoperative complications in patients who underwent an oncologic liver- or pancreatic resection between 2015 and 2016.

**Results:** We identified 22 patients in the prospective cohort. Half of this group scored MET below 7 at the VSAQ. Of these 11, 7 patients underwent a CPET, of whom 71% had an aerobic threshold < 11 ml/min/kg. Secondly, of 276 HPB patients, 28.2% had surgery in an anemic state and 26.6% in an undernourished state. Postoperative complications occurred significantly more often in anemic or undernourished patients (p 0.003 and p 0.020). Multivariate analysis showed an adjusted OR 2.019 (95% CI: 1.0-4.2) for the anemic patients and an adjusted OR 1.352 (95% CI: 0.7-2.8) for the malnourished patients. Anemic patients were 6.5 times as likely to receive a perioperative transfusion (95% CI: 1.9-21.9; p=0.002) compared with patients without anemia.

**Discussion:** HPB cancer patients are susceptible to get in an anemic, physical unfit, and undernourished state. This is associated with a higher risk at postoperative complications. Further research should be focused at the implementation of preoperative optimization (prehabilitation) of the patient.
Title: Predicting the emerging impact of minimally invasive distal pancreatectomy

Presenter: Sjors Klompmaker, Amsterdam

Background: New methodology is needed to predict the emerging impact of surgical innovations like minimally-invasive distal pancreatectomy (MIDP) and expedite their widespread implementation to improve patient outcomes.

Methods: We used real-word data to model safety (composite major morbidity [CMM]: death or severe complications) and efficiency (length of stay) as a function of implementing MIDP for elective resection of pancreatic neoplasms. We applied validated risk predictions derived from multivariable logistic- and Cox regression models. For design and simulation, we used American College of Surgeons National Surgical Quality Improvement Program® (NSQIP®) data collected at 106 sites in 2014. For external geographical validation, we used outcomes data from Beth Israel Deaconess Medical Center and 17 Dutch Pancreatic Cancer Group centres collected between 2005 and 2016.

Results: We included 858 patients in the design- and 803 patients in the validation cohort, of whom 670 (40 per cent) underwent MIDP. The only modifiable factor improving safety and efficiency was minimally-invasive surgery. Model simulations predicted a 32 per cent (n=58) reduction in CMM among the NSQIP® population, from 21 per cent (179/858) prior to implementation to 14 per cent (121/858) at full implementation. Additionally, length of stay decreased from 6 to 5 days (hazard ratio 1.64, CI 1.42-1.89). These reductions were independent of patient selection criteria.

Conclusion: This new methodology predicts the emerging impact of MIDP during its implementation. MIDP is likely to improve safety and efficiency independent of patient selection factors and proportional to the implementation rate.

Title: Robotic-Assisted ALPPS for ALPS: Technique and Considerations

Presenter: Michael Passeri, North Carolina

Objective: First described in 2012, Associating Liver Partition and Portal Vein Ligation for Staged hepatectomy (ALPPS) procedure is a two-staged resection of advanced primary and metastatic liver tumors predicated on the regenerative capacity of the liver. Our aim is to highlight the technique and considerations for performing a robotic-assisted ALPPS procedure.

Background: A 69-year old male with rectal cancer status post low anterior resection and metachronous liver tumors dominating the right hemi-liver along with small satellite lesions occupying segments 4a/b and segment 2 presented following completion of systemic chemotherapy with eight cycles of FOLFOX and bevacizumab. Preoperative CT volumetrics demonstrated a future liver remnant/total liver volume ration (FLR) of 27%. Right portal vein embolization was not feasible secondary to the tumor burden and proximity to the right portal vein.

Results: Using the da Vinci Xi Surgical System the first stage of the ALPPS procedure was performed in robotic-assisted fashion. The patient was discharged home on post-operative day two. Prior to the second stage, CT volumetrics demonstrated a FLR of 47%. On post-operative day seven, the second stage robotic-assisted ALPPS procedure was performed. Segments 4a/b, 5, 6, 7 and 8 were removed. The patient was discharged home on post-operative day eight. Surgical pathology confirmed negative margins.

Conclusion: The robotic-assisted approach to the ALPPS procedure is a feasible alternative to a laparoscopic or an open approach when performed at a high volume center with advanced robotic expertise. This is the first described robotic-assisted ALPPS procedure to our knowledge.

Title: Determinants of severity in acute pancreatitis – A nationwide multicentre prospective cohort study

Presenter: Hanna Sternby, Lund

Objective: To compare and validate the different classifications of severity in acute pancreatitis (AP), and to investigate which characteristics of the disease are associated with worst outcomes. Summary Background Data: AP is a heterogeneous disease, ranging from uneventful cases to patients with considerable suffering and
high mortality rates. Severity classifications based on legitimate determinants of severity are important to correctly describe the course of disease.

**Methods:** Prospective multicenter cohort study involving patients with AP from 23 hospitals in Spain. The Atlanta Classification (AC), Revised Atlanta Classification (RAC) and Determinant-based Classification (DBC) were compared. Binary logistic multivariate analysis was performed to investigate independent determinants of severity.

**Results:** A total of 1,655 patients were included. RAC and DBC were equally superior to AC for describing the clinical course of AP. While any kind of organ failure was associated with bad outcomes, persistent organ failure (POF) was the most significant determinant of severity. All local complications were associated to worse outcomes. Infected pancreatic necrosis correlated with high morbidity, but not higher mortality compared to sterile necrotizing pancreatitis if POF was present. Multiple-organ POF was associated to higher mortality than single-organ POF. Exacerbation of previous comorbidity correlated to both increased morbidity and mortality.

**Conclusions:** The RAC and DBC both signify an advance in the description and differentiation of AP patients. Herein we describe the characteristics of the disease independently associated to morbidity and mortality. Our findings are valuable when designing future studies on AP but also for the improvement of current classifications.
Results: It was shown that the expression of all investigated mRNA was increased in cholangiocarcinoma tissue. Some statistical significant data of mRNA expression levels were found for experimental groups. The increased expression levels of Anxa1 and Krt7 in liver of DMN-treated hamster were observed. The upregulated expression of Tgfb1, Anxa1, Ext1, Krt7 in liver of O. felineus-infected hamster was registered. The expression levels of Tgfb1, Anxa1, Krt7 in liver of O. felineus+DMN-treated hamster were also increased.

Conclusion: The findings indicate that increased levels of mRNA considered as cholangiocarcinoma markers for humans have been revealed in our experimental model. Thereby, the model can be used for translational studies of mechanisms of bile duct cancer development.

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

Presenter: Niccola Funel, Pisa

Context: Preclinical models close to PDAC are needed. Growth factors play a pivotal role on the aggressiveness and migration. TGF-β expression represents the master factor involved in epithelial mesenchymal transition (EMT) phenomenon. Objective. Aim of this study was to investigate cell migration in 3D tissue-engineered model of PDAC through TGF-β protein expression.

Methods: Primary PDAC cells were seeded into sterile polyvinyl alcohol/gelatin (PVA/G) scaffolds at a density of 1×10⁵ cells/mm³ and cultured for 4 different times (2, 5, 8 and 15 days). Six scaffolds for each time were performed. The medium was replaced as needs in group A, while in group B, the medium was not replaced. Twenty-four formalin-fixed paraffin embedded (FFPE) 3D model were obtained. Analyses included: viability, morphology, histology marker expressions by immunohistochemistry (PanCk, EGFR, TGF-β, MMP9) and cell migration by computerized analyses of images. ELISA test (EGF concentration in the medium). Data were analyzed using ANOVA and Student’s tests. A p value < 0.05 was considered significant.

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

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

Title: Comparative genomic analysis of small well-differentiated PanNETs reveals genetic alterations associated with distant metastases

Presenter: Antonio Pea, Verona

Introduction: Well-differentiated pancreatic neuroendocrine tumors (PanNETs) with small size usually behave in a non-aggressive manner. However, a limited subset progress with metastatic spread to the liver. The genomic landscape of PanNETs has been recently unravelled and increasing evidences suggests that the ALT activation is a late event associated with increased tumor size and metastatic progression.

Methods: To investigate molecular alterations associated with early metastasis, 32 metastatic PanNETs <3cm and other 55 PanNETs <3cm non-metastatic after a 5-year follow-up following resection were collected from multiple institutions. Telomere-specific FISH and DAXX/ATRX IHC were performed to assess the ALT status. 24 PanNETs from the metastatic group and other 24 from the control group matched for size and WHO-grade were selected for the genomic analysis. Targeted sequencing was performed to identify mutations and high-density SNP-array to evaluate copy number variations (CNV).

Results: Variables associated with liver metastasizes were Ki67, N-stage and ALT. CNVs cluster analysis identified biological subtypes of PanNETs: 15 tumors characterized by recurrent chromosomal gains and CN-
LOH exhibited also ALT; 73%(11/15) were metastatic. 19 tumors were characterized by limited copy number and mutational events; 42%(8/19) of them developed metastases, including 5 G1 tumors. 14 PanNETs with recurrent chr11 loss, harboured also a MEN1 mutation in 8 cases and 35% (5/14) were metastatic.

**Conclusions:** We identified genomic patterns of small PanNETs with different risk to develop liver metastases: ALT is a biomarker for aggressive disease also among small tumors. Most of G1 metastatic tumors are characterized by limited genomic events, whereas MEN1 chromosomal loss identified a subtype with lower metastatic potential.

### Title: Characteristics of postoperative pancreatic fistula on abdominal CT-Scan: A multicentre cohort study

**Presenter:** F. Jasmijn Smits, Utrecht

**Objective:** To correlate radiological characteristics to the presence of clinically severe pancreatic fistula after pancreatectoduodenectomy.

**Methods:** All consecutive patients undergoing abdominal computed tomography (CT)-scan for (suspected) pancreatic fistula after pancreatectoduodenectomy in 2015-2016 in 4 Dutch Pancreatic Cancer Group centers were included. CT-scans were systematically re-evaluated by two expert radiologists according to predefined criteria, including dehiscence of the pancreatic anastomosis and the presence of fluid and gas. The reference test (i.e. clinically severe pancreatic fistula) was defined as need for invasive intervention for pancreatic fistula (ISGPS) or clinical deterioration due to abdominal sepsis causing ICU admission or death within 24 hours after CT-scan.

**Results:** A preliminary analysis was performed in 213 abdominal CT-scans in 150 patients: 72 CT-scans were positive and 141 CT-scans were negative for the reference test. The pancreatic anastomosis was scored ‘dehiscent’ in 38 positive and 51 negative CT-scans (53% vs. 36%; P=0.03; positive predictive value [PPV]0.42, negative predictive value [NPV]0.72). Fluid in direct contact to the pancreatic anastomosis was present in 57 positive and 94 negative CT-scans (80% vs. 67%; P=0.06; PPV0.38; NPV0.76), these collections contained gas in 40 positive and 52 negative scans (70% vs. 55%; P=0.10; PPV0.43; NPV0.70).

**Conclusion:** Radiological characteristics of clinically severe pancreatic fistula after pancreatectoduodenectomy on CT-scan include dehiscence of the pancreatic anastomosis and fluid in direct contact to the anastomosis containing gas, although diagnostic accuracy of these individual features is low. Further analyses will focus on combining radiological and clinical data to ultimately create a model for early detection of severe postoperative pancreatic fistula.

### Title: Macrophage depletion overcomes resistance to immune checkpoint blockade following irradiation in pancreatic cancer

**Presenter:** Keaton Jones, Thame

**Introduction:** Whilst immune checkpoint blockade has been shown to improve survival in a range of solid organ tumours, it remains ineffective in pancreatic cancer. Combination therapy with ionising radiation has been shown to sensitize tumours and potentiate responses to checkpoint blockade. Here we show that radiation recruits immunosuppressive macrophages to the tumour microenvironment, and these must be depleted in order to render pancreatic tumours sensitive to immunotherapy.

**Methods:** Colorectal (MC38) and pancreatic (KPC) cell lines were used for in vitro and in vivo work. For in vivo radiation subcutaneous tumours were developed on the flanks of C57 or CD1-nude mice and irradiated using a Gulmay 320 irradiator.

**Results:** Following radiation there was a significant recruitment of macrophages exhibiting an immunosuppressive phenotype to the tumour microenvironment. Macrophage depletion (anti-CSF-1) lead to a significant delay in tumour regrowth following irradiation (10Gy). Infiltrating macrophages expressed high levels of PD-L1 and anti-CSF treatment resulted in a reduction in tumour PD-L1 and increase in CD8 T lymphocytes. A combination of anti-CSF and anti-PD-L1 following 10Gy irradiation resulted in complete tumour regression in a subset of mice bearing KPC tumours. These effects were abrogated in mice depleted of CD8 T cells.
Discussion These results suggest that infiltrating macrophages may limit the adaptive immune response initiated as a result of radiation. This is of particular importance in the context of radiation which can elicit a potent immune response as well as altered PD-L1 expression.

| 12 | **Title:** International validation of the updated ISGPS postoperative pancreatic fistula definition in distal pancreatectomy  
**Presenter:** Jony van Hilst, Amsterdam  
**Objective:** To validate the updated International Study Group on Pancreatic Surgery (ISGPS) postoperative pancreatic fistula (POPF) definition in patients after distal pancreatectomy (DP) in an international multicenter setting. Summary Background Data: POPF remains the most common complication after DP. The 2005 ISGPS definition of POPF is nowadays used worldwide. Recently, an update of the definition was published.  
**Methods:** An international retrospective validation study, including patients who underwent DP between 2005 and 2016 in 5 centers in Italy, the Netherlands, UK and the USA was performed. Main focus was the effect of changing POPF grade A to biochemical leak (defined as no POPF) and changing the threshold of grade B. Distribution of complications amongst POPF grades according to the old and updated definition were compared.  
**Results:** In total, 1089 patients were included. The incidence of POPF decreased with the updated definition from 47% to 24% (p<0.01), largely because of changing POPF grade A into biochemical leak (no POPF) and a decrease in POPF grade B. Comparable morbidity was seen in the old and updated ‘no POPF group’ (Clavien-Dindo grade ≥3 complications 29(5%) vs. 46(6%) p=0.320; ICU-admission 15(3%) vs. 20(2%) p=0.601; hospital stay (7[6-9] vs. 7[6-9] days p=0.301). The change in definition of POPF grade B resulted in more Clavien-Dindo grade ≥3 complications in the updated POPF grade B group (124(38%) vs. 119(51%) p<0.01) and longer hospital stay (9 [9-13] vs. 9 days [7-15] vs p<0.01)  
**Conclusions:** Applying the updated 2016 ISGPS POPF definition showed improved discrimination between POPF grades and should therefore preferably be used to report POPF after DP. |

| 13 | **Title:** Open versus laparoscopic liver resection for colorectal metastases located in the postero-superior segments: *Data from the Oslo-CoMet Trial*  
**Presenter:** Davit Aghayan, Oslo  
**Background:** Laparoscopic liver resection of tumors located in the postero-superior (PS) segments is considered to be technically challenging. This study aimed to compare the perioperative outcomes for laparoscopic versus open resection of colorectal liver metastases located in the PS segments.  
**Methods:** This is a sub-study of the Oslo-CoMet trial. In this trial, 280 patients were randomly assigned to open or laparoscopic parenchyma-sparing liver resections of colorectal metastases. Inclusion was from February 2012 to February 2016. Patients with metastases in postero-superior segments were identified, and perioperative and short-term oncological outcomes were collected from the prospective trial database. The Accordion system and the Comprehensive Complication Index were used for grading of postoperative complications.  
**Results:** 62 patients underwent laparoscopic and 74 patients open liver resections. A total of 257 lesions were removed. The blood loss was less in open group (median, 500 vs. 250 ml, P = 0.001), whereas the operative time (median, 145 vs. 143 min) was equivalent in the two groups. Postoperative complications developed in 23 cases (31%) in open group and 16 cases (26%) in laparoscopic group (P = 0.49). The comprehensive complication index was higher in open group, no statistically significant difference between groups (mean, 32.4 vs. 26.4, P = 0.19). The median postoperative hospital stay was 2 days in the laparoscopic and 4 days in the open group (P < 0.001).  
**Conclusion:** We found similar postoperative complications rate and decreased hospital stay, following laparoscopic resection of posterior-superior segments in patients with CRLM. |
Title: New molecular diagnostic approaches based on fluorescence microscopy in pancreatic ductal adenocarcinoma (PDAC): validation of the prognostic value of CYB5A and of FAD lifetime imaging for margin discrimination

Presenter: Niccola Funel, Pisa, Italy

Context: Several clinicopathologic factors, such as stage, are prognostic variables in PDAC. Nevertheless, initial staging currently relies on relatively non-discriminatory imaging and stage definition, which is not known until resection, appears of limited use for the choice of the best therapeutic approach. Analysis of biomarkers in biopsies collected before surgery could improve stratification of patients to different clinical management. However, intracellular localization of biomarkers at submicron-scale is a key factor in the comprehension of effective prognostic factors, and this issue can be addressed only by cutting-edge imaging based on fluorescence microscopy. Objective. Through a multidisciplinary scientific enterprise including physicians, biophysicists, computational/experimental chemists and one industrial partner (Biomedica-Mangoni) we will achieve high-sensitivity and high spatial-resolution detection, by the use of microscopy techniques based on the spatial modulation of light excitation.

Methods: We will use computationally-designed recognition motifs with super-bright fluorescent qDots to afford novel probes for high-sensitivity detection of selected biomarkers, such as CYB5A (Giovannetti et al, JNCI 2014), in biopsies and tissue-microrays of (N>200) PDACs. Further, recent data emphasized how some optical properties of the endogenous fluorophores NADH and FAD, such as fluorescence lifetime, can unravel the metabolic difference between tumor and normal tissues. Therefore, we tested an established method of confocal fluorescence microscopy, namely the phasor approach to lifetime imaging, in order to distinguish tumor from normal tissue taking advantage of FAD endogenous fluorescence. with a confocal microscopy apparatus interfaced with a pulsed laser source (470 nm) and a spectral acquisition system able to follow fluorescence decay in the 490-600 nm range by time-correlated single photon detection.

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

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