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OP001 COLONOSCOPIC PERFORATIONS IN THE ENGLISH NHS BOWEL CANCER SCREENING PROGRAMME (NHSBCSP) - BEWARE DIAGNOSTIC PERFORATIONS AND THE SIGMOID COLON

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Introduction: Colonoscopies in the English National Health Service Bowel Cancer Screening Programme (NHSBCSP) are offered to 60-74 year olds with an abnormal Faecal Occult Blood Test and are performed at 61 Bowel Cancer Screening Centres (BCSCs) in England. There is a robust system for capturing details of adverse events, including perforation, following colonoscopy; patients are contacted at least twice post procedure and details are entered onto a national web based database.
Aims & Methods: This study aimed to (1) determine the overall rate of perforation in the NHSBCSP (2) describe perforation presentation, management and outcomes (3) determine post perforation surgery, stoma, morbidity and mortality rates and (4) identify factors associated with poorer patient outcomes.
We identified all reported colonoscopic perforations from the start of the NHSBCSP in 2006 up to 13/03/2014. The NHSBCSP defines perforation as: air, luminal contents or instrumentation outside the gastrointestinal tract. The database was interrogated to identify patient and procedure details. Bowel Cancer Screening Centres completed a detailed online questionnaire on patient presentation, management and outcome. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 20. Fisher's exact test and Pearson's chi-square were used to assess explanatory and outcome variables. A p value < 0.05 was considered signifcant.
Results: From 263,129 endoscopic procedures, 147 perforations were identified, a rate of 0.06%. Complete data was received on 117 perforations. 69.2% of perforations were therapeutic. The endoscopist visualised the perforation in 12.8% of cases applying endoclips in 10.2%. Most diagnostic perforations occurred in the sigmoid colon ($n = 12$). Of 115 patients admitted to hospital, 54.8% had surgery. Diagnostic perforations were significantly associated with the need for surgery ($p = 0.001$) (RR:1.86, 95% CI 1.39-2.49). A stoma was formed in 26.1% of those having surgery, male sex ($p = 0.015$) (RR:2.07, 95% CI 1.05–4.07) and a colorectal location in the sigmoid colon when compared with all other colorectal locations ($p = 0.000$) (RR:2.56, 95% CI 1.50-4.38) were significantly associated with stoma formation. 19.7% had post perforation morbidity defined as an in-patient complication or new diagnosis following admission. Diagnostic perforations ($P = 0.009$) (RR:2.70, 95% CI 1.37-5.35) and surgery ($p = 0.000$) (RR:38.18, 95% CI 2.37-613.81) were significantly associated with post perforation morbidity. Median hospital stay was 9.5 days (range 0-51 days). 25.2% of patients were admitted to the Intensive Care Unit. The mortality rate was 0.87%.
Conclusion: (1) This is the largest cases series, to our knowledge, specifically reporting outcomes after colonoscopic perforation in Europe. (2) Over a half of perforations admitted are likely to require surgery and over a quarter are likely to leave hospital with a stoma (3) A post-perforation morbidity rate of 19.7% and mortality rate of 0.87% compares favourably with other series (4) Diagnostic Perforations carry a significant risk of poorer patient outcomes including surgery and post perforation morbidity (5) Perforations in the sigmoid colon carry a significant risk of stoma formation.
Disclosure of Interest: None declared

OP002 A PANCREATIC DIFFERENTIATION PLATFORM TO STUDY CYSTIC FIBROSIS IN A DISH

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Introduction: Current scientific efforts mainly focus on the pulmonary manifestation of cystic fibrosis (CF) but the pancreatic phenotype represents particularly in long-term survivors an increasingly important hurdle. Recently, it has been shown that different mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) determine different risks of pancreatitis. Present literature implicates CFTR-function already in the development of pancreatic progenitor cells. Induced pluripotent stem cells (iPSC) present a powerful tool to investigate embryonic development but also to model diseases.
Aims & Methods: The precise mechanism how CFTR-mutations lead to exocrine but also endocrine insufficiency and regulate development of the pancreas is poorly understood and relevant preclinical models are lacking. Herein, we applied a series of experimental tools to patient-specific induced pluripotent stem cells to bridge the gap between CFTR genotype and pancreatic phenotype.
Results: First, we report the generation of induced pluripotent stem cells from several cystic fibrosis patients and healthy control individuals from plucked human hair-keratinocytes. **Second**, we developed a step-wise differentiation protocol to recapitulate pancreatic exocrine and ductal commitment in the dish. Briefly, precise titrations of a complex cocktail of signalling clues mimicking pancreatic development allowed us to obtain virtually pure cultures of definitive endoderm but most importantly up to 60% of true pancreatic Nkx6.1/Pdx1-double positive progenitors. Subsequently, we developed these progenitors to form three-dimensional organoids, which can be passaged >6 passages *in vitro*. Detailed characterisation of these organoids including confocal laser microscopy and quantitative PCR techniques revealed mostly ductal but also exocrine pancreatic tissue. **Third**, we applied our CFTR-mutated and control iPSCs to this culture system and compared their step-wise pancreatic commitment capacity. Interestingly, there was no relevant difference between both genotypes reaching similar efficiencies of definitive endoderm, pancreatic endoderm and exocrine/ductal cells. **Finally**, we applied a series of assays to these cultures to phenotype the CFTR-genotype in the dish. While CFTR-mutated exocrine cultures appeared less robust but were still able to form pancreatic organoids, functional CFTR-activation revealed a dramatic difference: Forskolin, an established CFTR-activator, was applied to our organoid-cultures and lead to a pronounced and rapid swelling in wild-type cultures but to no relevant reaction in CFTR-mutant organoids.
Conclusion: Summarized, we provide a patient-specific platform to mimic and study pancreatic phenotypes of cystic fibrosis in a dish, a system never reported so far. Hereby, we ultimately erase a remaining hypothesis that CF-patients have defects in pancreatic development. Moreover, we reproduce the CF phenotype in our novel culture system to provide a patient- and pancreas- specific drug-screening platform.
Disclosure of Interest: None declared

OP003 TLR SIGNALLING IS DYSREGULATED IN OESOPHAGEAL ADENOCARCINOMA THROUGH SOMATIC MUTATIONS

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Introduction: Altered innate immune signalling may disrupt host-microbe homeostasis and promote an inflammatory microenvironment that favours tumourigenesis. The objective of this project was to assess whether somatic mutations in oesophageal adenocarcinoma (OAC) could interfere with Toll-like receptor (TLR) signalling, with a specific focus on TLR4.
Aims & Methods: We interrogated the mutational profiles of TLR genes in 170 OAC samples, which had undergone whole genome sequencing as part of the oesophageal ICGC study. We performed site-directed mutagenesis and created ten plasmids expressing mutant TLR4 with a CMV promoter (nine single nucleotide variants (SNVs), and one plasmid combined two SNVs). Luciferase reporter gene assays were performed in HEK293 cells stimulated with synthetic monophosphoryl lipid A (MPLA) to assess how the mutants altered TLR4 signalling and downstream activation of nuclear factor kappa B (NF-κB). Three of the TLR4 mutants were taken forward for transfection into the OAC cell lines OE33 and JH-EsoAd1, and ELISA was used to measure cytokine secretion after stimulation with MPLA and lipopolysaccharide (LPS).
Results: The TLR signalling pathway appeared to be recurrently mutated with missense mutations in 23/170 (13.5%) of tumour samples, including mutations in TLR1 (1.2%), TLR2 (0.6%), TLR4 (4.7%), TLR5 (0.6%), TLR7 (1.8%), TLR9 (1.2%), and MYD88 (1.5%). Based on our data and another recent study by Dulak *et al.*[1], TLR4 mutations were the most frequent (5.4% combined data). One tumour sample contained two TLR4 mutations, E439G and F703C. Interestingly, the mutation E439G was identified both in our dataset and in the study by Dulak *et al*. Furthermore, *in silico* modelling suggested that the E439G mutation is located proximal to the dimerization interface and may disrupt hydrogen bonds in the binding site of LPS and MD2. The use of NF-κB luciferase reporter assays demonstrated a significant decrease in ligand-dependent signalling for 7/9 of the TLR4 mutations tested in HEK293 cells. A double mutation of E439G with F703C revealed a further decrease in TLR4 signalling. Similarly, the concentration of IL-8 was significantly lower for TLR4 mutants R787H and E439G + F703C transfected into OE33 and JH-EsoAd1 cells stimulated with either MPLA or LPS, in comparison to wild-type TLR4. A similar trend was observed for IL-6. Interestingly, no significant decrease in TLR4 signalling was observed for mutant E439G stimulated with LPS in the OAC cell lines, suggesting that the strong agonist LPS is still able to bind the mutated ligand binding site, in contrast to the weak agonist MPLA.
Conclusion: TLR4 is recurrently mutated in OAC, and the majority of these mutations showed decreased TLR4 signalling in response to ligand stimulation in HEK293, OE33 and JH-EsoAd1 cells. The biological relevance of this in relation to host-microbe homeostasis and carcinogenesis is being explored.

Reference

1. Dulak AM, et al. Exome and whole-genome sequencing of esophageal adenocarcinoma identifies recurrent driver events and mutational complexity. *Nature Genetics* 2013 May; 45(5): 478–86.

Disclosure of Interest: None declared

OP004 A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF OZANIMOD, AN ORAL S1P RECEPTOR MODULATOR, IN MODERATE TO SEVERE ULCERATIVE COLITIS: RESULTS OF THE MAINTENANCE PERIOD OF THE TOUCHSTONE STUDY

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Introduction: Ozanimod (RPC1063) is an oral, selective sphingosine 1-phosphate (S1P) 1 and 5 receptor modulator in clinical development for the treatment of ulcerative colitis (UC) and relapsing multiple sclerosis. The objective of the maintenance period of TOUCHSTONE was to evaluate the longer-term efficacy and safety of 0.5 mg (low dose, LD) and 1.0 mg (high dose, HD) ozanimod in comparison to placebo (PBO), in patients with moderate to severe UC.

Aims & Methods: This randomized, double-blind, placebo-controlled trial assessed the efficacy, safety and tolerability of two orally administered doses of ozanimod vs placebo in patients with moderate to severe UC. A total of 197 patients were randomized (1:1:1) and treated once daily with PBO (n = 65), LD (n = 65) or HD (n = 67). As previously reported[1], a significantly greater proportion of patients receiving HD were in clinical remission, clinical response, and had mucosal improvement than LD or placebo patients at week 8, the primary endpoint for induction. The patients who achieved clinical response at week 8 continued into the maintenance period (MP) with their original treatment for an additional 24 weeks.

Results: Of 197 patients in the induction period, 103 (52.3%), continued in the MP, and 91 (88.3%) completed. At Week 32, clinical remission occurred in 20.9%, HD ($p = 0.0108$ vs. PBO), 26.2%, LD ($p = 0.0021$), and 6.2%, PBO. Clinical response occurred in 50.7%, HD ($p = 0.0002$), 35.4%, LD ($p = 0.0571$), and 20.0%, PBO. Mucosal improvement (Mayo endo-subscore ≤ 1) occurred in 32.8% for HD ($p = 0.0046$), 33.8%, LD ($p = 0.0036$), and 12.3%, PBO. The improvement in total Mayo score at Week 32 from baseline was 3.4, HD ($p = 0.0026$), 2.5, LD ($p = 0.2073$), and 1.9, PBO.
During the MP, the frequency of TEAEs were generally similar among treatment groups: (HD, 11/42 [26.2%]; LD, 6/36 [16.7%]; PBO, 9/25 [36.0%]). The most common TEAEs were: worsening of UC (HD, 1 [2.4%]; LD, 0 [0%]; PBO, 3 [12.0%]) and UTI (HD, 0 [0%]; LD, 1 [2.8%]; PBO, 1 [4.0%]). No AEs of special interest (cardiac, pulmonary, ophthalmologic, hepatic, malignancy or serious infections) were reported during the MP.

Conclusion: Patients with moderate to severe UC who continued treatment with ozanimod were more likely to both achieve and maintain clinical remission, clinical response and mucosal improvement than those receiving placebo. These data support the longer-term efficacy and safety/tolerability profile of ozanimod in the treatment of moderate to severe UC.

Reference

1. Sandborn W, Feagan B, Wolf D, et al. A randomized, double-blind, placebo-controlled induction trial of an oral S1P receptor modulator (RPC1063) in moderate to severe ulcerative colitis: results of the TOUCHSTONE study. 10th Congress of ECCO, 18-21 Feb 2015. Abstract OP024.

Disclosure of Interest: W. Sandborn Financial support for research: Receptos, Consultancy: Receptos, B. Feagan Consultancy: Receptos, D. Wolf Financial support for research: Receptos, Consultancy: Receptos, G. D'Haens Consultancy: Receptos, S. Vermeire Consultancy: Receptos, S. Hanauer Consultancy: Receptos, S. Ghosh Consultancy: Receptos, H. Smith Shareholder: Receptos, M. Cravets Shareholder: Receptos, P. Frohna Shareholder: Receptos, Directorship(s): Receptos, R. Aranda Shareholder: Receptos, Directorship(s): Receptos, S. Gujrathi Shareholder: Receptos, Directorship(s): Receptos, A. Olson Shareholder: Receptos

MONDAY, OCTOBER 26, 2015 11:00–12:30
MANAGEMENT OF CROHN'S DISEASE BEFORE AND AFTER SURGERY – ROOM F2

OP005 EARLY SURGERY OR IMMUNOSUPPRESSION IN CROHN'S DISEASE - EASY STUDY

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Introduction: Studies addressing the timing of surgery or medical treatment are scarce in Crohn's disease (CD) patients.

Aims & Methods: We aimed to compare the outcomes of CD patients submitted to immunomodulators or surgery in the first 6 months after diagnosis. A national, multicentric restrospective study in CD patients diagnosed and followed for more than 3 years. Global disability was defined if: 1 surgery or hospital admission in the first 5 years after index episode occurred; >1 surgery or 2 hospital admissions; >2 courses of steroids/year, steroid dependence or refractoriness; need to switch immunomodulator or the appearance of new clinical events.

Results: 516 patients were included and followed for 9.0 years (IQR: 5.7-14.2). We identified 3 cohorts: A-surgery in the 1st 6 months after diagnosis without any immunosuppression ($n = 87$), B-surgery in the 1st 6 months after diagnosis and immunosuppressors started 6 months after surgery ($n = 187$), C-immunosuppression in the 1st 6 months after diagnosis and without any surgery in this period ($n = 242$). Group A was the one with the lowest proportion of global disability (18% vs. B: 78% vs. C: 69%, $p < 0.001$). Diagnosis with >40 years old (OR 4.250, $p = 0.024$) was risk factor for belonging to group C in univariate analysis and in multivariate analysis, localization (L2-OR 0.162, $p = 0.016$ or L3 - OR 0.513, $p = 0.010$) was an independent risk factor. For early immunosuppression, localization (L2 -OR = 4,917, $p = 0.001$; L3 - (OR = 1,744, $p = 0.010$); behavior (B2-OR = 0.162, $p = < 0.001$, B3- OR = 0.130, $p < 0.001$) and age at diagnosis (A2- OR = 0.344, $p = 0.036$) were independent risk factors. Surgery rate/patient/10 year of follow-up (with index surgery) was lower in group C (0.35 vs. A: 1.20 vs. B: 1.45, $p < 0.001$).

Conclusion: The early introduction of immunomodulators showed to be best strategy in bowel sparing, however surgery in the first 6 months was associated with lower global disability particularly in those with more than 40 years at diagnosis.

Disclosure of Interest: None declared

OP006 ASSOCIATION OF BODY MASS INDEX (BMI) ON RISK OF FIRST INTESTINAL RESECTION IN CROHN'S DISEASE: NATIONAL POPULATION-BASED COHORT STUDY

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Introduction: Obesity in patients with Crohn's disease (CD) is increasing but the clinical impact of a higher BMI on long-term outcomes in CD is unknown. Obesity is considered a pro-inflammatory state and could potentially have an adverse impact.

Aims & Methods: We aimed to evaluate the association between BMI as recorded at diagnosis and rates of first intestinal resection in CD patients.

Methods: We constructed a population based adult cohort of incident cases of CD diagnosed between 1989-2010 using data from The Clinical Practice Research Datalink. We assigned patients to 4 groups based on BMI recorded within 30 days of initial diagnosis of CD. Kaplan-Meier analysis was used to calculate cumulative probability of surgery stratified by WHO definition of weight status. We used Cox regression to compute hazard ratios for factors associated with surgery.

Results: We identified 6183 eligible patients with CD. The median age at diagnosis was 33 years (IQR 25-52) and did not vary between the BMI subgroups. 58% of the cohort was female. The prevalence of obesity increased ~3 fold from 5% in those diagnosed between 1989-93 to 14% in those diagnosed 2006-10 ($p < 0.05$ chi-squared test for trend). The 5 and 10 year cumulative risk of intestinal resection in underweight, normal, overweight and obese patients was 9, 7, 5, 4% and 17, 12, 8, 9% respectively ($p < 0.001$ chi-squared test for trend). Risk of intestinal resection was significantly lower in overweight (HR 0.75; 95% CI 0.54 – 0.94) patients compared to normal weight. We also used BMI as a continuous rather than a categorical variable and found that increasing BMI was associated with a lower risk of surgery (HR -0.003, 95% CI -0.005 to -0.002) per unit increase in BMI. The associated need for thiopurines but not corticosteroids also reduced with increasing BMI with an HR of -0.79 (95% CI -1.06 to -0.52) and -0.27 (95% CI -0.57 to 0.03) respectively per unit increase in BMI.

Conclusion: The risk of subsequent intestinal resection is 25% lower in overweight patients with CD compared with those who are normal or underweight at diagnosis. Higher BMI is associated with lower rates of intestinal resection and thiopurine use and predicts a more stable disease course. The effect of improving BMI and nutritional status on CD patients at diagnosis needs further research.

Disclosure of Interest: S. Chatu: None declared, S. Saxena Conflict with: SS is funded by a National Institute for Health Research Career Development Fellowship (NIHR CDF-2011-04-048). This article presents independent research commissioned by the National Institute for Health Research (NIHR). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health., R. Pollok: None declared, V. Chhaya: None declared, V. Curcin: None declared, A. Majeed: None declared, V. Subramanian: None declared

OP007 POST-OPERATIVE ENDOSCOPIC RECURRENCE IN CROHN'S DISEASE: A PROSPECTIVE STUDY OF THE REMIND GROUP

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Introduction: Operative resection in Crohn's disease is not curative. After ileocecal resection, endoscopic recurrence is frequently observed on the anastomosis and/or on the neo-terminal ileum.

Aims & Methods: The aim of this study is to identify predictors of post-operative endoscopic recurrence. This is a prospective study performed in 9 centers of the REMIND group, collecting data at time of surgery and at 6 months, with extensive bio-banking. Inclusion criteria were: age > 18 years old; ileal or ileocecal CD; indication of surgery. Post-operative treatment was given according to a pre-established algorithm. Clinical, biological and endoscopic parameters (elementary lesions, Rutgeerts score) were collected at month 6. Factors associated with endoscopic recurrence were searched by univariate and multivariate regression analysis.

Results: 235 patients were included (109 male (47%) , 29 years old (IQR 26-39); disease duration 6 years (0-35)). At time of surgery, 77 patients (33%) were active smoker, 42 (18%) had a previous resection, and 51 patients (22%) had perianal lesions. Indication for surgery was stricturing disease (148), penetrating disease (91), and failure of medical therapy (29). At time of surgery, 139 patients (59%) had received anti-TNF therapy; most of them (78%) within the last 3 months. Also, 150 patients (64%) had been exposed to thiopurines. Endoscopy at month 6 was performed in 152 patients at time of analysis. After surgery, 25 patients received thiopurines alone, and 48 received anti-TNF therapy, combined with immunosuppressant in only 6 patients. An endoscopic recurrence (Rutgeerts score > 1) was observed in 70 patients (46%). In multivariate analysis, factors associated with post-operative recurrence (Rutgeerts score > 1) were: male gender (OR 3.2; IC95% 1.5-7.2), anti-TNF post-operative therapy (OR 0.41; IC95% 0.2-0.9), surgical indication for failure of medical therapy (OR 12; IC95% 2-27) or stricturing disease (OR 0.41; IC95% 0.2-0.9), active smoking (OR 7.6; IC95% 2.9-20), joint manifestations (OR 4.3; IC95% 1.4-13). Total absence of lesions (Rutgeerts score = 0) was observed in 51 patients (33%). The factors associated with a Rutgeerts score > 0 were: smoking (OR 3.2; IC95% 1.2-8.4), anti-TNF post-operative therapy (OR 0.44; IC95% 0.2-0.9) and presence of granuloma (OR 2.7; IC95% 1.04-6.9).

Conclusion: Despite a pre-established algorithm for prevention, almost half of patients had a significant endoscopic recurrence at month 6 with a Rutgeerts score of more than 1, and only one third of patients had no lesions. Several factors were associated with post-operative recurrence, including smoking behavior and anti-TNF therapy.

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Disclosure of Interest: M. Allez Lecture fee(s): Abbvie, MSD, Ferring, Consultancy: Novo Nordisk, Genentech, Pfizer, UCB, Janssen, C. Stefanescu: None declared, S. Nancey: None declared, A. Buisson: None declared, P. Desreumaux: None declared, P. Marteau: None declared, M. Fumery: None declared, J.-M. Gornet: None declared, N. Barnich: None declared, H. Sokol: None declared, P. Hofman: None declared, X. Treton: None declared, M.-C. Perier: None declared, X. Jouven: None declared, P. Seksik: None declared

OP008 APPRECIA: ADALIMUMAB VS AZATHIOPRINE IN THE PREVENTION OF CROHN'S DISEASE RECURRENCE AFTER SURGICAL RESECTION. A GETECCU MULTICENTER RANDOMIZED TRIAL

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Introduction: Postoperative recurrence of Crohn's disease (CD) is almost constant if no preventive therapy is adopted. Adalimumab (ADA) is effective in CD, but data in this setting are scarce.

Aims & Methods: To evaluate the efficacy of ADA compared to azathioprine (AZA) in preventing CD recurrence, we conducted a phase-3, 52-week, multicentric, randomized, evaluator-blind, superiority study (ClinicalTrials.gov NCT015564823). 22 Spanish centres included patients with ileocolic resection, randomized to ADA 160-80-40 mg SC or AZA 2.5 mg·kg·d PO (metronidazole in both arms). Ileocolonoscopy was performed at 1 yr, with central blinded reading. Primary endpoint was endoscopic recurrence* (Rutgeerts' 2b, 3, 4). MRI was performed at end of the study. Patient losses were considered non-responders (Non Responder Imputation).

Results: 91 patients were recruited, 84 randomized and treated, fulfilling the predefined sample size for a binary outcome superiority trial. Mean age was 36.9 ys, 50% females, disease duration 7.7 ys, 23.8% smokers, 7.1% previous resections, no differences between groups. Treatment was prematurely discontinued in 12/39 (30.8%) in AZA group and 4/45 (8.9%) in ADA group, due to adverse events in 11 cases (13.1%), significantly less in ADA group (4.4%) than in AZA group (23.1%) (p = 0.01).

ITT analysis (84 patients). Therapy failure was observed in 23/39 in AZA group (59.0%) versus 19/45 in ADA group (42.2%) (p = 0.12).

Per Protocol analysis (61 patients with centrally evaluable images). Endoscopic recurrence appeared in 8/24 in AZA group (33.3%), versus 11/37 in ADA group (29.7%) (p = 0.77).

MR recurrence (Sailer's MR2 and MR3 degrees) was present in 33.3% in AZA group and 28.1% in ADA group (p 0.68).

No differences were found in markers of activity (CRP, calprotectin), surgeries, admissions or quality of life indexes between both treatment groups.

Conclusion: It was not possible to demonstrate superiority of ADA over AZA as prophylaxis of CD after ileocolic resection. Adverse events and treatment discontinuations were less frequent in ADA group. As a general rule, ADA should not replace AZA in the prophylaxis of POR, but its tolerance is significantly better.

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Disclosure of Interest: A. Lopez-Sanroman Lecture fee(s): ABBVIE, MSD, FERRING, TILLOTTS, SHIRE, Consultancy: ABBVIE, MSD, FERRING, TILLOTTS, TAKEDA, I. Vera-Mendoza: None declared, E. Domènech: None declared, C. Taxonera: None declared, V. Vega: None declared, I. Marín-Jiménez: None declared, J. Guardiola: None declared, L. Castro: None declared, M. Esteve: None declared, V. García: None declared, D. Ceballos: None declared, P. Martínez-Montiel: None declared, J. Gisbert: None declared, M. Mínguez: None declared, A. Echarri: None declared, X. Calvet: None declared, J. Barrio: None declared, J. Hinojosa: None declared, M. D. Martín-Arranz: None declared, M. Andreu: None declared, F. Bermejo: None declared, J. Rimola Lecture fee(s): ABBVIE, MSD, Consultancy: ABBVIE, MSD, TAKEDA, ROBARTS, V. Pons: None declared, P. Nos Lecture fee(s): ABBVIE, MSD, FERRING, TILLOTTS, SHIRE, Consultancy: ABBVIE, MSD, FERRING, TILLOTTS, TAKEDA

OP009 RATE OF POSTOPERATIVE CLINICAL RECURRENCE IN CROHN'S DISEASE PATIENTS CLASSIFIED I2 ON RUTGEERTS SCORE WITH LESIONS CONFINED TO THE ILEOCOLONIC ANASTOMOSIS IS NOT DIFFERENT COMPARED TO PATIENTS WITH MODERATE LESIONS ON THE TERMINAL ILEUM

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Introduction: The Rutgeerts score, that have 5 grades of severity (i0-i4), is a suitable endoscopic model to predict clinical recurrence after small bowel resection in Crohn's disease (CD). i2 score is a heterogeneous group defined by moderate lesions on the terminal ileum (i2A) or lesions confined to the ileocolonic anastomosis (i2B). It has been suggested that patients classified i2B had less severe outcome compared to patients classified i2A. The aim of the present study was to evaluate rate of clinical recurrence in patients with i2A or i2B score.

Aims & Methods: We conducted a multicenter retrospective study, including all CD patients who underwent curative ileocolonic resection and who were classified i2 according to the Rutgeerts score at the first ileo-colonoscopy after surgery. Median (IQR) delay between surgery and first endoscopic evaluation was 7.3 months (6-12). Primary outcome was to evaluate the rate of clinical recurrence (CR) in patients classified i2A and i2B; secondary outcome was to evaluate the

rate of global recidive (GR) in both group; GR was defined as clinical recurrence and/or radiological recurrence and/or worsening of endoscopic lesions and/or by the optimization of the medical treatment and/or new intestinal resection.
Results: Fifty patients were included, in whom 27 were classified i2A and 23 classified i2B according to the first ileo-colonoscopy after surgery. Demographic and clinical characteristics (including surgical indication, previous treatment before surgery, treatment introduced or modified after surgery, treatment introduced or modified after first colonoscopy, and smoking status) were not different between the two groups. Probability of CR in the whole population was 21%, 48% and 55% at 1, 3 and 5 years respectively. There was no significant difference concerning probability of CR between patients classified i2A and i2B (19%, 40%, 52% and 24%, 52%, 58% at 1, 3 and 5 years respectively, p = 0.64). Median (IQR) time to CR after ileo-colonoscopy was not different between i2A and i2B (1007 (321-1215) and 460 (131-839) days respectively, p = 0.33). Probability of GR in the whole population was 21%, 51% and 65% at 1, 3 and 5 years respectively, with no significant difference between patients classified i2A and i2B, (p = 0.19).
Conclusion: Among patients with CD classified i2 on Rutgeerts score, rate of postoperative recurrence is not different in patients with lesions confined to the ileocolonic anastomosis compared to patients with moderate lesions on the terminal ileum. These results suggest that same therapeutic strategy should be applied in patients in classified i2 on Rutgeerts score with ileal lesions or with confined anastomotic lesions.

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Disclosure of Interest: None declared

OP010 POSTOPERATIVE COMPLICATIONS AFTER ILEO-CAECAL RESECTION FOR CROHN'S DISEASE: A PROSPECTIVE MULTICENTRE STUDY

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Introduction: Most of the data investigating postoperative complications after ileocaecal resection for Crohn's Disease (CD) come from retrospective studies or monocentric cohort. We aimed to determine the frequency and risk factors for early post-operative complication after ileocaecal resection in a well-characterized mutlicentric prospective cohort of CD.
Aims & Methods: The REMIND group conducted a nationwide study in 9 French academic centres. Patients undergoing ileocaecal resection between 1st September 2010 and 31th September 2014 were included in a prospective cohort. Clinical, biological, surgical data and medical therapies within the 3 months before surgery were prospectively collected. Early postoperative complication was defined by a medical or surgical event within 30 days after surgery. Factors associated with early post-operative complication were searched by univariate and multivariate regression analysis.
Results: 211 patients were included. 50% were male with a median age at surgery of 29 years (IQR 25-39). Indications for ileocecal resection were stricturing disease (n = 110, 52%), penetrating disease (n = 66, 31%), both stricturing and penetrating disease (n = 21.10%), and inflammatory disease with failure of medical therapy (n = 14, 7%). Seventy-two (34%) patients were exposed to corticosteroids within 3 months before surgery. Ninety-five (45%) and 41 (19%) patients were treated with anti-TNF within 3 and 1 months before surgery. Median duration between the last anti-TNF administration and surgery was 18 days (14-50). Laparoscopy was performed in 117 (73%) patients; 16 (13%) of them needed conversion to laparotomy. Initial stoma was performed in 35 (16%) patients. There was no postoperative death. Forty-three (21%) patients had a total of 56 early post-operative complications after a median time of 5 days (4-12): wound abscess (n = 17), intra-abdominal collection (n = 16), anastomotic leakage (n = 10), extra-intestinal infections (n = 9), and haemorrhage (n = 5). Reoperation was necessary in 16 patients and stoma in 7. Median duration of temporary stoma was 3.7 months (2.9-4.5). Multivariate analysis found that corticosteroids therapy within 3 months before surgery was the only factor associated to postoperative complications (p = 0.04, HR 2.0, IC95%[1.01-4.0]).
Conclusion: In this large multicentre prospective cohort, early postoperative complications after ileocecal resection were observed in 21% of patients. Corticosteroids therapy was the only factor associated to postoperative complications. The impact of nutritional status and through levels of ant-TNF at surgery on the risk of postoperative complications is being analysed.
Disclosure of Interest: None declared

OP011 POLYGLYCOLIC ACID SHEETS WITH FIBRIN GLUE FOR THE PREVENTION OF POSTOPERATIVE STRICTURE AFTER ESOPHAGEAL ENDOSCOPIC SUBMUCOSAL DISSECTION

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Introduction: Postoperative stricture after endoscopic submucosal dissection (ESD) for wide-spreading superficial esophageal neoplasms is a very common yet severe complication, with an occurrence rate of 66-90% in cases with resection of over 3/4 the circumference of the esophagus. Although the use of steroids after ESD is known to decrease the incidence of postoperative stricture, this method is accompanied with a risk of severe adverse effects, and there is a clinical need for a safer method of prevention. The use of polyglycolic acid (PGA) sheets, a surgical suture material, adhered with fibrin glue, has been reported to safely minimize scar contracture in other medical fields. The aim of this study was to evaluate the efficacy of applying PGA sheets with fibrin glue to the post-ESD defect for the prevention of postoperative stricture after esophageal ESD.
Aims & Methods: After ethics committee approval and trial registry in July 2013, we enrolled subjects with a diagnosis of superficial esophageal squamous cell carcinoma covering over half the circumference of the esophagus in the study group. Immediately after the enrolled subjects underwent esophageal ESD, a PGA sheet was adhered to the post-ESD defect with fibrin glue. Following protocol treatment, all subjects underwent outpatient follow-up for a minimum of three months. As a historical control group, we listed all subjects at our institute who had undergone ESD for superficial esophageal squamous cell carcinoma covering over half the circumference of the esophagus during 2004 to April 2013. Statistical analysis of the incidence of postoperative stricture and required endoscopic balloon dilation (EBD) sessions was performed. In order to accurately access the efficacy of PGA sheets and fibrin glue, subjects with steroid use after ESD were excluded from analysis.
Results: Between September 2013 and July 2014, 13 subjects were enrolled in the study group. For the historical control group, there were a total of 36 consecutive subjects who met our inclusion criteria, with a follow-up period of over 3 months. After exclusion of subjects with steroid use, 12 subjects in the study group and 35 subjects in the historical control group were analyzed. There were no statistical differences in the background factors between the groups. The incidence of stricture was significantly lower in the study group (25.0% vs. 62.9%, $p = 0.02$). The number of required EBD sessions was also significantly lower in the study group (0.9 ± 2.1 vs. 6.8 ± 8.6, $p = 0.01$). There were no other adverse events in either group.
Conclusion: The application of PGA sheets with fibrin glue seems to be an effective and safe method for the prevention of postoperative stricture after esophageal ESD. Although further improvements of this method and prospective studies for confirmation of efficacy are required, this method is a promising novel technique.
Disclosure of Interest: Y. Sakaguchi: None declared, Y. Tsuji Lecture fee(s): Olympus Medical Systems, HOYA Pentax, Eisai, GUNZE, CSL Behring, Y. Kataoka: None declared, I. Saito: None declared, S. Shichijo: None declared, D. Yamaguchi: None declared, K. Niimi: None declared, S. Ono: None declared, S. Kodashima: None declared, M. Fujishiro Financial support for research: Astellas Pharmaceutical, Takeda Pharmaceutical, Zeria Pharmaceutical, Otsuka Pharmaceutical, Astrazeneca Pharmaceutical, Dainihon-Sumitomo Pharmaceutical, Taiho Pharmaceutical, Ajinomoto Pharmaceutical, and Eisai for his department outside the submitted work, Lecture fee(s): Olympus Medical Systems, HOYA Pentax, Eisai, MSD, Daiichi-Sankyo Pharmaceutical, Astrazeneca Pharmaceutical, Aska Pharmaceutical, Taisho-Toyama Pharmaceutical, Otsuka Pharmaceutical, Zeria Pharmaceutical, Takeda Pharmaceutical, Astellas Pharmaceutical, Seikagaku Corp., Johnson & Johnson, Ajinomoto Pharmaceutical, Amco, Novartis Pharmaceutical, Boston Scientific, and, Boehringer-Ingelheim outside the submitted work, Conflict with: non-financial support from HOYA Pentax, Olympus Medical Systems, and, Fujifilm for his department outside the submitted work, K. Koike: None declared

OP012 DOUBLE CELL SHEET TRANSPLANTATION FOR ESOPHAGEAL STRICTURE PREVENTION AFTER LARGE ENDOSCOPIC SUBMUCOSAL DISSECTION IN A PORCINE MODEL

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Introduction: Extended esophageal endoscopic submucosal dissection (ESD) is highly responsible for esophageal stricture. We conducted a comparative study in a porcine model to evaluate the effectiveness of adipose tissue-derived stromal cell (ADSC) double cell sheet transplantation.
Aims & Methods: Twelve female pigs were treated with 5 cm long hemi-circumferential ESD and randomized in two groups. ADSC group (n = 6) received 4 double cell sheets of allogenic ADSC on a paper support membrane and control group (n = 6) received 4 paper support membranes. ADSC were labelled

with PKH-67 fluorophore to allow probe-based confocal laser endomicroscopie (pCLE) monitoring. After 28 days follow-up, animals were sacrificed. At days 3, 14 and 28, endoscopic evaluation with pCLE and esophagography were performed.
Results: One animal from the control group was excluded (anesthetic complication). Animals from ADSC group showed less frequent alimentary trouble (17% vs 80%; $P=0.08$) and higher gain weight on day 28. pCLE demonstrated a compatible cell signal in 4 animals of the ADSC group at day 3. In ADSC group, endoscopy showed that 1 out of 6(17%) animals developed a severe esophageal stricture comparatively to 100% (5/5) in the control group; $P=0.015$. Esophagography demonstrated a decreased degree of stricture in the ADSC group on day 14 (44% vs 81%; $P=0.017$) and day 28 (46% vs 90%; $P=0.035$). Histological analysis showed a decreased fibrosis development in the ADSC group, in terms of surface (9.7 vs 26.1 mm^2; $P=0.017$) and maximal depth (1.6 vs 3.2 mm; $P=0.052$).
Conclusion: In this model, transplantation of allogenic ADSC organized in double cell sheets after extended esophegeal ESD is strongly associated with a lower esophageal stricture's rate.

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Disclosure of Interest: None declared

MONDAY, OCTOBER 26, 2015 11:00–12:30
UPDATE ON COELIAC DISEASE – ROOM A3

OP013 DETECTION OF GLUTEN PEPTIDES IN URINE OF CELIAC PATIENTS: CORRELATE WITH MUCOSAL DAMAGE

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Introduction: Ingestion of gluten found in wheat, barley, rye and in some circumstances, oats, leads to autoimmunity and small intestinal mucosal injury in patients with celiac disease (CD). To date, the mainstay of the management of CD is a strict life-long adherence to gluten-free diet (GFD). However, strict GFD is difficult because it is one of the most frequent ingredients in processed foods.
Aims & Methods: We have developed a novel method to determine gluten intake and to assess adherence to the GFD in celiac patients by detection of gluten immunogenic peptides (GIP) in urine. Urine samples of 76 healthy subjects and 58 celiac patients were collected. Urine GIP content was estimated by solid phase extraction and a quantitative lateral flow test with the highly sensitive and specific anti-α-gliadin monoclonal antibody G12.
Results: We detected the presence of GIP in concentrated urine samples from healthy individuals subjected to different dietary conditions as early as 4-6 h after gluten intake. GIP were detectable in healthy individuals' urine for 1-2 days after a GFD followed by a single gluten intake. The sensitivity of the assay was high, with detection of consumption of as little as 50 mg of gluten. The assay also appeared to detect GFD infringement or gluten contamination in CD patients, as over 50% of the patients studied presented detectable GIP in urine. Importantly, there was a correlation between urinary gluten and mucosal atrophy in CD patients. Retrospective analysis of duodenal biopsies, available in 27 CD patients, showed that 90% of CD patients with no villus atrophy had no detectable GIP in urine.
Conclusion: GIP could be sensitively detected in human urine. This sensitive, quantitative, specific and simple technique could be useful to monitor GFD compliance of CD patients as well as for therapeutic research applications. This trial was registered in ClincialTrials.gov as NCT02344758.
Disclosure of Interest: M. D. L. Moreno Amador: None declared, Á. Cebolla Ramírez Conflict with: own stock in Biomedal S.L., A. Muñoz Suano: None declared, C. Carrillo Carrión: None declared, I. Comino Montilla: None declared, Á. Pizarro Moreno: None declared, F. León Conflict with: own stock in Biomedal S.L., A. Rodríguez Herrera: None declared, C. Sousa Martín: None declared

OP014 ASSESSMENT OF BREAST MILK MYCOTOXIN CONTENT IN MOTHERS WITH COELIAC DISEASE: A PRELIMINARY OUTLINE

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Introduction: Gluten-free diet (GFD) is characterized by a higher consumption of corn that may undergo some xenobiotic contamination. Mycotoxins are secondary metabolites produced by several microscopic fungi genera such as Aspergillus, Fusarium and Penicillium. The aim of our study was to assess the risk of mycotoxin exposure (aflatoxin M1, ochratoxin A and zearalenone) in woman with coeliac disease (CD) and healthy control breastfeeding mothers (as well as in their offsprings) by quantifying these contaminants in breast milk.
Aims & Methods: From January 2011 to December 2013, 33 women with CD and 22 healthy brestfeeding controls completed the study. Human milk was collected throughout three days, during a complete 24h period, as following: one milk sample after overnight fasting, one 4 hours after lunch, and one 2 hours after dinner. Mycotoxin content in breast milk was investigated by a high-performance liquid chromatography (HPLC) method with fluorimetric detection. Dietary history on cereal consumption was recorded during the three days of breast milk collection.
Results: Aflatoxin M1 (AFM1) was detected in 37% (n = 96) of samples belonging to women with CD [mean ± SD = 0.012 ± 0.011 ng/mL; range = 0.0035 ÷0.340 ng/mL]. The slightly higher concentration in those samples collected during fasting [0.017 ± 0.028 ng/mL] resulted statistically significant when compared to those collected 4 hours after lunch and 2 hours after dinner [0.011 ± 0.010 ng/mL and 0.009 ± 0.006 ng/mL respectively] (ANOVA, p-value < 0.001, significance level 0.05). When comparing to mothers with CD, the control group showed lower AFM1 concentration level in 22% of samples [mean 0.008 ± 0.007 ng/mL; range = 0.0035 ÷0.0370 ng/mL] resulting statistically significant with a p-value 0.004 (significance level 0.05).Estimating a daily average milk consumption of 530g for a hypothetical body weight of 3.4 kg, the exposure of newborns from mother with CD and from healthy control mothers resulted 1.87 and 1.24 ng/kg bw/d, respectively. No statististical significant difference was found as regards breast milk zearalenone (ZEA) content in both groups. Ochratoxin A was not significantly present in the investigated human milk samples of both groups.
Conclusion: The presence of AFM1 in breast milk is a marker both for infant and mother exposure. In our assessment, the AFM1 breast milk content was higher among mother with CD than among healthy breastfeeding controls. However, the maximum tolerable level set by the EU Regulation 1881/2006 (0.11 ng/kg bw/d) was exceeded in both groups and this warrants further investigations.
Disclosure of Interest: None declared

MONDAY, OCTOBER 26, 2015 11:00–12:30
HOT TOPICS FROM LATIN AMERICA – ROOM 7.1

OP015 PREDICTION OF HISTOLOGY BY CONFOCAL LASER ENDOMICROSCOPY IN LUGOL-UNSTAINED ESOPHAGEAL SUPERFICIAL LESIONS OF PATIENTS WITH HEAD AND NECK CANCER

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Introduction: Surveillance programs of patients with head and neck cancer (HNC) detect synchronous or metachronous esophageal squamous cell carcinoma (ESCC) in up to 15% of the patients. The detection of ESCC in patients with HNC at early stage is desirable since it affects prognosis. Endoscopic surveillance of the esophagus with narrow band imaging (NBI) or Lugol chromoendoscopy presents high sensitivity but low specificity for the detection of early ESCC. Esophagitis may also present as Lugol-unstained areas. A non-invasive probe-based confocal laser endomicroscopy (pCLE) technique may improve the diagnosis allowing acquisition of high-resolution in vivo images at the cellular and microvascular levels.
Aims & Methods
Aim: To evaluate the accuracy of pCLE for the diagnostic differentiation of non-neoplastic and neoplastic Lugol-unstained esophageal lesions in patients with HNC.
Methods: Twenty-one patients with HNC who presented one or more Lugol-unstained esophageal lesions at surveillance endoscopy were prospectively included for pCLE. All patients repeated conventional white-light endoscopic examination with NBI and pCLE. After intravenous injection of fluorescein, a 1.8 mm GastroFlex probe (Cellvizio) was inserted into the esophagus. Diagnostic pCLE were followed by subsequent biopsies or endoscopic resection of suspected lesions. A senior pathologist was masked to the pCLE results.
Results: Patients mean age was 58.4 years (SD = 8.8), and 76.2% were men. All patients were smokers, and 16 patients (76.2%) had a history of alcohol abuse. The locations of HNC were larynx (n = 10), oral cavity (n = 7), and pharynx (n = 4). Twenty-four lesions from 19 patients were studied. The final diagnosis of the 24 suspicious lesions were: ESCC in 11 and benign lesions in 13. Two other patients with 8 mm and 10 mm lesions were referred directly to endoscopic resection, since NBI and pCLE results were suspicious for ESCC. The size of Lugol-unstained lesions varied from 6 mm to 80 mm (mean = 17.7 mm, SD =

17.1). The mean size of malignant lesions was larger than the size of inflammatory ones (30.6 mm versus 9.3 mm, p = 0.001). However, there were three cases of ESCC smaller than 15 mm. pCLE made the correct diagnosis in 95.8% of the lesions (23/24 lesions). pCLE misdiagnosed one lesion in one patient who had two ESCC. All 13 benign lesions were correctly diagnosed by pCLE. Sensitivity, Specificity and Accuracy of pCLE for the histologic diagnosis of ESCC in patients with HNC were: 90.9%, 100% and 95.8%, respectively.
Conclusion: 1. pCLE is highly accurate for real time histology of Lugol-unstained esophageal lesions in patients with HNC. 2. pCLE has the potential to change the management of patients under surveillance for ESCC, guiding biopsies and endoscopic resection, avoiding further diagnostic workup or therapy of benign lesions.

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Disclosure of Interest: None declared

OP016 EVOLUTION OF THE HUMAN GENOME AND HELICOBACTER PYLORI AND ITS IMPLICATIONS FOR THE RISK OF GASTRIC CANCER IN THE ANDES OF COLOMBIA

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Introduction: *Helicobacter pylori* is the principal cause of gastric cancer (GC), the second leading cause of cancer mortality worldwide. However, *H. pylori* prevalence generally does not predict cancer incidence.
Aims & Methods
Aims: To determine if the coevolution between host and pathogen influences the risk of GC in two Colombian populations: Tumaco, a coastal population with low risk of GC, and Tuquerres, a Andes mountain population with high risk of GC. Our hypothesis postulates an association between the severity of gastric lesions and the patterns of genomic variation in matched human and *H. pylori* samples.
Methods: 292 patients were recruited from the two populations. Histological diagnostics were based on the Sydney classification. 252 strains of *H. pylori* were included for MLST analysis. Human DNA was genotyped using the Immunochip to characterize the human ancestry. The Admixture model of STRUCTURE assigns proportions of ancestry to each individual sample across *K*-inferred ancestral clusters.
Results: All *H. pylori* isolates contained the genetic signatures of multiples ancestries. *H. pylori* isolates with an ancestral African cluster predominating in a low-risk (coastal population), and a European cluster in a high-risk (Andes mountain population). The human ancestries of the biopsied individuals also varied with geography, with mostly African ancestry in the coastal region (58%), and mostly Amerindian ancestry in the mountain region (67%).
Conclusion: The interaction between the host and pathogen ancestries completely accounted for the difference in the severity of gastric lesions in the two regions of Colombia. In particular, African *H. pylori* ancestry was relatively benign in humans of African ancestry but was deleterious in individuals with substantial Amerindian ancestry. Thus, coevolution probably shapes disease risk of the disease , and the disruption of coevolved human and *H. pylori* genomes can explain the high incidence of gastric disease in mountain population.

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Disclosure of Interest: None declared

OP017 NON-INVASIVE EVALUATION OF PANCREATIC FIBROSIS USING SHEAR WAVE ELASTOGRAPHY

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Introduction: It is difficult to collect pathological pancreatic parenchyma surgically for diagnosis of pancreatic fibrosis[1)]. Shear wave elastography using transabdominal ultrasonography (SW) is a potential technology for diagnosing stage of chronic pancreatitis, because SW can calculate the tissue elasticity as correlation value of Young's modulus[2)].
Aims & Methods: The aim of this study was to evaluate the accuracy of diagnosing pancreatic parenchymal fibrosis using SW. From September 2012 to May 2014, 155 patients who underwent SW estimating pancreatic parenchymal fibrosis were enrolled in this study. All patients were assessed for elastic modulus using SW with iU22 (Philips Healthcare, Bothell, WA, USA). We performed SW measurements more than five times at the same area. Elastic modulus was expressed as kPa and presented as mean value of 5 or more measurements. We checked measurement success rate (number of success measurement / number of all measurement * 100), and the patients whose success rate was less than 60% were excluded from this study. 120 patients (normal pancreas: NP group) underwent SW (head: 32, body: 70, tail: 18). 35 patients had pancreas tumors and underwent pancreatectomy (resected pancreas: RP group). RP group patients underwent SW at pancreatic parenchyma on the cranial or caudal side of the tumor preoperatively, and their elastic modulus were compared with degree of pancreatic fibrosis (DPF) postopereatively. DPF was classified to the 13 score (DPFS) using the scoring system reported previously[3)]. Evaluated points were as follows: 1) Diagnosis accuracy of SW in NP group.2) Correlation elastic modulus with degree of pancreatic fibrosis in RP group. This study was approved by the IRB of our hospital and registered in UMIN-CTR (000016497).
Results: 1) In NP group, 16 patients failed in SW measurement and excluded from this study. 104 patients (86.7%) were included in this study. The mean value of elastic modulus and success rate were 3.73 ± 1.84kPa and 79.4%, respectively, and these values in each pancreas lesion were head:3.74kPa/84.1%, body: 3.67kPa/78.1% and tail: 3.98kPa/77.1%, respectively, no significant difference (elastic modulus; $P = 0.93$, success rate; $P = 0.17$) .2) In RP group, the mean value of DPFS and elastic modulus were 4.26 ± 4.43 and 7.18 ± 5.50kPa. DPFS was significantly correlated with elastic modulus ($r = 0.724$, $P < 0.001$). In ROC analysis, the AUCs of elastic modulus for the diagnosis of mild grade fibrosis (DPFS > 3), moderate grade fibrosis (DPFS > 6), and severe grade fibrosis (DPFS > 10) were 0.920, 0.843 and 0.817, respectively.
Conclusion: Shear wave elastography using transabdominal ultrasonography was highly accurate and non-invasive in the diagnosis of pancreatic fibrosis.

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Disclosure of Interest: None declared

OP018 GENOTYPE-PHENOTYPE CORRELATIONS IN CYSTIC FIBROSIS PATIENTS WITH PANCREATITIS HIGHLIGHTS AN INCREASED LIKELIHOOD OF PANCREATIC INSUFFICIENCY AND IDENTIFIES UNIQUE MUTATION PAIRS THAT POTENTIALLY PREDISPOSE TO AND PROTECT FROM PANCREATITIS

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Introduction: 1-2% of cystic fibrosis (CF) patients develop symptomatic pancreatitis. Studies have shown these patients present later in life, are pancreatic sufficient (PS) & have a less severe CF phenotype. This study aimed to evaluate the genotype:phenotype relationship of CF patients with pancreatitis in a tertiary referral centre for CF.
Aims & Methods: CF patients with a history of pancreatitis were identified from 1216 patients in The Royal Brompton Hospital CF database. Each case was age & sex matched with controls. Clinical information on age, sex, PS status, age

when CF diagnosed, CF genotype & mortality were collected. To compare pancreatitis patients with controls, a two tailed t-test (age of CF diagnosis, R117H mutation rate) & Kaplan-Meir survival curves (rate of PI and mortality rates) were utilised.
Results: 37 patients (51% females) with pancreatitis were matched to 135 controls (3:1/4:1). Mean age of CF diagnosis was significantly higher in the pancreatitis group (19yrs) than controls (10.6yrs; p = 0.046). Median time between CF diagnosis and pancreatitis was 17 yrs (range 8-36 yrs). 65% (n = 24) of pancreatitis sufferers were PS at presentation to adult services; of these 63% (n = 15) remained PS until their most recent review or death. Furthermore, 67% (n = 16) suffered with recurrent or chronic pancreatitis. Using Log-rank (Mantal-Cox), there was no difference in survival between pancreatitis patients and controls (p = 0.97). However, pancreatitis patients were significantly more likely to develop PI (p = 0.012). The ^F508:R117H mutation pair was noted more frequently in pancreatitis patients (18.9%;n = 7) than controls (3.8%;n = 5) but not significancantly so (p = 0.56). Interestingly in 43% (n = 16) of the remaining pancreatitis patients, 15 mutation pairs unique to this group were identified. Similarly in controls, 50% (n = 65) had mutation pairs unique to this group.
Conclusion: CF patients who suffer with pancreatitis are significantly more likely to develop PI than those who do not. They present with CF at an older age but this does not affect their survival. The R117H mutation is seen more frequently in the pancreatitis group but not significantly so for this phenotype. We have identified a number of mutation pairs that seem to either predispose or protect CF patients from pancreatitis.
Disclosure of Interest: None declared

OP019 STUDY OF THE GUT MICROBIOME IN CHRONIC PANCREATITIS: ASSOCIATION WITH PANCREATOGENIC DIABETES (TYPE 3C) AND EXOCRINE INSUFFICIENCY

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Introduction: Chronic pancreatitis (CP) is characterised by progressive fibrosis, pain, pancreatic exocrine (PEI) and endocrine insufficiency (Type3c diabetes mellitus [DM]). Studies have shown gut dysbiosis in Type 1 and Type 2 diabetes.
Aims & Methods: We aim to evaluate the gut microbiota in CP and its association with Type3c DM and PEI. 40 participants [16 CP without Type3c DM, 14 CP with Type3c DM and 10 healthy controls] were enrolled after informed consent. Clinical characteristics (history, biochemical and imaging parameters) and nutritional characteristics (anthropometry, Transferrin, Vitamin D, Vitamin B_{12}, Prealbumin and serum calcium) were recorded. Individuals having diarrhoea/constipation & who had antibiotics in past 3 months were excluded. Type3c DM was confirmed by serum C-peptide; PEI was measured using fecal elastase test. Bacterial 16S rRNA was sequenced using Illumina MiSeq 2000 platform. Metagenome data was uploaded in MG-RAST server and analyzed. Spearman's correlation was evaluated between disease characteristics, bacterial abundance and altered functional pathways. Pathway analyses was performed using KEGG and Biocyc platforms.
Results: Mean total sequence reads in the three groups were 1,999,561,23; 1,778,651,39; and 1,320,277,85 bp's respectively. Alpha diversities were 7309.5, 6699.71, and 7401.6 respectively in the three groups. Firmicutes: Bacteroidetes among CP patients with Type3c DM was higher compared to those without Type3c DM (2.04 vs 1.54). *Fecalibacterium* (butyrate producing bacteria) was found to be lower in CP with Type3c DM compared to those without Type3c DM. In CP with Type3c DM and PEI, *Bifidobacterium* was significantly lower than those with Type3c DM without PEI (7.25% vs 51.53%; $p < 0.05$). We observed positive correlation between *Fecalibacterium* and *Ruminococcus* with the glycemic status, whereas a negative correlation between *Fecalibacterium*, *Ruminococcus* and *Bifidobacterium* with malnutrition in CP with Type3c DM and PEI. *Clostridium*, *Eubacterium* and *Bacillus* also showed negative correlation with malnutrition. Species within these genus were found to have metabolic pathways related to disease characteristics. Enterotyping was done for CP with and without Type3c DM. Enterotype 1 (*Bacteroidetes* predominant) was higher in CP without Type3c DM whereas Enterotype 2 (*Prevotella* predominant) was higher in CP with Type3c DM. Fermentation pathways, one- carbon metabolisms and central carbon metabolisms were found to be abundant in all the 3 groups, whereas, pterine and folate metabolisms were found to be abundant in enterotype 2. Cell-wall biosynthesis, fatty acid biosynthesis and sugar alcohol metabolism were found to be least abundant in the 3 groups.
Conclusion: We report for the first time that PEI could be a contributing factor for dysbiosis in CP with Type3c DM.
Disclosure of Interest: None declared

OP020 ANTIOXIDANT COCKTAIL AND PREGABALIN COMBINATION AMELIORATES PAIN IN CHRONIC PANCREATITIS AFTER DUCTAL CLEARANCE: RESULTS OF A RANDOMIZED, DOUBLE BLINDED, PLACEBO-CONTROLLED TRIAL

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Introduction: Chronic pancreatitis is a complex disorder. A single modality for pain is unlikely to be effective. A substantial proportion of patients with CP has pain recurrence after ductal decompression.
Aims & Methods: To evaluate the effect of antioxidant cocktail and pregabalin in patients with CP who develops pain after ductal clearance.
CP patients with pain recurrence following endotherapy/LPJ were randomized to receive either methionine containing antioxidant cocktail and pregabalin combination, or matching placebo. Daily dosages were: Methionine 2g; Selenium 600mg; Beta-carotene 54mg; Alpha-tocopherol 280mg; Ascorbic acid 540mg; and pregabalin 150mg twice daily for one week followed by 300mg twice daily. Compliance, daily pain records and adverse events were captured during weekly telephone interview and end of study hospital visit. Study duration was 2mths. Primary outcome was pain score reduction; secondary outcomes were: change in neuropathic pain score, complete pain resolution, quality of life (QOL), adverse events, and depression score. Following tools were used: Visual analog scale (VAS) and Izbicki score for overall pain; painDETECT for neuropathic pain; Beck's inventory for depression; EORTC-QLQ30 with Pan28 questionnaire for QOL. Effect size was expressed as risk ratio (RR) (95%CI) and number needed-to-treat (NNT). Analysis was intention-to-treat
Results: After sample size calculation (80% power; 0.05 alpha; adjusted for 10% drop-out), we randomized 42 and 45 patients in the treatment and placebo arms respectively. Three patients in the treatment arm while one in the placebo lost to follow-up. Both arms matched for age, gender, duration between endotherapy/LPJ and enrolment, exocrine and endocrine insufficiency, type of ductal decompression, pain scores. At 2mths, there was significantly higher reduction in VAS (-45.5(±28.5) v/s -24.0(±32.6); p = 0.002) and painDETECT score was lower (2.6[±4.1] v/s 6.03[±4.9] p = 0.001) in the treatment group. 46.5% patients in the treatment arm had complete pain resolution compared to 26.7% in placebo (p = 0.04) (RR 1.87 [95%CI 1.0-3.2]); and NNT was 5.1 for complete pain resolution. Mean(SD) number of painful days was lower in treated patients [14.7(15.2) v/s 21.8(17.4)days; p = 0.05]. No improvement was observed in depression score and QOL. 23.8% and 38.1% of treatment arm patients experienced nausea/vomiting and drowsiness respectively.

	Antioxidant + Pregabalin (n = 42)	Placebo (n = 45)	p value
VAS (mean; SD)	29.7 (23.4)	62.1 (22.5)	<0.0001
Izbicki score (Mean; SD)	14.8 (14.7)	30.5 ((23.01)	<0.0001
PainDETECT score (Mean; SD)	2.6 (4.1)	6.02 (4.9)	0.001
Pc reduction in pain (Mean; SD)	-60.5 (34.4)	-28.3 (44.1)	<0.0001
Patients with complete pain relief (n; %)	20 (46.5)	12 (26.7)	0.04
Patients with pain reduction (n; %)	36 (83.7)	32 (71.1)	0.22
Need for analgesics (n; %)	13 (30.9)	22 (48.9)	0.24

Conclusion: Combination of antioxidants with pregabalin results in significant relief in CP pain recurrence after endotherapy and/or LPJ.

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Disclosure of Interest: None declared

OP021 LACTATED RINGER'S SOLUTION VERSUS NORMAL SALINE FOR FLUID RESUSCITATION IN ACUTE PANCREATITIS, A RANDOMIZED CONTROLLED TRIAL

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Introduction: Basic research as well as an open label randomized controlled trial (RCT) (1) suggest that fluid resuscitation with Lactated Ringer's solution (LR) may be associated to reduced inflammation in patients with acute pancreatitis (AP) compared to normal saline (NS).
Aims & Methods: Our aim was to investigate the effect of LR and NS on inflammation and outcome of AP.
We performed a double blind RCT. Adult patients with a first episode of AP were randomized to receive LR or NS as fluid resuscitation during the first 3 days after hospital admission. The fluids were repacked in blinded bags and fluid rate

was determined by the study protocol. Complications were defined according to the Revised Atlanta Classification.
Results: Forty patients were included, 19 (47.5%) received LR and 21 (52.5%) NS. There were no statistically significant differences between both groups regarding basal characteristics (age, sex, etiology, body mass index, hematocrit, BUN, BISAP score and number of SRIS criteria).
Median (p25-p75) C-reactive protein (CRP) plasma levels at 48h were 2.8 (0.2-13.4) and 17.4 (8.1-29.2) for LR and NS respectively ($p < 0.05$); at 72h CRP levels were 2.5 (0.3-16.9) and 21.7 (5.9-32.3) mg/dl ($p < 0.05$). Median (p25-p75) number of SIRS criteria at 72h were 0 (0-1) and 1 (1-2) for LR and NS respectively ($p < 0.05$). LR was associated with 4 (21.2%) necrotizing AP versus 10 (47.6%) for NS, $p = 0.08$. Organ failure, hospital stay, ICU admission, need for nutritional support and mortality were not significantly different.
Conclusion: Lactated Ringer, when compared to normal saline, is associated to a decreased inflammatory response in patients with acute pancreatitis.

Reference

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Disclosure of Interest: None declared

OP022 ROLE OF AMMONIA PET-CT IN ASSESSING THE PANCREATIC NECROSIS IN PATIENTS WITH ACUTE PANCREATITIS

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Introduction: Contrast enhanced CT scan (CECT) is imaging modality of choice to evaluate necrosis and severity of acute pancreatitis. Ammonia (^{13}NH3) PET can also be alternative especially in setting of acute renal failure, however the comparative studies between these two is still lacking.
Aims & Methods: To evaluate whether Ammonia (^{13}NH3) PET reflects the perfusion status of pancreas in patients of acute pancreatitis(AP) to detect pancreatic necrosis and compare it with necrosis detected on contrast enhanced CT scan(CECT).
35 patients with AP were enrolled in the study. NH3 PET was done in all the patients while CECT was done in 32 patients and 3 patients with renal failure had only PET done for imaging. CECT images were interpreted and the percentage of necrosis, presence and absence of collection were recorded and CTSI (CT severity index) and MCTSI (modified CT severity index) were calculated. Ammonia PET images were separately analyzed and PET CTSI & MPET CTSI were calculated along with the amount of necrosis and collection both observers blinded to each other. Data was recorded in excel sheet and statistical analysis was done using SPSS v17.0.
Results: The mean age of our study population was 40.65 ± 15.1 years. Of these 24 (68.6%) patients were males and 11 (31.4%) were females. 25 patients had organ failure at presentation, with 3 (9%) having acute kidney injury and 22 (63%) patients having ARDS. A comparative analysis of CTSI with PET CTSI showed significant correlation between the two scores (P- 0.000). The scores showed a good agreement (kappa-0.451, P-0.000), suggesting that the two imaging identify patients with pancreatitis with a comparable severity estimation. Necrosis on both CECT and PET was compared separately, however no significant agreement was found (kappa-0.170, P-0.25). Ammonia PET identified 9 patients as having minimal necrosis while CECT showed no necrosis in them, probably suggesting that PET is either more sensitive in identifying necrosis than CECT or may be overestimating it in few patients with only mild pancreatitis. The agreement between two imaging in estimating collections was also analyzed. It showed a good agreement between the two (kappa-0.668 P-0.000). In 22 both CECT and PET diagnosed collection and in 6 they both denied evidence of any collection. Among the remaining 4 patients PET alone identified collection in 3 while CECT alone showed collection in 1 patient. For further confirmation in support of our study we also calculated the modified PET CTSI and the MCTSI scores and they were also correlated. They also showed a significant correlation (P-0.000).
Conclusion: Ammonia PET could be an alternative imaging modality for diagnosis of acute pancreatitis and assessing the severity of acute pancreatitis.
Disclosure of Interest: None declared

MONDAY, OCTOBER 26, 2015 11:00–12:30
NEW FRONTIERS IN MOLECULAR DIAGNOSIS AND MONITORING OF GI CANCER – ROOM E4

OP023 ROLE OF SQUALENE EPOXIDASE (SQLE) IN PROMOTING FATTY LIVER DISEASE-ASSOCIATED LIVER CANCER

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Introduction: Non-alcohol steatoheptitis (NASH) is a major risk factor for the development of hepatocellular carcinoma (HCC). Using whole transcriptome sequencing (RNA-seq), we have identified squalene epoxidase (*SQLE*) as a novel gene up-regulated in human NASH-associated HCC. *SQLE* is located at human chromosome 8q24.1, a frequently amplified region in HCC, and encodes a rate -limiting enzyme in the cholesterol biosynthetic pathway. The role of SQLE in human cancer remains unclear.
Aims & Methods: We aimed to investigate the biological function, molecular mechanism and clinical implication of SQLE in NASH-HCC. SQLE expression was validated in NASH-HCC patients and genetic obese *Foz/Foz* mice model. The biological functions of SQLE were determined in cell lines in vitro and xenografts in nude mice. The molecular mechanism of SQLE was identified by PCR array and Human Methylation 450K array analyses. Clinical application of serum SQLE levels in diagnosis of NASH was assessed in 220 NAFLD/NASH patients serum.
Results: *SQLE* was overexpressed in 17 out of 27 (63%) human NASH-HCC tumor samples compared with their adjacent non-tumor liver tissues. *SQLE* was also overexpressed in *Foz/Foz* mice fed a high-fat, high-cholesterol diet compared to a high-fat diet alone, indicating that cholesterol can induce *Sqle* expression. SQLE possessed an oncogenic function in NASH-HCC, as its overexpression in liver cell lines (LO2 and Huh7) significantly promoted cell proliferation, cell cycle progression and tumorigenicity in nude mice. Conversely, the silencing of SQLE in BEL-7404 cells and HepG2 cells had an opposite effect.
We investigated the role of cholesterol in regulating the expression of SQLE. *In vitro* treatment with cholesterol induced the expression of *SQLE* in LO2 and Huh7 cells through increasing the intracellular accumulation of acetyl-CoA. To identify the downstream molecules that mediate the oncogenic effect of SQLE, we performed PCR array analysis in SQLE overexpressing cells and revealed that SQLE induced alterations of genes involved in fatty acid metabolism and epigenetic programming. SQLE overexpression increased intracellular cholesterol and triglyceride levels. The accumulation of intracellular cholesterol activated ROS, ER stress and consequently inducing the AP1 and NF-kB pro-inflammatory pathways that contribute to NASH and NASH associated-HCC. Moreover, SQLE triggered a major epigenetic reprogramming via the up-regulation of DNMT3A, a de novo DNA methyltransferase. Consequently, SQLE expression induced promoter methylation of key tumor suppressor genes including PTEN and histone deacetylase 9 (HDAC9). HDAC9 silencing, in turn, promoted histone phosphorylation level (H3S10) and activated WNT pathway that contributes to tumorigenesis.
Finally, we assessed clinical significance of SQLE overexpression in NASH, and we demonstrated that serum SQLE levels exhibited a high overall accuracy in discriminating NASH subjects from control subjects with the area under the receiver operating characteristic curve (AUROC) of 0.773 (95% CI: 0.709–0.839), indicating that SQLE is a promising biomarker for NASH.
Conclusion: SQLE is a novel tumor-promoting gene which can be induced by cholesterol. SQLE links abnormal cholesterol metabolism to the malignant progression of NASH and NASH-associated HCC. SQLE is a potential biomarker for the clinical diagnosis of NAFLD and NASH patients.
Disclosure of Interest: None declared

OP024 INCREASED CELL-FREE DNA INFLUENCES CANCER GROWTH IN A MOUSE MODEL

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Introduction: Circulating free DNA (cfDNA) level is increased in tumorous deseases and regular physical activity. The positive effect of sport in cancer prevention is well-known. Activation of DNA-binding receptors may induce signal transduction pathways connected to cell circle or immune cell activation.
Aims & Methods: Our aim was to study the effect of increased cfDNA level on tumor progression using an animal model. Efficacy of sport was also evaluated as physiologically increased cell-free DNA condition. We studied fifteen C57BL/6 mice in four groups. C38 non-necrotic colorectal adenocarcinoma tissue was implanted subcutaneously in each mouse at the same time. Group I was treated with high concentration subcutaneously injected healthy C57BL/6 spleen-derived DNA (sdDNA), Group II with C38 tumor tissue-derived DNA (tdDNA). Both treatment started at the time of tumor implantation and was continued until the end of the study, three times per week. DNA was isolated from C38 tumor tissue and healthy spleen by our standard method using Zymo DNA columns (DNA Clean & Concentrator^{TM}-500, Zymo Research). Group III was strained by five hours long physical activity five times per week in a rodent wheel. Group IV was used as a control group injected with PBS. Tumor sizes were measured twice a week. Mice were slaughtered on the 22nd day and peripheral blood, fresh frozen and paraffin embedded tumor tissue and colon samples were collected. Hematoxylin-eosin stained sections were prepared. Cytokeratin, Ki-67, CD3 immunohistochemistry stainings were performed to analyse cell proliferation, necrosis and T-cell invasion. We verified our results on HT29 human colorectal carcinoma cell line. We created three groups using human healthy DNA, HT29 derived DNA treatment and PBS, as controls. Cell cycle analysis was performed by flow cytometry following propidium iodide staining.
Results: The size of tumor in group I (sdDNA) was 48%, in group III (sport) was 51% compared to control group. In Group II (tdDNA) 34% of animals died during the experiment, 20% of tumors were exulcerated due to increased growth, and all mice were cachectic. Histological investigation of implanted tumor tissues showed increased cell proliferation and dedifferentiated tumor tissue in tdDNA treated group. Number of living tumor cells showed significant differences in Group I and III: 44% and 34% respectively, in comparison to 78% in Group II. CD3 expression was lower in group II (4%) and showed

Abstract number: OP025

Indicators /Type of lesions	Sensitivity (95%CI)	Specificity (95%CI)	Positive predictive value(95%CI)	Negative predictive value(95%CI)	Kappa value(95%CI)
Non-metaplasic non-neoplastic	0.928 (0.926–0.93)	0.982 (0.98–0.983)	0.97 (0.968–0.972)	0.955 (0.954–0.957)	0.917 (0.913-0.92)
Metaplastic	0.928 (0.925-0.93)	0.945 (0.944-0.947)	0.90 (0.898-0.903)	0.961 (0.96-0.962)	0.867 (0.863-0.871)
Neoplastic	0.893 (0.89-0.897)	0.954 (0.953-0.955)	0.872 (0.868-0.875)	0.962 (0.961-0.964)	0.84 (0.835-0.845)

strong positivity in group I and II (19% and 17%) compared to the control group (7%). In group II the number of lymphoid tissue plaques decreased and the mucosa layer of colon samples was destructed. On DNA histogram of HT29 cells increased proliferation was observed following HT29 DNA treatment and increased apoptosis following normal DNA treatment, in correlation with observations of our animal experiments.

Conclusion: Physical activity and normal DNA treatment may have similar cancer preventive effect by increased amount of lymphoid tissue and inhibited proliferation of tumor cells. The present findings may emphasize the importance of physical activity in cancer prevention. The positive autocrin effect of tumor derived cfDNA on tumor cells is a new and important factor and a unique observation.

Disclosure of Interest: None declared

MONDAY, OCTOBER 26, 2015 11:00–12:30

ADVANCES IN ENDOSCOPIC IMAGING OF THE UPPER GI TRACT – ROOM E3

OP025 COMPUTER-AIDED DIAGNOSTIC SYSTEM FOR THE REAL-TIME PATHOLOGY PREDICTION AND CLINICAL DECISION SUPPORT DURING NARROW BAND IMAGING MAGNIFICATION ENDOSCOPY IN STOMACH

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Introduction: Narrow-band imaging endoscopy with magnification (NBI-M) is recommended to be utilized for clinical decision-making during screening or follow-up of individuals at high risk for gastric cancer [1]. Nevertheless, its application in clinical practice has some challenges due to the presence of various histological and endoscopic pattern changes of gastric mucosa. Nowadays computer-aided decision support systems in endoscopy are being designed to assist a medical expert in mastering advanced techniques that require a high level of expertise.

Aims & Methods: The aim of this study was to design a computer-aided diagnosis hardware-software complex for real time clinical decision support during NBI-M in stomach. This complex was incorporated into endoscopic documentation system for real-time pathology prediction based on the automated assessment of mucosal patterns of saved images. Image processing techniques were applied for extracting of geometrical and topological features. For creating a multi-class classifier a naive Bayesian approach was used to combine results of several binary Adaboost classifiers. We selected and analyzed 91 endoscopy NBI-M images of gastric lesions from 52 patients (Olympus Exera GIF Q160Z, Lucera GIF Q260Z). All images were independently assessed by an expert and computer-aided system according to validated simplified NBI-classification [2]: type A (circular), B (tubulo-villous), C (irregular). Histology was used as the ground truth information. Training and testing were performed for every image by a bootstrap method.

Results: Among 91 images 25 had type A pattern (16 normal mucosa, 9 chronic gastritis), 31 had type B pattern (22 intestinal metaplasia, 9 pseudopyloric metaplasia), and irregular 35 has type C pattern (9 high-grade dysplasia, 26 adenocarcinoma). The average percentage of correctly recognized areas was $91.8 \pm 4.4\%$ (92% in type A, 92% in B, 89% in C). The results of computer-aided classification are summarized in the table.

Conclusion: The newly designed endoscopic computer-aided diagnostic hardware-software system could provide effective recognition of three main types of gastric mucosal patterns and thus may lead to real-time pathology prediction and support for clinical decision-making.

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Disclosure of Interest: None declared

OP026 PROSPECTIVE CONTROLLED TRIAL OF NARROW BAND IMAGING FOR DETECTION OF GASTRIC CANCER PRECURSORS

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Introduction: Gastric intestinal metaplasia (GIM) is a precursor lesion of gastric cancer. Narrow band imaging (NBI) enhances the mucosal and vascular pattern of the gastric surface. Recently a simplified NBI approach for evaluation of gastric cancer precursors was introduced.[1]

Aims & Methods: AIM was to compare in a prospective tandem manner whether NBI improves detection of GIM compared to white light exam and random biopsy protocols in a population with high (67%) prevalence of *H. pylori*.

Methods: Patients with symptoms of dyspepsia, epigastric pain, and iron deficiency anemia but not active bleeding or known gastric metaplasia/neoplasia were evaluated by upper endoscopy. Each patient underwent white light exam by one endoscopist, followed by NBI exam by a second endoscopist blinded to the white light findings. Targeted biopsies were performed of abnormal areas detected by white light and NBI. All patients then underwent a random biopsy protocol comprised of 2 biopsies from the lesser curvature (body and antrum), 2 biopsies from the greater curvature (body and antrum), and one from the incisura. Biopsies directed by 3 methods (white light, NBI, and random biopsy protocol) were coded and read by a pathologist blinded to the modality which guided the biopsies. PRIMARY OUTCOME was the proportion of patients with GIM, according to NBI, white light, and random biopsy. The yield of the 3 modalities to detect GIM on a per lesion (abnormal region) basis was a secondary outcome.

Results: 70 patients were included in this interim analysis (32% of the proposed sample of 220); and all had at least 3 sites biopsied (total sites = 294). Indications for upper endoscopy were dyspepsia in 25, epigastric pain in 27, and iron deficiency in 18. Overall, 24 (34%) of patients were confirmed on biopsy to have gastric intestinal metaplasia; it was localized to the antrum in 13 but multifocal in 7. The overall accuracy rate for patients was 77% for white light, 90% for NBI, and 90% for random biopsy. While white light identified 8/24 (33%) of individuals with metaplasia, NBI and random biopsy identified 17 (71%) (McNemar's $p = 0.02$)(Table 1). Among the 24 patients, intestinal metaplasia was detected only by NBI in 6 patients, only by random biopsy in 6, and a combination of methods in the remainder. NBI required less biopsies, a mean of 10 to detect each patient with GIM compared to 18 for the random biopsy protocol.

Table 1

		Correct identification of metaplasia		
	Prevalence of Metaplasia N (%)	White Light	Narrow Band Imaging	Random Biopsy Protocol
Patients with GIM (per patient analysis) N = 70	24 (34%)	8 (33%)	17 (71%)	17 (71%)
Individual sites (per site analysis) N = 294	39 (13%)	11 (28%)	20 (51%)	23 (59%)
Biopsies targeted by each modality		89	171	300

Conclusion: Gastric intestinal metaplasia is frequently missed by white light endoscopy. In this preliminary analysis, NBI and random biopsies appear to improve detection, with NBI requiring less biopsies.

Reference

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Disclosure of Interest: None declared

OP027 MORPHOLOGICAL CLASSIFICATION AND CLINICAL SIGNIFICANCE OF WHITE OPAQUE SUBSTANCE WITHIN GASTRIC NEOPLASIA VISUALIZED BY MAGNIFYING ENDOSCOPY WITH NARROW-BAND IMAGING

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Introduction: White opaque substance (WOS) within gastric neoplasia is a unique finding of magnifying endoscopy with narrow-band imaging (ME-NBI) and indicates intramucosal accumulation of lipid droplets. We presented the morphological classification of WOS within gastric neoplasia at UEGW in 2014. However, the morphological classification of WOS within gastric neoplasia and the accuracy of this classification has not been thoroughly investigated by studies with large sample sizes.

Aims & Methods: The aim of the current study was to establish a morphological classification system for WOS and investigate whether this system can be used to discriminate between adenoma and early carcinoma. This study retrospectively investigated 308 patients with 343 gastric neoplasias (40 adenomas and 303 early carcinomas) who underwent ME-NBI before endoscopic resection at our hospital between January 2010 and February 2015. We studied the frequency of WOS in these gastric neoplasias and identified the following morphological patterns: 1) dotted pattern, scattered and distributed as dots; 2) linear pattern, shaped like a line composed of aggregated dots; 3) reticular pattern, shaped like a honeycomb composed of connected lines; 4) speckled pattern, mottled and composed of aggregated dots; and 5) diffuse pattern, diffusely distributed with dense WOS in the intervening part. We also investigated the irregularity of WOS within adenomas and early carcinomas. We defined irregular WOS as a disorganized and asymmetrical distribution of WOS on any pattern.

Results: WOS was more frequently observed in adenomas (17/40: 42.5%) than in early carcinomas (98/303: 32.3%). The sensitivity, specificity, and accuracy of dotted WOS for discriminating carcinoma from adenoma were 53.1%, 76.5%, and 56.5%, respectively. The sensitivity, specificity, and accuracy of reticular WOS for discriminating adenoma from carcinoma were 47.1%, 87.8%, and 80.0%, respectively. The sensitivity, specificity, and accuracy of irregular WOS for discriminating carcinoma from adenoma were 98.0%, 58.8%, and 92.2%, respectively. WOS within adenomas showed a symmetrical distribution with a regular reticular pattern. WOS within carcinomas showed an asymmetrical distribution with an irregularly dotted pattern.

	Adenoma (17)	Carcinoma (98)	*P value*
Dotted pattern	4/17 (23.5%)	52/98 (53.1%)	<0.05
Linear pattern	7/17 (41.2%)	23/98 (23.5%)	0.217
Reticular pattern	8/17 (47.1%)	12/98 (12.2%)	<0.01
Speckled pattern	6/17 (35.3%)	48/98 (49.0%)	0.435
Diffuse pattern	2/17 (11.8%)	8/98 (8.2%)	0.98
Irregular WOS	7/17 (41.2%)	96/98 (98.0%)	<0.01

Conclusion: In gastric neoplasias, the findings of WOS with reticular, dotted, and irregular patterns are useful for discriminating between adenoma and early carcinoma. This study focuses on the utility and effectiveness of the morphological classification of WOS when examining WOS within gastric neoplasias using ME-NBI.

Disclosure of Interest: None declared

OP028 ATLAS OF HIGH-QUALITY HISTOLOGICAL CORRELATIONS OF VOLUMETRIC LASER ENDOMICROSCOPY IMAGES OF BARRETT'S ESOPHAGUS FOR IDENTIFICATION OF EARLY NEOPLASIA

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Introduction: Early neoplastic lesions in Barrett's esophagus (BE) are difficult to detect with white-light endoscopy. Volumetric Laser Endomicroscopy (VLE) is a novel balloon-based OCT imaging technique that provides a 6-cm long circumferential volumetric scan of the esophageal wall layers to a depth of 3 mm with a resolution comparable to low-power microscopy. Correlation of VLE to histology is essential to be able to identify VLE features of early BE neoplasia.

Aims & Methods: The aim was to compose high-quality one-to-one correlated histology-VLE images for identification of VLE features of early BE neoplasia. An ex-vivo VLE scan of endoscopic resection (ER) specimens including reference markers from BE patients with and without neoplasia was performed. Tissue blocks were carefully sectioned from the ER specimens alongside the reference markers. Histology slides were sectioned from each tissue block and when necessary extensive sectioning of tissue blocks was performed in order to visualize all markers. All histology slides were evaluated by an expert BE pathologist and annotated using a custom-made program for epithelium type, grade of dysplasia and (sub)mucosal structures. All VLE scans and corresponding histology slides were evaluated by 2 observers and considered a match when on both modalities ≥ 2 reference markers were visible and mucosal patterns matched. In each match areas of interest (AoIs) were identified based on the histological diagnosis and division of the match by the reference markers. In an unblinded learning phase all AoIs were evaluated for potential VLE features predictive of neoplasia.

Results: In total 52 ER specimens were obtained in 29 BE patients ((66 yrs, 19 male, overall histological diagnosis 16 early adenocarcinoma (EAC), 5 high-grade dysplasia (HGD), 2 low-grade dysplasia (LGD) , 6 non-dysplastic (ND)BE)). 86 histology-VLE matches were constructed including 185 AoIs (31 squamous epithelium, 43 gastric epithelium, 41 NDBE, 22 LGD, 20 HGD, 27 EAC. In a first evaluation the following VLE features were identified as potentially predictive for dysplasia: lack of layering, homogeneity ,surface maturation and irregular glands.

Conclusion: This study presents the first atlas of high-quality histology-VLE correlations of BE and neoplasia, allowing further research on development of VLE features to distinguish early neoplasia in BE. The learning phase identified several potential VLE features for early BE neoplasia, which is the first step towards validation of VLE for detection of early BE neoplasia.

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OP029 FLUORESCENCE DETECTION OF HEAD AND NECK SQUAMOUS CELL CARCINOMA BY TOPICALLY SPRAYING A GAMMA-GLUTAMYLTRANSPEPTIDASE-ACTIVATED PROBE

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Introduction: Although early detection of head and neck squamous cell carcinoma (HNSCC) is imperative for better outcome, it is difficult to detect early HNSCC endoscopically, because there are few morphological changes. Lugol chromoendoscopy has been widely accepted for the detection of early esophageal squamous cell carcinoma; however, it can not be applied to the head and neck lesion due to severe mucosal irritation. Therefore, a valuable method to detect early HNSCC is required.

γ-glutamyl transpeptidase (GGT), a cell surface enzyme, is overexpressed in several cancers, and it has been reported that an enzymatically activatable fluorescent probe, γ-glutamyl hydroxymethyl rhodamine green (gGlu-HMRG), which becomes fluorescent after cleavage of a GGT-specific sequence, can be activated within a few minutes after spraying in a cancer-bearing animal model (Sci Transl Med 3:110ra119, 2011).

Aims & Methods: To evaluate whether early HNSCC can be detected by spraying gGlu-HMRG, using fresh clinical samples obtained by endoscopic submucosal dissection (ESD) or surgical resection.

gGlu-HMRG was applied to four HNSCC cell lines (HSC2, HSC3, HSC4, SCC25), and fluorescence was observed by fluorescent microscopy and flow cytometry. Immunohistological examination was performed to the past three ESD cases to investigate the expression of GGT. Fluorescent imaging with gGlu-HMRG for five cases resected by ESD or surgery was performed. Fluorescent intensity of region of interest (ROI) of tumor and normal mucosa was measured.

Results: All four cell lines applied gGlu-HMRG emitted green fluorescence. Immunohistological examination demonstrated that GGT was highly expressed in HNSCC but barely expressed in normal component. Fluorescent imaging showed that lugol-voiding lesion became fluorescent within a few minutes after spraying gGlu-HMRG in all five resected cases. Fluorescent intensity of ROI in tumor region was significantly higher than in normal mucosa in five minutes after spraying gGlu-HMRG ($p < 0.05$).

Conclusion: Fluorescent imaging with gGlu-HMRG is useful for early detection of HNSCC.

Disclosure of Interest: None declared

OP030 A NOVEL ENDOSCOPIC DIAGNOSIS OF CANCER FUNCTION USING HYPOXIA IMAGING ENDOSCOPY EQUIPPED WITH LASER LIGHT SOURCE

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Introduction: Recent endoscopy has evolved into image-enhanced endoscopy (IEE), such as Narrow Band Imaging and Blue Laser Imaging. IEE focused on increasing abnormal microvessels in the surface of early cancers. In contrast, hypoxia is one of the functional characteristics in cancer, with strong

association to the biological features. The investigation of cancer hypoxia was started in the 1960s, and there have been many reports. Therefore, hypoxia imaging was innovated to visualize directly the biological and functional changes in cancer.
Aims & Methods: The aim of this prospective study is to evaluate the visualization of human cancers using hypoxia imaging endoscopy in the first in human clinical trials. In endoscopic equipment, we utilized a difference of absorption between oxy- and deoxy-hemoglobin in visible light wavelength. The signals converted from laser light were calculated in oxygen saturation (StO_2) by processor. Hypoxia imaging was obtained in real-time, displaying two types of StO_2 images. One was a pseudocolor image showing StO_2 levels as different hues, and the other was an overlay image that overlapped low StO_2 levels in blue on a white light illumination image of background mucosa. In the initial trial, patients who had been confirmed to have pharyngeal, esophageal, gastric, or colorectal neoplasia by previous endoscopy were enrolled. To compare histologic findings to hypoxia imaging, all patients received endoscopic resection immediately after conventional and hypoxia imaging endoscopy. We determined the corresponding areas of neoplasia and non-neoplasia in the endoscopic images and obtained StO_2 levels from the StO_2 map. In the second clinical trial, we investigated the changes of hypoxia imaging before and after chemotherapy, and efficacy of chemotherapy in advanced cancers of the esophagus, stomach, and colorectum.
Results: Forty patients with early-sided lesions in the pharynx, esophagus, stomach and colorectum were analysed. The hypoxic area was completely corresponded to the portion of early cancer. Furthermore, 8 colorectal low-grade adenomas were also detected as hypoxia, ranging from 3 to 10 mm in diameter. All esophageal cancers including 2 Barrett's cancers were detected in hypoxia images. Median StO_2 differences between neoplastic and non-neoplastic areas in the pharynx, esophagus, stomach and colorectum were -15.4%, -14.5%, -5.1% and -21.5%, respectively. Significant differences of StO_2 levels were seen in the esophagus ($p = 0.0078$, $n = 8$) and colorectum ($p = 0.0001$, $n = 14$), but not in the stomach ($p = 0.9341$, $n = 15$) or pharynx ($p = 0.2500$, $n = 3$). In the advanced cancers, hypoxia imaging before chemotherapy could be partly related to efficacy of chemotherapy.
Conclusion: Hypoxia imaging with the laser endoscope enables us to visualize spatial and temporal information of hypoxic conditions in adenoma, early and advanced cancers. Hypoxia imaging illustrates a novel aspect of cancer biology as a potential biomarker and can be widely utilized in cancer diagnosis.
Disclosure of Interest: None declared

MONDAY, OCTOBER 26, 2015 11:00–12:30
LIVER: FROM INFLAMMATION TO FIBROSIS – ROOM E5

OP031 THE PERFORMANCE OF POINT SHEAR WAVE ELASTOGRAPHY USING ARFI TECHNIQUE -ELASTPQ IN CHRONIC HEPATOPATHIES

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Introduction: In the last decade , different types of ultrasound based elastographic methods that noninvasively quantify liver fibrosis, have been developed.
Aims & Methods: The aim of this study was to compare the performance of point shear wave elastography using ARFI technique- ElastPQ, in patients with different liver diseases, using Transient Elastography (TE) as the reference method, since it is a validated method for liver fibrosis assessment.
The study included 121 consecutive subjects with chronic hepatopathies (33.9% HBV, 23.9% HCV, 5.8% NASH, 1.7% ASH, 4.1% colestatic liver disease) and 30.6% with liver cirrhosis by means of TE. Liver stiffness (LS) was evaluated in the same session by means of 2 elastographic **Methods:** TE (Fibroscan, Echosens) and ElastPQ (Philips, Affinity) technique.
Reliable LS measurements were defined as follows: for TE – the median value of 10 LS measurements with a success rate $\geq 60\%$ and an interquartile range $< 30\%$, for ElastPQ- the median value of 10 LS measurements in the liver parenchyma avoiding large vessels. For TE M and XL probes are used. LS was expressed in kPa for both TE and ElastPQ. For differentiating between stages of liver fibrosis we used the following cut-off values: for TE - significant fibrosis ($F \geq 2$) - 7.2 kPa and for liver cirrhosis (F4) -14.5kPa (Tsochatzis, 2011); for ElastPQ $F \geq 2$ -5.9 kPa, $F4 = 12$ kPa (Ferraioli, 2013). Reliable liver stiffness evaluation were obtained in 74.4% by means of TE and 99.3% with ElastPQ.
Results: In the final analysis were included 90 subjects (90/121 - 74.4%) with reliable LS measurements by means of TE. By using ElastPQ with the proposed cut-offs, as evaluation method, the frequency of no or mild fibrosis ($F < 2$), significant fibrosis ($F \geq 2$) and cirrhosis ($F = 4$) in our cohort was: 62.2% ($F < 2$), 17.8% ($F \geq 2$) and 20% ($F = 4$). Considering TE as the reference method, the sensitivity (Se) and specificity (Sp) for the diagnose of absence or mild fibrosis by means of ElastPQ were: 87.7% and 91.2%.
For significant fibrosis ($F \geq 2$) we obtained a sensitivity (Se) of 57.9% and specificity (Sp) of 91.2%, while for cirrhosis, the Se was 83.3% and the Sp 95.8%. ElastPQ was significantly better for diagnosing cirrhosis than significant fibrosis: accuracy 93.3% vs. 82% ($p = 0.03$), while for absence or mild fibrosis vs. significant fibrosis the accuracies were similar: 87.7% vs. 82% ($p = 0.39$).
Conclusion: ElastPQ is a promising non-invasive elastographic method that can accurately diagnose liver cirrhosis.

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Disclosure of Interest: None declared

OP032 SIGNIFICANCE OF INTEGRIN ALPHA 11 IN PHENOTYPIC REGULATION OF HEPATIC STELLATE CELLS IN LIVER FIBROSIS

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Introduction: Liver fibrosis, characterized by excessive accumulation of ECM produced by proliferative and differentiated hepatic stellate cells (myofibroblasts), is the growing cause of mortality worldwide. Thus, understanding of the factors that induce myofibroblasts differentiation is paramount to prevent the fibrotic process. Previous studies have shown that mechanical stress derived from the integrin-mediated interaction between extracellular matrix and the cytoskeleton promotes myofibroblasts differentiation.
Aims & Methods: Integrin alpha 11 (ITGA11) is collagen receptor expressed on fibroblasts and in this study we aimed to explore the significance of this receptor in hepatic stellate cells during liver fibrosis. Liver fibrosis was induced in mice by intraperitoneal administrations of CCl_4 for 4 weeks (intermediate) and 8 weeks (advanced). Protein and mRNA expression levels of various fibrotic parameters and ITGA11 were examined using QPCR and immunostaining. We also analyzed ITGA11 expression in human cirrhotic liver tissues and in TGFβ-activated human hepatic stellate cells (LX2). To elucidate the possible role of ITGA11, we knocked-down its expression in LX2 cells using ITGA11-shRNA plasmid. Morphological changes and fibrotic parameters in control and ITGA11 knock-down cells were studied with and without TGFβ activation, using immunostainings, quantitative PCR and RT^2 profiler human fibrosis array. Furthermore, to assess its functional role in fibrosis-related processes, we performed collagen I adhesion assay, 3D-collagen gel contraction assay, wound closure/migration assays and indirect effect on angiogenesis (tube formation assay).
Results: *In vivo* in liver fibrosis mouse models, we found an increase of the ITGA11 expression with increasing degree of fibrosis as well as it was highly expressed in human cirrhotic livers. The ITGA11 expression was found to be co-localized with α-SMA positive myofibroblasts in both mice and human cirrhotic livers. *In vitro*, ITGA11 expression levels (mRNA and protein) were highly up-regulated in TGFβ-activated human hepatic stellate cells while remained undetected in hepatocytes and monocytes. Following stable ITGA11 knock-down, we observed 80% reduction in ITGA11 which resulted in decreased mRNA expression levels of a-SMA, IGF2, vimentin, TIMP1 and paxillin. We further found drastic reduction in TGFβ-induced collagen I, a-SMA and vimentin protein expression in ITGA11 knock-down versus control cells. Strikingly, in RT^2 profiler human fibrosis array, ITGA11 knock-down cells showed a significant reduction in 19 fibrosis-related genes, as compared to control cells. Interestingly, ITGA11 knock-down cells displayed decreased proliferation and diminished filopodia and lamellipodia extensions signifying ITGA11 importance in maintaining the HSCs phenotype. In the functional assays, ITGA11 knock-down resulted in attenuated would healing, reduced adhesion to collagen-I matrix, impaired collagen contractility and inhibited HSC-induced endothelial cell tube formation (angiogenesis).
Conclusion: These findings suggest that ITGA11 is a promising target in myofibroblasts during liver fibrosis which regulates proliferation, differentiation and fibrosis-related functions of myofibroblasts.
Disclosure of Interest: None declared

OP033 ROLE OF THE PROTEASE-INHIBITOR SERPINB3 IN THE REGULATION OF WNT FAMILY MEMBERS IN MONONUCLEAR CELLS

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Introduction: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death world-wide. HCC nearly always develops in the setting of liver cirrhosis and hepatitis B and C viral infection. Recent publications revealed that Notch/WNT pathway orchestrates liver stem cell activation and differentiation and that deregulation of this pathway is associated with HCC development. Our recent data demonstrate that SerpinB3, a member of the ovalbumin-serin protease inhibitor family, plays a primary role in hepatocellular carcinoma development. In addition, its detection in the liver progenitor cells niche, suggests an involvement in staminal cell activation. Furthermore, SerpinB3 induces EMT and modulates miR122 which is involved in WNT-1 production. The aim of this study was to evaluate the role of SerpinB3 in the modulation of Notch-WNT signalling in macrophages, principal players in the modulation of liver staminal niche through WNT paracrine signalling
Aims & Methods
Methods: Primary human mononuclear cells were isolated from healthy donors and treated with or without recombinant SerpinB3 (200 ng/ml) or medium as

control up to 168 hours. WNT-family mRNA expression was evaluated by Q-PCR, while cell viability was measured daily up to 7 days.
Monocyte-derived THP-1 cell line was also transfected with a plasmid vector containing SerpinB3 or a empty vector as control, and characterised after 48 h. To evaluate the effect of SerpinB3 in inflammatory cells, mononuclear cells were pre-treated with recombinant SerpinB3, stimulated with 1 μM LPS and analyzed up to 24 hours.
Results: In human monocytes the addition of SerpinB3 induced a 30% cell viability increase at day 7. In monocytes stimulated with SerpinB3 a significant up-regulation of WNT-1, but not of WNT-3a, WNT-5a and WNT-7a, compared to controls, was detected. In mononuclear cells stimulated with LPS, to mimic inflammation, WNT-1 was weakly expressed, but pre-treatment with SerpinB3 determined a remarkable up-regulation of this molecule. In monocyte-derived THP-1 cells transfected with SerpinB3, WNT-1 was slightly increased and its expression was further enhanced after exposure to LPS. In this latter experimental condition a significant increase of WNT-5a was also observed.
Conclusion: SerpinB3 prevents natural cell death of primary human monocytes in vitro. The modulation of WNT-family members is differently influenced by SerpinB3 in relation to inflammatory conditions, suggesting that this serpin may affect the liver staminal niche behaviour by modulating the WNT-family member profile.
Disclosure of Interest: None declared

OP034 IL-10-PRODUCING REGULATORY B CELLS ENHANCED REGULATORY T CELLS FUNCTION: A NEW IMMUNOSUPPRESSIVE MECHANISM DURING HBV-RELATED LIVER FIBROSIS

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Introduction: Chronic hepatitis B (CHB) infection is a leading cause of liver fibrosis, cirrhosis and even hepatocellular carcinoma. Although hepatitis B virus (HBV) itself is non-cytopathic, both HBV-related liver damage and viral control are immune-mediated. There were abundant evidences to believe that regulatory T (Treg) cells play pivotal roles in the immunopathogenesis of HBV and its related liver diseases, especially in immune tolerance phase and persistent virus infection. Nowadays, a new subset of IL-10-producing B cells, also known as regulatory B (Breg) cells has been shown to play vital roles in modulating autoimmune diseases. However, its relationship with infectious disease has rarely been studied.
Aims & Methods
Aims: Here, we evaluated the role of Breg cells in the pathogenesis of HBV-related liver fibrosis (HBV-LF) and assess their impact on the proliferation of CD4 + T cells and further investigated the immunoregulatory effects on Treg cells.
Methods: A total of 67 treatment-naïve patients who were diagnosed as chronic hepatitis B (CHB) patients underwent liver biopsies and 25 healthy donors took part in the study. Firstly, peripheral blood mononuclear cells (PBMC) were isolated for the study of Breg subset markers (CD19, CD24, CD27, CD38, CD25, CD40, IgM, IgD, IL-10). And then, we determined the changes in number and function of Breg cells in CHB patients compared with that of healthy controls. For the *in-vitro* experiments, human Breg, CD4 + T and Treg cells were purified using flowcytometry. Purified anti-CD3 antibody stimulated CD4 + T cells were cultured alone or with autologous Breg cells and their proliferation response was determined by the thymidine method. Simultaneously, to elucidate the exact effects of Bregs on Tregs and the potential methanism during HBV-LF, human Breg and Treg cells were co-cultured in the stimulation with HBcAg, anti-IL-10 and anti-TGF-β antibody.
Results: B cells and Breg cells were both enriched in patients, and among which, Breg cells frequencies had a close relationship with viral load, liver inflammation and degree of fibrosis. Stimultaneously, we demonstrated the phenotype of these Breg cells: memory B cells ($CD24^{hi}CD27^{+}$B cell) and transitional B cells ($CD24^{hi}CD38^{hi}$B cell), and the phenotype was pridominantly characterized as $CD19^{+}CD24^{hi}CD38^{hi}$B cell subset. In the co-culture of Breg cells from CHB patients with autologous CD4 + T cells, the proliferation capacity of CD4 + T cells was significantly reduced in a dose-dependent manner compared with controls. In addition, Breg cells from patients with CHB were found to have further enhanced effect on the proliferation of Treg cells as well as the release of IL-10 and TGF-β cytokines than such cells from healthy donors. Furthermore, blockage of IL-10 and CTLA-4 but not TGF-β decreased the inhibitory effect of Breg cells on Treg cells. The regulatory function of Breg cells on Treg cells was mainly dependent on direct cell-cell contact as well as IL-10 but not TGF-β-dependent manner.
Conclusion: Our data revealed that elevated Breg cells, which can inhibit the proliferation of CD4 + T cells and regulate Treg cells immunity, maybe an indicator for the development of HBV-related liver fibrosis.
Disclosure of Interest: None declared

OP035 TARGETING NOTCH SIGNALING PATHWAY BY SMALL MOLECULE Γ-SECRETASE INHIBITOR BMS-708163 ATTENUATES EARLY LIVER FIBROGENESIS IN VIVO

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Introduction: Hepatic fibrosis, mainly caused by viral infections, alcohol abuse or metabolic syndrome leading to liver dysfunction, is the growing cause of mortality worldwide. Currently, there is no clinically-approved therapy available for the treatment of this disease. Hepatic stellate cells (HSCs) known as "master producers" and macrophages (inflammatory cells) as "master regulators" of fibrosis, are the key cell types that strongly contribute to the initiation and progression of liver fibrosis. Therefore, therapeutic inactivation of these key cell types may lead to reversal of fibrosis.
Aims & Methods: Since aberrant activation of the notch signaling cascade occurs in patients with liver fibrosis, we hypothesized to target this pathway for intervention in liver fibrosis using BMS-708163, a small molecule that specifically inhibits γ-secretase. Activation of Notch signaling pathway was examined *in vitro* in activated HSCs (LX2), M1- and M2-differentiated RAW macrophages and *in vivo* in liver fibrosis mouse models. Effects of Notch signaling inhibitor BMS-708163 on fibrotic parameters and contractility were evaluated in TGFβ-activated LX2. In addition, effect of the BMS-708163 were examined in M1 (inflammatory) and M2 (restorative) differentiated macrophages. Effect on cell viability was examined in both cell types at increasing concentrations of BMS-708163 using alamar blue assay. Finally, BMS-708163 was evaluated for anti-fibrotic effects in CCl_4-induced acute liver injury mouse model.
Results: Notch signaling pathway components were significantly up-regulated in TGFβ-activated HSCs (Notch3, JAG1 and Hes1), M1-differentiated macrophages (Notch1,2,3, Jag1, Dll1,4 and Hes1) and *in vivo* in in acute liver injury and advanced fibrosis mouse models (Notch1,3, Jag1, Dll1,4 and Hes1). *In vitro*, in TGFβ-activated human LX2 cells, BMS-708163 significantly inhibited protein and gene expression of major fibrotic parameters (Collagen I, α-SMA and Vimentin) and 3D-collagen I gel contractility. Furthermore, in M1- and M2-differentiated murine macrophages, BMS-708163 significantly suppressed M1 markers (IL-1β, IL-6, iNOS and nitric oxide release) while no effect on M2 markers (Arginase I and MRC1) were observed. No significant effects on cell viability was observed with increasing concentrations of BMS-708163. *In vivo* in CCl_4-induced acute liver injury mouse model, post-disease administration of BMS-708163 (10 mg/kg) significantly attenuated collagen accumulation, HSC activation and proliferation. Interestingly, BMS-708163 significantly inhibited inflammatory M1 macrophages and up-regulated M2 macrophages.
Conclusion: Because no effective treatment for liver fibrosis exists, selective inhibition of notch signaling pathway suggests a potential unique therapeutic approach targeting key pathogenic cell types (both hepatic stellate cells and macrophages) in liver fibrosis.
Disclosure of Interest: None declared

OP036 ASSESSMENT OF LIVER FIBROSIS WITH SHEAR WAVE ELASTOGRAPHY IN CHRONIC HEPATITIS B VIRUS INFECTION

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Introduction: Real-time shear wave elastography (SWE), as the latest generation of hepatic elastography technique, is promising in noninvasive liver fibrosis measurement but with limited data in Chronic Hepatitis B (CHB).
Aims & Methods
Aims: The purpose of this study is to investigate the diagnostic performance and influence factors of SWE with CHB.
Methods: Patients with CHB from the First Affiliated Hospital of Sun Yat-sen University from July 2013 to February 2015. All had undergone SWE, anthropometry measurement, blood cell count and liver function while 37 patients received liver biopsy. Liver fibrosis was staged from F0 to F4 by METAVIR score. Simple noninvasive fibrosis screening scores APRI and FIB-4 [1]were also calculated with published formulas. Following items were evaluated: Diagnostic accuracy was compared between SWE, APRI and FIB-4 respectively and cooperatively with Receiver operating characteristic curve (ROC) using liver hepatic pathology and decompensated cirrhosis as gold standards. The cut-off value of SWE for liver fibrosis due to HCV was applied to differentiated liver fibrosis stage in these patients[2]. A multiple linear regression model was performed to estimate the correlation between anthropometry, liver function and SWE.
Results: 248 patients with CHB (30 decompensated cirrhosis) were included. 170 (68.5%) patients were males and the average age was 37.4(18∼52) years. Distribution of liver fibrosis stage in 67 patients (37 obtained liver biopsy, 30 decompensated cirrhosis) were as follow: F0:3, F1:21, F2:12, F3:4, F4:30. The Area Under ROC (AUC) for liver stiffness measurement with SWE were 0.891, 0.921 and 0.947 for the diagnosis of significant fibrosis ($\geq$ F2), advanced fibrosis ($\geq$ F3) and cirrhosis (F4), respectively, which is superior to the AUC of APRI [0.798 ($p = 0.094$), 0.823 ($p = 0.046$), 0.806 ($p = 0.038$)] and FIB4 [0.669($p = 0.002$), 0.796($p = 0.016$), 0.838 ($p = 0.048$)]. A multifactor logistic regression combined model of SWE, APRI and FIB4 was build, the AUC of which is 0.902 ($p = 0.97$), 0.942 ($p = 0.620$), 0.933 ($p = 0.796$), respectively, showing no significant differences in SWE alone. When predicting the liver fibrosis stage with cut-off values of SWE from HCV patients[2], misdiagnostic rate of significant fibrosis was 13.1%, omission diagnostic rate was 23.8%. Body Mass Index (BMI) ($\beta = 11.59$, $p = 0.026$), GGT ($\beta = 0.113$, $p = 0.000$) and total bilirubin ($\beta = 0.19$, $p = 0.000$) represent a significant positive correlation with SWE.
Conclusion: SWE have a good value for the noninvasive liver fibrosis assessment, but combination with APRI and FIB4 do not improved diagnostic accuracy. The cut-off values of SWE from HCV patients are not suitable to CHB. SWE may be influenced by BMI, GGT and total bilirubin.

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Disclosure of Interest: None declared

MONDAY, OCTOBER 26, 2015 11:00–12:30
THE INFLAMED STOMACH – ROOM E6

OP037 TARGETED COMPARATIVE PROTEOMICS OF HELICOBACTER PYLORI ISOLATED FROM GASTRIC DISEASES

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Introduction: The infection with the bacterial pathogen *Helicobacter pylori* (HP) is among the risk factors for the occurrence of several gastric diseases, including Gastric Cancer (GC), Duodenal Ulcer (DU), and Atrophic Autoimmune Gastritis (AAG). The characterization of HP differential proteomes in gastric diseases may undoubtedly improve the knowledge of the molecular events associated to the pathological scenario.

Aims & Methods: Therefore, in this work we analysed the differentially expressed proteins of HP in patients affected by DU or GC or AAG by 2D-DIGE, to identify potential HP molecular sentinels to be specifically associated with gastric diseases.

After image analyses with Decyder, a total of 30 proteins were totally found as differentially expressed in a first comparative analysis 'DU *versus* GC', while 36 differentially expressed spots were revealed a second comparative analysis 'AAG *versus* either DU or GC'. Proteins were identified after MALDI-TOF and peptide mass fingerprinting.

Results: Most proteins of HP up-regulated in DU *vs*. GC were oxidoreductases and were involved in various biosynthetic/metabolic processes. The HP proteins overexpressed in GC *vs*. DU were related to protein synthesis and DNA replication/transcription translation. While a higher antioxidant activity was found in AAG-associated HP strains, which were hypothesized to be less motile/virulent and able to neutralize the high local hydrogen concentration as well as to accomplish protein biosynthesis, in comparison with DU- or GC-associated HP.

The overall found differential proteins were then characterized in terms of network connections, biological processes and molecular functions.

Conclusion: The differential protein panels we obtained in HP strains specifically associated with the different pathologies may represent candidate disease markers to be further validated and offer a tool for further analyses aimed to get better insight the pathogenic physiology of some HP strains.

Disclosure of Interest: None declared

OP038 DIFFERENCE OF MICOROMUCOSAL PATTERNS OF THE GASTRIC CORPUS MUCOSA BETWEEN HELICOBACTER PYLORI-ASSOCIATED AND AUTOIMMUNE GASTRITIS PATIENTS

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Introduction: *Helicobacter pylori* (*H. pylori*)-associated and autoimmune gastritis are two major entities of chronic atrophic gastritis. However, characteristics of micromucosal structure observed by magnifying endoscopy of these diseases has not been fully investigated.

Aims & Methods: Aim of this study is to compare magnifying endoscopic appearance between *H. pylori*-associated and autoimmune gastritis. Seven *H. pylori* naïve, 21 *H. pylori*-associated gastritis and 7 autoimmune gastritis patients gave written informed consent to enroll in this study. A videoendoscope: EVIS GIF-FQ260Z that can be used in high-resolution white light, autofluorescence (AFI) and magnifying narrow band imaging (NBI) modes was used. Extent of mucosal atrophy in the corpus was determined as extent of greenish mucosa in AFI image. A 2×2 cm area at the lesser curvature of the corpus about 4 cm proximal to the angulus was set as a region of interest for evaluation of micromucosal patterns. The micromucosal patterns were classified into Foveola and Groove type according to magnifying chromoendoscopic and NBI images. The Foveola type mucosa was characterized as mucosa with round, oval, or short linear foveolae (gastric pits) on magnifying chromoendoscopy, and, on NBI, had dark brown subepithelial capillary that surround light brown epithelium. The Groove type mucosa was characterized by mucosal crests or papillae that were divided by continuous grooves on magnifying chromoendoscopy, and had ridged or papillary light brown epithelium that encase dark brown subepithelial capillary. Proportion of the micromucosal patterns were categorized as, Foveola 80%<; Foveola 50-80%; Groove 50-80%; and Groove 80%<. Biopsy sample was taken from the region of interest.

Results: The corpus mucosa of all of *H. pylori*-naïve patients was purple in the AFI image. 15 of 21 (71%) *H. pylori*-associated gastritis patients had medium to large greenish atrophic mucosa at the corpus lesser curvature and all autoimmune gastritis patients had large area of greenish mucosa in the entire corpus ($p < 0.0001$). The micromucosal pattern of all *H. pylori*-naïve patients was Foveola type. 19 of 21 (90%) patients with *H. pylori*-associated gastritis had various proportion of Groove type mucosa in the region of interest, whereas 5 of 7 (71%) autoimmune gastritis patients showed Foveola type mucosa that is similar to those of *H. pylori*-naïve patients ($p = 0.001$). *H. pylori*-associated gastritis showed higher grade of intestinal metaplasia than autoimmune gastritis in the biopsy specimen.

Conclusion: Micromucosal pattern of the corpus mucosa in patients with *H. pylori*-associated gastritis is likely to show Groove type that mimic the antral or intestinal mucosa, while that of autoimmune gastritis was Foveola type suggesting different pathogenesis of these diseases.

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Disclosure of Interest: None declared

OP039 CO-INFECTION WITH HELICOBACTER PYLORI AND EPSTEIN-BARR VIRUS IN BENIGN UPPER DIGESTIVE DISORDERS. A PROSPECTIVE ENDOSCOPIC-SEROLOGIC PILOT STUDY

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Introduction: About 10-30% of gastric carcinomas are associated with Epstein-Barr virus.[1] The prevalence of *Helicobacter pylori* + Epstein-Barr virus co-infection in benign upper digestive disorders is less known.

Aims & Methods: 104 patients were included in a prospective endoscopic-serologic study. *Helicobacter pylori* IgG was determined by chemiluminescence, Epstein-Barr virus IgG, IgM and viral capsid antigen titers were assayed by ELISA test. *Helicobacter pylori* was determined from 2 antrum and 2 corpus biopsies by the modified Giemsa stain. The prevalence of bacterial and viral infection and that of any co-infection with both agents was calculated in the whole group, as well as in peptic ulcer, functional dyspepsia and reflux patients. Significance between the groups was calculated by the chi-square test.

Results: The overall prevalence of *Helicobacter pylori* was 56.7%. Duodenal ulcer patients were infected in 72.5% of the cases, the prevalence being 33.3% in functional dyspesia ($p = 0.0008$) and 25.8% reflux patients ($p = 0.0001$). Epstein-Barr virus IgG was detected in 73 sera of the whole group (70.1%) and was found in 75% peptic ulcer patients, 51.2% in functional dyspepsia ($p = 0.04$) and 51.6% in reflux disease cases ($p = 0.04$). Co-infection with *Helicobacter pylori* + Epstein-Barr virus was detected in 60% of peptic ulcer patients, 18.1% in functional dyspepsia ($p = 0.00014$) and 12.9 in reflux disease ($p = 0.00012$) Anti-viral IgG titer was of 30.87 ± 2.98 cut-off index in *H. pylori* positive cases and 20.30 ± 2.56 in those negative ($p = 0.01$) The IgG titer was of 31.7 ± 3.0 cut-off index in peptic ulcer, 20.5 ± 3.5 in functional dyspepsia ($p = 0.01$) and 21.4 ± 3.6 in reflux cases ($p = 0.03$). Viral capsid antigen was found in 75% of the peptic ulcer cases, 60.6% ($p = 0.12$) of dyspeptic patients and 51.3% ($p = 0.02$) in reflux cases; its level, however, was not siginificantly different in *H. pylori*-positive and negative patients.

Conclusion: Both *Helicobacter pylori,* Epstein-Barr virus and co-infection with these agents were significantly more prevalent in duodenal ulcer patients than in dyspeptic or reflux cases. Anti-viral IgG titer was also higher in *H. pylori*-positive patients than in those negative. In gastric cancer cases, the virus was found in association with the tumor and non-atrophic gastritis, supporting its role in early precursor lesions.[2] The viral DNA load is higher in *Helicobacter pylori*-positive patients.[3] Co-infection with *H. pylori* and Epstein-Barr virus is associated with more severe gastritis in children.[4] The significance of this viral infection in duodenal ulcer must be further studied.

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Disclosure of Interest: None declared

OP040 THE EFFECT OF HUMEN HERPESVIRUSES PERSISTENCE IN THE GASTRIC MUCOSA ON THE INFLAMMATION IN CHILDREN WITH CHRONIC GASTRITIS

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Introduction: The role of herpesviruses did not study enough in children with chronic gastritis.
Aims & Methods: The evaluation of the role of some Herpesviridae representatives in formation of chronic inflammation in the gastric mucosa in children.
The study involved 320 children aged 7 to 17 years with chronic gastritis (CG). All the patients underwent esophagogastroduodenoscopy and morphological examination of the gastric mucosa (GM) with an establishment of the persistence of human herpes viruses 4, 6 and 8 using the polymerase chain reaction.
Results: No case of the persistence of humen herpes simplex virus type 8 in GM is reported. Humen herpesvirus 6 (HHV-6) and 4 (Epstein-Barr - EBV) were observed in 63.4% and 49.2% of patients respectively. Detection of HHV-6 was comparable in subgroups of patients with various degrees of inflammation. Comparative clinical-endoscopic and morphological examination of patients did not found any effect of virus persistence on the nature of the chronic inflammatory process. At the same time, pathogenic role of EBV in GM with its chronic inflammation in children was established. It is manifested with a sharp increase in the number of EBV-positive patients with the progression of the process: from 11.1% with its absence up to 66.7% in case of severe inflammation ($p < 0.01$). *Helicobacter pylori* (Hp) in the EBV-positive patients was detected in 78% of cases, while in the EBV-negative group it was only 55% ($p < 0.01$). Alternatively, in the presence of Hp Epstein-Barr virus was detected in 52% of children and only in 27% when there was no Hp ($p < 0.005$). Thus, these infections are conjugated. It was established that the presence of a mixed infection (Hp + EBV) in comparison with Hp-associated variant of CG without concomitant EBV persistence is accompanied by generalizing of inflammation in GM up to pangastritis (52%). EBV contributed to the process enhancement both in the fundus and in the antrum, which was reflected by the change in the macroscopic picture. In the majority of cases (76%) the process was hyperplastic, whereas without EBV persistence a superficial inflammation predominated (55%). According to the data of morphological examination, signs of GM atrophy, mainly in the antrum, were significantly more often detected in this group of patients; in 16% of cases GM atrophy was moderate. Severe inflammation was manifested as a quite frequent detection of focal hyperplasia, microerosions and lymphoid follicles in GM. The persistence of EBV was almost double as often associated with colonization of GM with highly pathogenic strains of Hp (35.9% vs. 20.2%, $p < 0.05$)
Conclusion: In children with chronic gastritis high rates of persistence of human herpesvirus type 6 have been found, which had no effect on inflammation in the gastric mucosa. Almost half of the patients revealed the presence of Epstein-Barr virus. The combination of Hp and EBV contributes to the formation of severe and generalized inflammation. In a significant part of patients it was associated with the colonization of the gastric mucosa with highly pathogenic strains of Hp.
Disclosure of Interest: None declared

OP041 PREVALENCE OF, AND RISK FACTORS FOR, ATROPHIC GASTRITIS WITH OR WITHOUT INTESTINAL METAPLASIA IN THE ITALIAN GENERAL POPULATION: AN HISTOPATHOLOGICAL STUDY

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Introduction: Epidemiology of atrophic gastritis and intestinal metaplasia in the general population is still unclear.
Aims & Methods: We aimed to evaluate the prevalence of, and the risk factors for, atrophic gastritis with or without intestinal metaplasia in a representative sample of the Italian general population. A total of 1533 inhabitants of two villages were invited to undergo gastroscopy with multiple gastric biopsies and ^{13}C-urea breath test. Gastric biopsy specimens were available in 1003 subjects. Biopsy specimens were classified and graded using the visual analogue scales according to the Updated Sydney System. Data on demographic and lifestyle characteristics were also collected for each subject. Potential risk factors were evaluated using a multivariable logistic regression analysis.
Results: Of the 1003 subjects, 323 (32.2%) had atrophic gastritis: 247 (24.6% of the study sample) had atrophic gastritis with intestinal metaplasia and 76 (7.6% of the study sample) without intestinal metaplasia. Of the 323 subjects, 252 (78%) had antrum-restricted atrophic gastritis and 11 (3.4%) corpus-restricted atrophic gastritis, whereas 60 (18.6%) had atrophic gastritis in both the antrum and corpus. The prevalence of antrum-restricted, corpus-restricted and both antrum and corpus atrophic gastritis in the study sample was 25.1%, 1.1% and 6%, respectively. Atrophic gastritis was classified as mild in 212 subjects (21.1% of the study sample), moderate in 61 subjects (6.1% of the study sample) and severe in 50 subjects (5% of the study sample). Moderate-severe atrophic gastritis was significantly more frequent in subjects with both antrum and corpus atrophic gastritis (Odds Ratio (OR): 4.67, 95% confidence interval (CI), 2.58-8.47). *H. pylori* infection, age over 51 years, cigarette smoking and positive first degree family history of gastric cancer were independently associated with presence of atrophic gastritis. A negative association was found between obesity and atrophic gastritis.
Conclusion: Atrophic gastritis with or without intestinal metaplasia seems to be present in about one third of the Italian general population. Most subjects have antrum-restricted atrophic gastritis, whereas only 1% of the general population has a corpus-restricted atrophic gastritis. Subjects with both antrum and corpus atrophic gastritis are more likely to carry a more severe atrophy. *H. pylori*, age > 51 years, smoking and a positive family history of gastric cancer are positively and independently associated with atrophic gastritis, while obesity seems to be negatively associated.
Disclosure of Interest: None declared

OP042 PEPSINOGEN AND INCIDENT CHRONIC ATROPHIC GASTRITIS AND INTESTINAL METAPLASIA: A LONGITUDINAL STUDY

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Introduction: Pepsinogen (PG) I and II are the two main precursors of pepsin, and are both produced by chief cells and mucous neck cells of the stomach.[1, 2] PG II is also produced by pyloric gland cells. When atrophic mucosal change develops, the chief cells are replaced by pyloric glands, leading to a decrease in PGI. However, PG II decreases in very small amount.[2] Thus, low serum PG I level and low PG I/II ratio are well known to be serological markers of gastric atrophy.
Aims & Methods: This study was performed to investigate association between serum pepsinogen (PG) level and incidence of chronic atrophic gastritis (CAG) and intestinal metaplasia (IM).
This is a retrospective cohort study. Our data were composed of 3,927 participants (over 30 years of age) who underwent upper endoscopy and serum PG test between March 2008 and December 2009 whose baseline endoscopy showed no evidence of CAG and IM. Of these, 2,166 participants underwent follow-up endoscopy after at least 1 year. Thus, the final study subjects consisted of 2,166 adults with follow-up data. Structured questionnaires were reviewed about purported risk factors for CAG and IM such as family history of gastric cancer, current smoking, and alcohol consumption. Serum PG I and PG II were measured by a latex-enhanced turbidimetric Immunoassay. Serum anti-*Helicobacter pylori* (*H. pylori*) IgG was detected by enzyme-linked immunosorbent assay. Follow-up endoscopy was performed either at 1-year or 2-year intervals by taking into account factors such as age, family history of gastric cancer, and patients' preference. CAG and IM were diagnosed endoscopically by experienced board-certified endoscopists.
Results: Median follow-up in the 2,166 participants was 1490.5 days (interquartile range, 772.8-1898.0). There were a total of 783 patients with CAG and 166 patients with IM during the follow-up. Subjects with a PG I/II ratio of ≤3.0 showed higher incidence of CAG and IM compared with those with a PG I/II ratio of >3.0 by using log-rank test ($p < 0.001$, both for CAG and IM). The results of Cox's regression analysis confirmed that the PG I/II ratio was significantly inversely associated with incident CAG (HR, 0.86; 95% CI, 0.82-0.90; $p < 0.001$) after full adjustment for risk factors. The PG I/II ratio was also significantly inversely associated with incident IM (HR, 0.76; 95% CI, 0.68-0.85; $p < 0.001$). To test diagnostic performance of the PG I/II ratio for incident CAG, we performed a receiver-operating curve analysis. The cutoff value that is farthest from the line of equality was PG ratio of 4.6, with modest sensitivity (54.5%; 95% CI, 51.0% > 58.1%) and specificity (66.1%; 95% CI, 63.5% > 68.6%).
Conclusion: The PG I/II ratio was found to be significantly inversely associated with development of CAG and IM in asymptomatic population without CAG and/or IM at baseline.
Disclosure of Interest: None declared

MONDAY, OCTOBER 26, 2015 11:00-12:30
BIOLOGY OF COLORECTAL CANCER - ROOM B3

OP043 DIAGNOSTIC COLORECTAL ADENOMA-CARCINOMA RELATED MIRNA SIGNATURES IN MATCHED TISSUE PLASMA SPECIMENS

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Introduction: Several microRNA has been found to play critical role in colorectal carcinoma developement. Recently, miRNA-specific high-throughput arrays became available to detect expression alterations of the whole miRnome in colorectal cancer (CRC). While miRNA expression markers are well characterized in CRC, less is known about miRNA expression profiles in colorectal adenoma.
Aims & Methods: The purpose of this study was to identify miRNA expression patterns through colorectal adenoma dysplasia sequence.Furthermore, our aim was to analyze the expression level of miRNA in matched plasma samples focusing on biomarker candidates.
Sixty fresh frozen colorectal biopsy tissue (normal [**N**] n = 20; tubular adenoma [$\mathbf{AD_T}$] n = 11; tubulovillous adenoma [$\mathbf{AD_{TV}}$] n = 9; colorectal cancer [**CRC**] n = 20) and 16 matched plasma samples (n = 4 N, n = 4 AD_T, n = 4 AD_{TV}, n = 4 CRC) were collected and total RNA including miRNA was isolated. MiRNA microarray experiments were conducted by GeneChip® miRNA 3.0

Array (Affymetrix). Then, a series of pools of RNA from the same groups of tissue samples was made to validate the data of microarray by RT-qPCR (microRNA Ready-to-use PCR Human Panel I + II V2.R; Exiqon). Plasma samples from the same patients set was selected to confirm the microarray results on the same array, RT-qPCR platform. Data were analyzed using Expression Console (Affymetrix).

Results: Out of the 1733, the detectable miRNAs, which could be found in each group was N = 442, AD = 460, CRC = 441 in tissue and N = 306, AD = 334, CRC = 321 in plasma. Interestingly, 12 miRNA were upregulated (e.g. miR-31 logFC = 3, $p < 0.001$) and 11 miRNA were downregulated only (e.g. miR-10b, logFC = -1.7 $p < 0.001$) in neoplastic lesions (AD + CRC) compared to N tissue samples. 11 miRNA showed altered expression between AD_T and AD_{TV} (e.g. miR-183 LogFC = 1.5 $p < 0.007$). Expression levels of 9 miRNA were found to be changed between $AD_{T,TV}$ and CRC groups based on tissue biopsy microarray data (e.g. miR-196a logFC = -1.8 $p < 0.001$). Three miRNA(-31;-4506;-452*) have been found to be differentially expressed in adenoma compared to normal in both matched tissue plasma samples analyzed by microarray. Significant positive overexpression was observed in tissue (logFC = 5 $p = 0.003$) and in plasma (logFC = 0.3 $p = 0.02$) in case of miR-31 in adenoma. Moreover, increased expressions were detected in CRC compared to healthy controls in tissue and plasma levels of miR-187;-675;-3591-3p ($p < 0.05$). MiRNA expression data could be confirmed by RT-PCR in both plasma and tissue samples.

Conclusion: 23 miRNA showed characteristic expression changes in CRC development in biopsy tissue. Our observations suggest that miRNA are also present in plasma fraction and positively correlate with matched tissue expression levels. The identified miRNA expression changes could be verified by other more simple RT-PCR methods eventually for routine application.

Disclosure of Interest: None declared

OP044 ORIGIN AND ALTERED SECRETION OF ALIX POSITIVE EXOSOMES IN COLORECTAL ADENOMA-CARCINOMA SEQUENCE

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Introduction: During carcinoma formation the exosomes as intercellular regulators play important role in convey of complex signals between epithelial/carcinoma cells and their abnormal microenvironment including α-SMA+ blast-like cells.

Aims & Methods: Our aim was to examine the alteration in exosome-based communication during colorectal adenoma-carcinoma sequence (ACS) by the determination the changes of epithelial/epithelial-origin carcinoma and stromal ALIX exosome marker expression in protein level. Our study was performed on healthy (n = 30), adenomas with low-grade (n = 15) and high-grade (n = 30) dysplasia as well as non-invasive (n = 12; Dukes A and B) and invasive (n = 26; Dukes C and D) colorectal carcinoma (CRC) samples. Immunohistochemistry was performed for ALIX exosome, cytokeratin epithelial, podoplanin (PDPN) lymphatic vessel, Ki-67 proliferative, α-SMA myofibroblast and Musashi-1 (MSI1) stem cell markers. We determined the intensity of ALIX expression with Q-score method and the percentage of cells with granular ALIX expression (PCGE) by counting 800-1300 cells both in epithelial and stromal cells in 5 representative core/ sample groups with Pannoramic Viewer digital microscope.

Results: We found strong/moderate diffuse cytoplasmic ALIX expression in normal epithelium which significantly ($p < 0.05$) decreased both in adenoma and CRC samples. In parallel with decreased ALIX intensity, we found altered expression pattern (i.e. diffuse to granular cytoplasmic) with significantly increased ($p < 0.05$) frequency of PCGEs both in epithelial/CRC and stromal compartment (including α-SMA+ blast-like cells) in all examined pre-neoplastic and neoplastic lesions. The granular ALIX expression was not limited to the Ki-67+ proliferative and MSI1+ stem/cancer stem cells, but it could be observed in budding, cytokeratin+ stromal cells, as well as in the lumen of lymphatic vessels in invasive CRCs.

Conclusion: The heterogenic ALIX expression pattern in pre-neoplastic lesions suggests that the abnormal exosome transport may play important role in adenoma to carcinoma transformation. Furthermore, the appearing of ALIX expression in budding tumor cells in the stroma and in the lumen of lymphatic vessels may help in the development of pre-metastatic microenvironments of invasive CRC patients.

Disclosure of Interest: None declared

OP045 PREVALENCE OF APC/MYH GERMLINE MUTATIONS DETECTED IN A POPULATION BASED COLORECTAL CANCER SCREENING PROGRAMME IN SPAIN

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Introduction: Adenomatous polyposis syndromes such as familial adenomatous polyposis (FAP) / MUTYH-associated polyposis (MAP)/ attenuated polyposis (AFAP) are inherited genetic conditions, being FAP and MAP in an autosomal-dominant manner and AFAP in an autosomal-recessive pattern. Such genetic conditions have an increased predisposition to multiple colorectal adenomatous polyps, and hence to colorectal cancer. Germline mutations in the base excision repair gene MUTYH have been associated with a recessively inherited form of the disease. Population-based CRC screening programmes with FOBT have demonstrated polypectomy during colonoscopy reduces incidence and mortality by CRC. Such screening programmes not only detect adenomatous lesions through colonoscopy but also may reduce mortality from CRC in patients with such hereditary related colorrectal polyposis. CRC is the most frequent cancer in Spain with 28.551 new cases in 2008 according to Globocan. In Murcia, a population-based CRC screening programme was initiated in 2006, since 2008 such programme was extended to our Hospital.

Aims & Methods: To evaluate the proportion of APC/MUTYH gene mutation in individuals included in the CRC screening programme, where colonoscopy performed after positive FOBT, detects 10 or more adenomatous polyps.

Since January 2010 to December 2014 participants between 50 and 69 years with no personal history of CRC, IBD, FAP or HNPCC, have been included in the CRC screening program. All participants with a positive FOBT, who underwent colonoscopy and had more than 10 adenomas resected were included in this study. After histopathology confirmed the presence of adenomatous polyps, patients were referred to Genetic counseling. Informed consent was obtained from each participant to investigate the presence of APC and MYH germline mutation. In serum DNA all exons and nearby regions to those genes were analysed through genome sequencing.

Results: A total of 32,034 participants underwent CRC screening with immunochemical FOBT (FIT). Of those, 4,388 had positive FIT and 3,909 participants had colonoscopy done. Amongh those who underwent colonoscopy 107 patients (2.7%) with ≥ 10 adenomas were identified, of them 9 had APC mutation, 4 of which corresponded to a variant of uncertain significance (VUS), 1 had a double mutation in MUTYH gene and 2 had one MUTYH mutation. The same APC germinal pathogenic mutation was identified in four of the 5 remaining APC mutation carrier patients, none of them related with each other. Such germline mutation was previously identified in Murcia in other no related families all of which showed a very atenuated polyposis syndrome.

Conclusion: Prevalence of a germinal mutation in APC or MUTYH gene in asymptomatic participants of a population based CRC screening program with ≥10 adenomas resected is 11.2%. It is important to diagnose such genetic condition since interval for surveillance colonoscopy is different from average risk participants of a CRC screening program.

Disclosure of Interest: None declared

OP046 LATERALLY SPREADING TUMORS ARE A RISK FACTOR FOR SYNCHRONOUS NEOPLASMS

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Introduction: Lateral spreading tumors (LST) are challenging to recognize and resect endoscopically. A subset may progress more rapidly to cancer, indicating such lesions contribute to the occurrence of postcolonoscopy colorectal cancers. A comprehensive characterization of the clinical phenotype associated with presence of LSTs is presently lacking. In this large population-based study, we explored the incidence, clinical features and risk profile of patients with LSTs.

Aims & Methods: We have previously trained the endoscopists (faculty and trainees) at our institution in recognition of flat, depressed neoplasms, and serrated polyps. We reviewed prospectively collected clinical, endoscopic and histopathology data from all patients who underwent an elective colonoscopy at our hospital from Feb 2008 to Feb 2012. Furthermore, we asked all participants to fill in a questionnaire regarding risk profiles (i.e. smoking, alcohol intake, BMI, and aspirin use). We defined a LST as a flat appearing neoplasm > 10 mm in size. We excluded patients with hereditary CRC syndromes, inflammatory bowel disease or a history of colon resection.

Results: In total, 8033 patients undergoing colonoscopy for symptoms (84.6%), screening (6.7%) or surveillance (8.7%) were included. Of them 61.8% filled in the questionnaire. Overall, 180 patients with 224 LSTs and 2746 patients with any neoplasm (without LSTs) were identified. Of the 224 LSTs, 78.1% were proximally located. Patients with LSTs were significantly older than those with any lesion (66.5 vs 63.9 yrs, $p = 0.005$), and were more likely under surveillance at time of inclusion (21.1% vs 14.4%, age and gender adjusted OR: 1.6, 95% CI 1.1-2.3). Logistic regression analysis, adjusted for age and gender, showed that patients with LSTs had significantly more often adenomas, advanced adenomas and sessile serrated adenomas/polyps (SSA/Ps), and also greater numbers of synchronous neoplasms than patients with any neoplasm (without LSTs) (**Table**). Gender, smoking, alcohol intake, BMI and aspirin use did not differ significantly between groups.

Of the 224 LSTs, 160 were of nongranular, 54 granular and 10 of unknown subtype. Histopathologic examination showed 34 hyperplastic polyps, 32 SSA/Ps, 140 adenomas, and 18 CRCs (8 TNM-stage I, 10 stage II-IV). Compared with polypoid neoplasms larger than 10 mm (n = 964), LSTs contained less often villous histology (28.6 vs 41.8%, $p < 0.001$) and more often serrated histology (14.2 vs 4.0%, $p < 0.001$).

Conclusion: Patients with LSTs have often synchronous advanced adenomas and sessile serrated adenomas/polyps. A second look clearing colonoscopy in patients with LST may safeguard the effectiveness of cancer prevention.

Disclosure of Interest: R. Bogie: None declared, C. le Clercq: None declared, M. Bouwens: None declared, B. Winkens: None declared, R. de Ridder: None declared, A. Masclee: None declared, S. Sanduleanu Consultancy: Pentax Medical Systems

Abstract number: OP046 Table: Clinical features of LSTs vs any neoplasm patients

Clinical features	Patients with ≥ 1 LST n = 180	Patients with any lesion (no LSTs) n = 2746	Unadjusted p-value	Adjusted OR (95% CI) **
Surveillance indication, n (%)	38 (21.1)	394 (14.4)	*<0.001*	*1.6 (1.1-2.3)*
Mean number of colonoscopies (SD)	1.9 (1.1)	1.2 (0.5)	*<0.001*	*3.1 (2.6-3.7)*
≥ 1 adenoma, n (%)	148 (82.2)	2055 (74.8)	*0.026*	*1.5 (1.0-2.2)*
≥ 1 advanced adenoma*, n (%)	88 (48.9)	723 (26.3)	*<0.001*	*2.6 (1.9-3.5)*
≥ 1 serrated polyp, n (%)	22 (12.2)	83 (3.0)	*<0.001*	*4.9 (2.9-8.0)*
≥ 1 sessile serrated adenoma, n (%)	17 (9.4)	66 (2.4)	*<0.001*	*4.1 (2.3-7.1)*

* Advanced adenoma: size excluded ** Adjusted for age and gender

OP047 COLORECTAL LARGE POLYPS MANAGEMENT: THE ROLE OF VEGF AS POSSIBLE MARKER OF MALIGNANCY

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Introduction: Endoscopical screening programs for colorectal cancer (CRC) have reduced the mortality rates by finding lesions at initial stages or by directly treating precancerous lesions. However, adenomatous polyps may not always be removable endoscopically and colonic resection may be still necessary. Nowadays, in these cases radical colonic resection with a full oncological lymphoadenectomy is still indicated due to the possible understimation of the invasiveness of large adenoma with focal bipsies negative for cancer. Vascular endothelial growth factor (VEGF) is a sub-family of growth factors that are signaling proteins involved in both vasculogenesis and angiogenesis.
Aims & Methods: The aim of the study was to evaluate the accuracy of VEGF expression as a marker of malignancy in colorectal adenoma.
We prospectively enrolled 92 healthy subjects and patients with colonic adenoma or adenocarcinoma who underwent screening colonoscopy or surgical colorectal resection. Real time RT-PCR for VEGF-A mRNA expression and immunohistochemistry for VEGF-A were performed. Immunoassay for VEGF-A, VEGF-C, VEGFR-1, VEGFR-2 and VEGFR-3 were also performed. Non parametric statistics, ROC curves analysis and logistic multiple regression analysis were used.
Results: VEGF-A mRNA expression was higher in patients with high-grade dysplasia or adenocarcinoma than in those with adenomas with low-grade dysplasia ($p = 0.01$). At IHC, VEGF-A expression was significantly higher in patients with adenocarcinoma than in those with adenomas ($p < 0.001$) and the accuracy of VEGF-A expression for prediction of the progression form adenoma to adenocarcinoma was 91.7 (95%CI = 78.7-97.9). VEGF-C protein expression was lower in CRC patients than in patients with simple adenomas ($p = 0.02$). VEGF-A levels were directly correlated to polyp size (rho = 0.73, $p = 0.0062$). Multivariate analysis demonstrated that malignancy and polyp size were independent predictors of VEGF-A mucosal levels.
Conclusion: This study demonstrated that VEGF-A levels can be a marker of malignancy of colorectal polypoid lesions with a high accuracy. The analysis of confounders showed that only the transformation from benign to malignant lesions and the dimensions of the lesion can influence VEGF-A levels.
Disclosure of Interest: None declared

OP048 MODULATION OF DNA MISMATCH REPAIR SYSTEM BY COLIBACTIN-PRODUCING ESCHERICHIA COLI IN SPORADIC COLORECTAL CANCER

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Introduction: Inactivation of DNA Mismatch Repair (MMR) genes as MLH1 is observed in 15% of sporadic colorectal cancer (CRC) exhibiting microsatellite instability phenotype (MSI). Colonic mucosa-associated *Escherichia coli (E. coli)* are more frequently identified in CRC patients. Some pathogenic *E. coli* strains acquired virulence factors, including colibactin toxin encoded by *pks* island, which interfere with eukaryotic cell cycle and induce DNA double-strand breaks, leading to genomic instability. Colibactin-producing *E. coli* are more frequently detected on gut of CRC patients. We evaluate, in CRC patients, colonic mucosa-associated and -internalized *E. coli* levels in relation to tumoral microsatellite stability status. Impact of colibactin-producing CRC-*E. coli* infection on MMR protein expression was then investigated.
Aims & Methods: MSI status was assessed by immunohistochemical staining of MMR nuclear proteins and by multiplex PCR in tumor sections from 90 CRC patients, and correlated to corresponding level of mucosal associated and internalized *E. coli*. Effect of infection by colibactin-producing *E. coli* strains on MLH1 expression in T-84 cells was studied by western blot analysis. Adhesion, internalization and persistence assays for colibactin-producing *E. coli* strains were performed in T-84 (MMR system-competent) and HCT-116 (MMR system-deficient) cells.
Results: MSI tumor phenotype was noted in 14.4% patients. There was significant increase in mucosa-associated ($p = 0.025$) and -internalized *E. coli* ($p = 0.028$) levels in patients with MSI tumor phenotype. We noted significant increase in normal mucosa-associated ($p = 0.018$) and internalized *E. coli* ($p = 0.031$) levels in patients with MLH1-negative tumors, suggesting *in vivo* interaction between *E. coli* and DNA MMR system in CRC. *In vitro*, higher proportion of *E. coli* was able to invade ($p = 0.009$) and persist ($p = 0.007$) in MMR-deficient cells, suggesting that gut *E. coli* colonization was favored in MMR-deficient patients. Immunoblots revealed marked reduction in MLH1 protein expression 3 hours after infection, compared to uninfected cells and cells infected with non-pathogenic K12-C600 *E. coli* strain. MLH1 inhibition was dependent on presence of *pks* island in CRC strains. Colibactin-producing *E.coli* isolated from CRC patients could thus inhibit a DNA repair system to induce genomic instability and to favor CRC.
Conclusion: Involvement of colibactin-producing *E. coli* in CRC is now well supported. We report the first clinical evidence of interaction between colibactin-producing *E. coli* and MMR deficiency.
Disclosure of Interest: None declared

MONDAY, OCTOBER 26, 2015 14:00–15:30
MANAGEMENT OF IBD AFTER ANTI-TNF FAILURE – ROOM B2

OP049 THE FRENCH REAL-LIFE EXPERIENCE OF VEDOLIZUMAB EFFICACY AND SAFETY IN CROHN'S DISEASE: A PROSPECTIVE OBSERVATIONAL MULTICENTER COHORT STUDY

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Introduction: Vedolizumab (VDZ) is a humanized monoclonal antibody that specifically antagonizes $\alpha 4\beta 7$ integrin by inhibiting its binding to the gut-specific intestinal mucosal address in MAdCAM1. Efficacy and safety of VDZ in Crohn's disease (CD) has been evaluated in two large phase 3 randomized controlled trials (GEMINI II and III), leading to the approval of the drug by both EMA and FDA. Herein, we assessed safety and efficacy of VDZ in a large real-life experience cohort of patients with CD.
Aims & Methods: All consecutive active CD patients treated with VDZ in France from Jun to Dec 2014 were assessed. From Jun to Sep, VDZ was available through a centralized pre-approval program piloted by the French regulatory agency (ANSM). After its approval by ANSM (reimbursement of the drug by social services is still pending), recruitment was extended until Dec 2014. Patients received VDZ at a dose of 300 mg at weeks 0, 2 and 6 as induction therapy and then every 8 weeks. Patients who did not respond to VDZ induction therapy at week 6 could receive VDZ 300 mg every 4 weeks. Patients were evaluated prospectively at W14. Remission was defined as a Harvey-Bradshaw index ≤ 4. Response was defined as a reduction in the Harvey-Bradshaw index of at least 3 points. C-reactive protein as well as safety were ascertained.
Results: One hundred and seventy patients (61 males, median age: 36.3 IQR [29.2-47.0] yrs) were included in 31 centres. Median disease duration was 10.7 [6.5-16.5] yrs; 165 (97%) patients have been previously treated with immunosuppressant, 168 (99%) with at least one anti-TNF and 83 (48.8%) underwent prior intestinal resection. VDZ was given for luminal disease in 91 (53.5M) patients and for luminal and perianal disease in 79 (46.5%). At baseline, mean Harvey-Bradshaw index was 10.3 ± 4.2 and mean CRP level was 30.5 ± 30.0 mg/L. At week 14, Response and remission rates were 59% and 38%, respectively; the steroid-free response and remission rates were 47% and 32%, respectively. The mean decrease of Harvey-Bradshaw index was 3.1 ± 4.9

($p < 0.001$). The mean CRP level decrease was 0.3 ± 40.1 ($p = 0.77$). Adverse events were reported in 34 (20%) patients and consisted in opportunistic infection (n = 18) including nasopharyngitis (n = 4), upper respiratory tract infection (n = 4), gastrointestinal infection (n = 4), intraabdominal abscess (n = 2), catheter-related bloodstream infection (n = 2), urinary tract infection (n = 1), herpes zoster ophthalmicus (n = 1), cutaneous reaction (n = 6), paresthesia (n = 6), infusion reaction (n = 1), headache (n = 2) and rectal adenocarcinoma (n = 1).
Conclusion: In this first real-life experience cohort of patients with refractory CD, VDZ induced clinical response in more than 50% of cases, with an acceptable safety profile.
Disclosure of Interest: None declared

OP050 RESPONDERS TO HAEMOPOIETIC STEM CELL TRANSPLANTATION FOR CROHN'S DISEASE

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Introduction: We recently reported that about one third of patients with Crohn's disease experience prolonged regression of ileocolonic disease following haemopoietic stem cell transplantation (HSCT). Here we compare the characteristics of responders and non-responders.
Aims & Methods: Patients with impaired quality-of-life from active Crohn's disease not amenable to surgery despite treatment with at least 3 immunosuppressive agents all underwent stem cell mobilisation before randomisation to immuno-ablation followed by unselected cyclophosphamide-based conditioning and HSCT after one month (Early HRCT) or one-year (Delayed HS CT). Patients in whom all endoscopic evidence of Crohn's disease disappeared (SES-CD score of zero) were classified as Responders. Supporting histology was available in 17 of them.
Results: Forty four patients with ileocolonic involvement underwent mobilisation before randomisation to Early or Delayed HSCT. Of 38 patients that could be classified 14 were Responders. Ten had SES-CD of zero after 1 year, (maintained in the second in 3 of 4 with available data) and 4 achieved responder status in year 2. Four of 6 followed to 4 years remain free of Crohn's disease vs 1 of 15 non-responders. Responders were significantly more likely to have histologically normal segments post HSCT

(Table)

% with normal histology	Site	Responder	Non Responder	p
Pre HSCT	Ileum	44%	40%	1.00
	Colon	59%	37%	0.045
Post HSCT	Ileum	91%	50%	0.069
	Colon	83%	52%	0.004

A Responder status tended to be more likely with no family history (39% vs 20%), in non-smokers (54% vs 30%), with early-onset of disease (Montreal A1, 46% vs 32%)) and with more than 10-year history (46% vs 17%); those with pure colonic involvement (L2) were less likely to respond than those with ileal involvement (L1, L3, 14% vs 43%) but these fell short of statistical significance on univariate analysis.
Conclusion: A group of patients can be identified who have a substantial and long lasting regression of Crohn's disease following HSCT. Endoscopic response following HSCT is associated with regression of histological evidence of Crohn's disease.
Disclosure of Interest: None declared

OP051 FAECAL DIVERSION FOR MANAGEMENT OF PERIANAL CROHN'S DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: Temporary faecal diversion (FD) is sometimes used for management of refractory perianal Crohn's disease (CD) with variable success. Diversion of faecal stream from the severely inflamed segments has long been known to decrease CD-related inflammation.
Aims & Methods: We performed a systematic review with meta-analysis to evaluate effectiveness, long-term outcomes, and factors associated with success with temporary FD for refractory perianal CD.
The title and abstract of studies identified in the search were reviewed by two authors independently (SS, ND). From a systematic literature review using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines until February 2015, we identified 14 cohort studies (472 patients) reporting outcomes after temporary FD. We estimated pooled rates (with 95% confidence interval [CI]) of early clinical response, attempted and successful restoration of bowel continuity after temporary FD (without symptomatic relapse), and rates of re-diversion (in patients with attempted restoration) and proctectomy (with or without colectomy and end-ileostomy). We identified factors associated with successful restoration of bowel continuity.
Results: From a total of 671 unique studies identified using our search strategy, we identified 14 studies as meeting all inclusion criteria. On meta-analysis, 68.5% (95% CI, 60.1-75.9) patients had early clinical response after FD for refractory perianal CD. Restoration of bowel continuity was attempted in 34.4% (95% CI, 26.4-43.3) of patients, and was successful in only 15.0% (95% CI, 10.1-21.9). Most attempts at restoration of bowel continuity were made on average between 1-1.5 years after FD. Of those in whom restoration was attempted, 31.5% (95% CI, 16.8-51.1) required re-diversion because of severe relapse. Overall, 44.7% (95% CI, 36.4-53.4) patients required proctectomy after failure of temporary FD. On multivariate analysis, Gu et al [1] observed that rectal involvement was associated with 7.5 fold higher risk of failure to achieve restoration of bowel continuity. Similarly, on univariate analysis, in two studies, Harper et al [2] and Regimbeau et al [3] observed that restoration of bowel continuity was possible in 85.8-87.5% of patients without rectal involvement, compared with 11.1-53.3% patients with rectal involvement.
There was no difference in successful restoration of bowel continuity after temporary FD in pre-biologic or biologic era (13.7% vs. 8.6%, $p = 0.51$), in part due to selection bias.
Conclusion: Temporary FD may be used for amelioration of severe perianal CD refractory to medical therapy, with good early clinical response in over 2/3rd of patients. However, bowel restoration is successful in only 15% patients. While factors associated with successful restoration of bowel continuity after temporary FD are poorly understood, healing of rectal disease should be a minimum prerequisite before restoration of bowel continuity.

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Disclosure of Interest: None declared

OP052 EFFICACY OF VEDOLIZUMAB WITH AND WITHOUT CONTINUED IMMUNOSUPPRESSANT USE IN GEMINI 1 AND GEMINI 2

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Introduction: In GEMINI 1 and GEMINI 2, vedolizumab (VDZ) was safe and effective in patients (pts) with ulcerative colitis (UC) or Crohn's disease (CD), respectively, on stable doses of immunosuppressants (IS).[1,2] The effect of discontinuing IS in pts who responded to VDZ induction therapy in these studies has not been characterised.
Aims & Methods: Pts who responded to VDZ at week (wk) 6 were re-randomised to placebo (VDZ/PBO) or VDZ every 4 or 8 wks (VDZ/VDZ Q4W or Q8W) for 46 wks. At United States (US) sites, re-randomised pts discontinued IS use at wk 6. At non-US sites, pts could continue IS use. Efficacy, VDZ serum concentration, and immunogenicity (via an enzyme-linked immunosorbent assay) data were evaluated post hoc in pts with baseline IS use stratified by region.
Results: At wk 52, rates of clinical remission and response (**Table**), mucosal healing (UC), durable clinical remission, and corticosteroid-free remission were higher with VDZ, mostly irrespective of IS use. Mean trough concentrations were similar between US and non-US pts at wk 46 (**Table**). Higher percentages of US VDZ/PBO pts were positive for anti-VDZ antibodies compared with non-US pts
Conclusion: Discontinuing IS did not appear to substantially affect efficacy of VDZ maintenance therapy. Interpretation of these post hoc analyses is limited by potential IS discontinuation in non-US pts and the relatively small sample sizes.

Reference

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Abstract number: OP052 (Table). Table: Maintenance VDZ With and Without Continued IS Use

	UC		CD	
	US (Discontinued IS)	Non-US (Continued IS)	US (Discontinued IS)	Non-US (Continued IS)
	VDZ/PBO n = 10; VDZ/VDZ n = 18	VDZ/PBO n = 41; VDZ/VDZ n = 70	VDZ/PBO n = 5; VDZ/VDZ n = 9	VDZ/PBO n = 44; VDZ/VDZ n = 94
Efficacy endpoints	**% Difference from PBO (95% CI) at wk 52**			
Clinical remission[a]	28.9 (-10.5, 63.3)	25.2 (8.0, 42.4)	4.4 (-49.6, 54.7)	17.3 (0.4, 34.1)
Clinical response[b]	18.9 (-20.8, 54.7)	35.0 (17.1, 52.9)	15.6 (-39.9, 63.8)	17.7 (0.2, 35.3)
Immunogenicity	**No. of pts with ≥1 positive sample**			
VDZ/PBO	3	1	1	4
VDZ/VDZ	1	2	0	0
VDZ Concentration	**Mean trough concentration, μg/ml at wk 46**			
VDZ/VDZ Q8W	13.0 (n = 2)	10.7 (n = 27)	9.4 (n = 2)	11.8 (n = 27)
VDZ/VDZ Q4W	39.0 (n = 6)	44.1 (n = 26)	38.8 (n = 3)	31.7 (n = 28)

[a] UC: complete Mayo score of ≤2 and no individual subscore >1. CD: CD Activity Index (CDAI) score ≤150.[b] UC: durable clinical response is a reduction in complete Mayo score of ≥3 and ≥30% from wk 0 with a decrease in rectal bleeding subscore (RBS) of ≥1 or absolute RBS of ≤1 at wks 6 and 52. CD: enhanced clinical response is a ≥100-point reduction in CDAI score from wk 0.

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OP053 VEDOLIZUMAB FOR INFLAMMATORY BOWEL DISEASE IN CLINICAL PRACTICE – EXPERIENCE FROM A PROSPECTIVE GERMAN REGISTRY

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Introduction: Vedolizumab (VDZ), targeting $\alpha4\beta7$ integrin became available for prescription in Germany in July 2014. Here we report its efficacy and safety in a real world setting.

Aims & Methods: 17 private and 9 academic centers included 318 patients (ulcerative colitis (UC) n = 165), Crohn's disease (CD) (n = 174), median age 40 years, disease duration 106 months, male n = 153). Patients received 300 mg i.v. VDZ induction at 0, 2, 6 and maintenance q8 weeks and were followed for 14 weeks. In UC, disease activity was scored using clinical parameters of the Mayo index, and in CD by Harvey Bradshaw Index (HBI) at weeks 0, 6 and 14, respectively. Where available, endocopy (UCCIS, SES-CD), lab and QoL data were collected.

Results: Most had extensive mucosal involvement in UC (50% pancolitis) and CD (60% ileocolonic) and were exposed to multiple anti-TNFs. 22% had prior surgery for IBD and 26% were hospitalized within the previous 12 months. At baseline, patients had moderately active disease with significant clinical improvement at weeks 6 and 14. Clinical or endoscopic remission were rare events at week 14. QoL improved only on the EQ5D derived VAS, but not IBDQ.

UC	N*	Week 0	N*	Week 6	N*	Week 14
CRP	134	0.49 ± 1.15	66	0.52 ± 1.07	59	0.36 ± 0.88
Calprotectin	74	1512.5 ± 1665	32	893.5 ± 1415	32	273.4 ± 622
IBDQ	46	135 ± 49	8	159.5 ± 58	25	159 ± 36
EQ5D VAS	40	30 ± 10	29	70 ± 25	29	80 ± 21
Part. Mayo	158	7 ± 3	84	5 ± 3	66	3.5 ± 4
UCCIS	77	63.6 ± 39.5	9	38.1 ± 53.2	24	13.3 ± 15.2
CD						
CRP	149	0.9 ± 2.3	74	1.05 ± 2.46	60	0.63 ± 3.05
Calprotectin	81	800 ± 1775	39	860 ± 1801	28	362.3 ± 1037
IBDQ	43	131 ± 53	20	131 ± 61	27	123 ± 46
EQ5D VAS	40	30 ± 18	48	60 ± 20	40	65 ± 24
HBI	160	10 ± 6	89	7 ± 6	66	7 ± 4
SES-CD	70	12 ± 7	4	11.5 ± 7	19	9 ± 7

* complete records entered as of April 1, 2015.

Conclusion: Clinical response preceded laboratory improvement. Endoscopic data can't be fully interpreted yet due to ongoing recruitment and analysis. Full data set to be presented at UEG.

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OP054 THE FRENCH REAL-LIFE EXPERIENCE OF VEDOLIZUMAB EFFICACY AND SAFETY IN ULCERATIVE COLITIS: A PROSPECTIVE OBSERVATIONAL MULTICENTER COHORT STUDY

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Introduction: Vedolizumab (VDZ) is a humanized monoclonal antibody that specifically antagonizes $\alpha 4\beta 7$ integrin, by inhibiting its binding to the gut-specific intestinal mucosal address in MAdCAM1. Efficacy and safety of VDZ in ulcerative colitis (UC) has been evaluated in a large phase 3 randomized controlled trials (GEMINI I) leading to the approval of the drug by both EMA and FDA. Herein, we assessed safety and efficacy of VDZ in a large real-life experience cohort of patients with UC.

Aims & Methods: All consecutive active, non-operated UC patients treated with VDZ in France from June to December 2014 were assessed. From June to September 2014, VDZ was available through a centralized pre-approval program piloted by the French regulatory agency (ANSM). After its approval by ANSM (reimbursement of the drug by social services is still pending), recruitment was extended until December 2014. Patients received VDZ (at a dose of 300 mg) at weeks 0, 2 and 6 as induction therapy and then every 8 weeks. Patients who did not respond to VDZ induction therapy at week 6 could receive VDZ 300 mg every 4 weeks. Patients were evaluated prospectively at W14. Remission was defined as a partial Mayo score <2. Response was defined as a reduction in the partial Mayo score of at least 3 points and a decrease of at least 30% from baseline. C-reactive protein as well as safety were ascertained.

Results: One hundred and twenty-one patients (67 males, median age: 40.4 IQR [29.7-55.2] years) were included in 33 centres. Median disease duration was 6.5 [3.8-11.4] years; 115 (95%) patients have been previously treated with immunosuppressant and 116 (96%) with at least one anti-TNF. At baseline, mean total Mayo score was 8.3 ± 2.4 and mean CRP level was 19.4 ± 21.1 mg/L. Response and remission rates at W14 were 52% and 35%, respectively. The steroid free response and remission rates were 45% and 31%, respectively. At week 14, the mean decrease of partial Mayo score was 2.5 ± 2.8 ($p < 0.001$) and the mean decrease of CRP level was 3.8 ± 22.5 ($p = 0.02$). Adverse events were reported in 22 (18%) patients and consisted in opportunistic infection (n = 13) including nasopharyngitis (n = 6), upper respiratory tract infection (n = 4) and *Clostridium difficile* superinfection (n = 1), cholecystitis (n = 1) and tuberculosis (n = 1), cutaneous reaction (n = 5), paresthesia (n = 2), strokes (n = 1) and deep venous thrombosis (n = 1).

Conclusion: In this first real-life experience cohort of patients with refractory UC, vedolizumab induced clinical response in more than 50% of cases, with an acceptable safety profile.

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MONDAY, OCTOBER 26, 2015 14:00–15:30

DIAGNOSIS AND TREATMENT OF CHRONIC CONSTIPATION – ROOM E1

OP055 CONSTIPATION SYMPTOMS IN THE U.S. GENERAL POPULATION: RESULTS FROM THE ROME NORMATIVE GASTROINTESTINAL SYMPTOMS SURVEY (RNGSS)

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Introduction: Rome III diagnostic criteria include 6 different symptoms of functional constipation (FC). Little is known about how frequently these symptoms occur in the U.S. general population and how they vary between demographic groups.

Aims & Methods: Data from the 2013 RNGSS were used to characterize these population constipation parameters. A national sample of 1,665 U.S. adults completed a secure Qualtrics internet survey including demographics, health history questions and the questions of the Rome III Diagnostic Questionnaire with the new validated response formats (*Gastroenterology* 2013;144(5),Suppl.1:S-916) planned for Rome IV. These new response scales assess frequency of the six Rome III functional constipation symptoms in the past 3 months in 10% increments from 0-100%, providing more detailed view of their frequency than previously available in Rome III. To minimize bias in the sample, survey invitations described the study as a physical symptoms survey rather than a survey of gastrointestinal symptoms. Stratified sampling was used to ensure equal gender proportions and minority representation close to census distribution. Responders providing inconsistent survey answers were excluded from analysis, leaving 1,277 response sets.

Results: The analysis sample was 648 females and 629 males, from all 50 U.S. states plus D.C. and Puerto Rico; 54.5% white race; mean age 46.4 years (range 18-94); 45.7% had a college degree. The majority of individuals (68.9%) reported 1 or more FC symptom at a frequency of 10% or higher of all BMs (or 10%+ of weeks in the case of infrequent stools). Average number of FC symptoms reported in the whole sample was 2.3. The 3 most common FC symptoms were straining, hard stools and feeling of incomplete BMs, each reported at 10% or higher frequency in about half of the entire sample (see Table). Digital facilitation of BM was the least common symptom, only reported by 20.5% of people. Compared to males, women had higher rates of presence of all 6 FC symptoms ($p < 0.0001$ for all), higher average number of symptoms in the past 3 months (2.7 vs. 2.1, $p < 0.0001$), and greater average frequency of the symptoms (14.3% vs. 9.3%, $p < 0.0001$). Individuals age 65+ reported slightly fewer constipation symptoms on average than subjects under 30 or those aged 30-64 (1.93 vs. 2.44 and 2.47 respectively; $p < 0.02$) and also had modestly lower mean frequency of constipation symptoms compared to the younger age groups (14.8% vs. 17.6% and 17.8%; $p < 0.008$).

Table: Frequency distribution of the six functional constipation symptoms among individuals in the sample

	Frequency of the symptom in the past 3 months					
	0%	10%	20%	30%	40%	50%+
Functional constipation symptom:						
Fewer than 3 BMs per week	73.2	9.7	3.2	3.3	1.1	6.1
Hard or lumpy stools	49.5	21.1	9.4	6	2.3	7.8
Straining during BM	46.0	24.2	8.1	7.2	2.9	8.6
Feeling of incomplete evacuation	50.4	19.1	10.2	5.2	3.1	3.4
Feeling of blocked passage	62.6	16	6.4	4.9	2.6	5.1
Digital faciltation of BM	79.5	8.8	3.4	2.3	1.1	3.2

Conclusion: Constipation symptoms are highly prevalent in the general population, with the majority experiencing at least 1 FC symptom (mean = 2.3) at 10% frequency or higher. Women have significantly greater number and frequency of constipation symptoms than men. Unlike some previous reports, we found a slight decrease in constipation symptoms in older individuals compared to younger subjects. [Supported by the Rome Foundation and R01 DK31369]

Disclosure of Interest: None declared

OP056 DIAGNOSIS OF DYSSYNERGIC DEFECATION BY QUESTIONNAIRE AND PHYSICAL EXAMINATION

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Introduction: It is important to distinguish dyssynergic defecation (DD) from other subtypes of constipation because DD has a distinct physiological mechanism and responds to different treatments. However, diagnosis currently depends on costly, invasive tests which are not widely available.

Aims & Methods

Aim: To evaluate the sensitivity and specificity of symptom questions and physical examination.

Methods: 307 Italian patients with refractory constipation were referred to author GC for management. Those who responded to a 30-day trial of fiber supplements or were non-adherent were excluded, leaving 238. Following a questionnaire and physical exam, they were evaluated by anorectal manometry, balloon evacuation test (BET), and defecography (selected patients only), and were assigned "gold standard" diagnoses as follows: Mechanical obstruction (MO) if rectal prolapse on physical exam or abnormal defecography plus BET >2 minutes; DD if paradoxical contraction or failure to relax pelvic floor muscles on anorectal manometry plus BET >2 minutes plus absence of MO; slow transit constipation (STC) if $>5/24$ Sitzmarks remained 5 days after ingestion plus BET <2 minutes; and normal transit constipation (NTC) in the absence of MO, DD, or STC. The predictor variables were the symptom questions and physical examination findings listed in Table 1. We randomly assigned the 238 patients to two groups of 119 each. We first tested the utility of each predictor variable for discriminating DD from other types of constipation in the Learning Sample and selected the best predictors for validation in the Validation Sample.

Results: Average age was 45.2 years, and 92% were females. Anorectal manometry, BET, and defecography identified 102 as having DD, 31 as STC, 37 as MO, and 63 as NTC. Five were not classifiable by these tests. Table 1 shows that the best predictor of DD status was a question on which muscles were used to defecate; a response of "anus" identified 91.1% of DD , and any other answer correctly identified 88.7% of those with other types of constipation. Test performance in the Validation Sample was similar (Table 1). The concordance between answers to this question on two occasions 30 days apart was 98.7%. The physical examination finding that the anal sphincter relaxes on straining correctly identified 97.8% of patients who did not have DD, and test performance was similar in

the Validation Sample. No symptoms or exam findings reliably identified other types of constipation.

Table 1: Sensitivity and Specificity of Minimally Invasive Tests

	Learning Sample		Validation Sample	
	Sensitivity	Specificity	Sensitivity	Specificity
Questionnaire:				
Incomplete evacuation	100	2.8	100	5.1
Anal blockage	55.6	58.3	63.2	54.2
Digital maneuvers	37.8	61.1	31.6	55.9
Squeeze anus to defecate	**91.1**	**88.7**	**82.1**	**86.2**
Physical Examination:				
Abd wall contracts to defecate	73.3	5.6	61.4	8.5
Anal sphincter relaxes to defecate	**76.4**	**97.8**	**72.9**	**94.7**

Conclusion: Asking patients which muscles they use to defecate has an overall accuracy of 87% for distinguishing patients with DD from those with other types of constipation. This question could be used in epidemiological studies to estimate the prevalence of DD, in primary care to guide treatment, and in pharmaceutical trials to select patients for inclusion. [Supported in part by grant R01 DK31369]
Disclosure of Interest: None declared

OP057 NALOXEGOL FOR OPIOID-INDUCED CONSTIPATION: MECHANISM OF ACTION AND CLINICAL IMPLICATIONS

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Introduction: Opioid-induced constipation (OIC) results from the binding of opioid agonists to mu-opioid receptors in the enteric nervous system.[1] Conventional therapies do not target all underlying mechanisms of OIC and have limited efficacy. Naloxegol (Movantik™, Moventig® in Europe), a peripherally acting mu-opioid receptor antagonist, was approved by the FDA and EMA in 2014.
Aims & Methods: To summarize the study results that characterized the mechanism of action and clinical effects of naloxegol. Assessments of naloxegol included in vitro determinations of its affinities for opioid receptor subtypes, functional antagonism at mu-opioid receptors, and properties as a P-glycoprotein (PGP) substrate using a Caco2 cell transport assay. Single (8–1000 mg) oral dose-ranging studies assessed pharmacodynamics of the antagonism of morphine-induced decreases in orocecal transit time (OCTT) and pupillary miosis, safety and tolerability, and pharmacokinetics (PK) in healthy men. The efficacy, safety, and tolerability of daily doses of naloxegol (12.5, 25 mg) were evaluated in phase 3 trials in patients with OIC and chronic noncancer pain.[2,3] Endpoints included response rate (sustained changes in spontaneous bowel movements), safety assessments, and changes in daily opioid dose, pain scores, and signs of opioid withdrawal.
Results: Naloxegol is a PEGylated derivative of naloxone and a potent ($K_i = 7.42$ nM), competitive antagonist of the human mu-opioid receptor. Naloxegol was a substrate for the PGP transporter, with low apparent permeability in the Caco2 transport assay, and penetrated the CNS 15 times slower than naloxone in a rat brain perfusion model. In healthy men, dose-ordered antagonism of the morphine-induced delay in OCTT was observed. The placebo:naloxegol OCTT ratio declined with increased naloxegol AUC, consistent with exposure-dependent antagonism of morphine-induced slowing of GI transit. Doses $\leq$125 mg produced negligible antagonism of morphine-induced miosis, indicating no antagonism of central mu-opioid receptors. In 2 identical randomized, double-blind, placebo-controlled 12-week phase 3 studies, response rates were significantly increased in patients treated with naloxegol 12.5 mg (KODIAC-04, $P = 0.02$ and 25 mg (KODIAC-04, $P = 0.001$; KODIAC-05, $P = 0.02$) vs placebo.[2] Patients treated with naloxegol for 12 or 52 (KODIAC-08, 25 mg) weeks exhibited good safety profiles. Most AEs were GI-related; discontinuations and AEs were higher with the 25-mg dose.[2,3] In the 12-week and 52-week studies, there were no significant changes in opioid dose and pain scores; signs of opioid withdrawal were infrequent.
Conclusion: Naloxegol exhibits PK properties important for selective action on mu receptors in the periphery, is efficacious, generally safe and well tolerated, and does not affect opioid-mediated analgesia at therapeutic doses in patients with OIC and chronic noncancer pain.

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OP058 EFFECTIVENESS OF LACTOBACILLUS REUTERI IN THE TREATMENT OF FUNCTIONAL CONSTIPATION IN CHILDREN: A RANDOMIZED, DOUBLE–BLIND, PLACEBO-CONTROLLED, MULTICENTER TRIAL

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Introduction: Functional constipation in childhood is treated with defecation training and macrogole/lactulose administration but a number of patients do not respond to the therapy or present with some complaints even if number of bowel movements increases. This is the reason to look for additional treatment methods on top of macrogole or lactulose. Several probiotic strains have been tested in a few trials but the results in children were negative- still most of the studies were performed in children responding very well to standard lactulose therapy. *Lactobacillus reuteri* has been proven to improve symptoms in functional gastrointestinal disorders including constipation.
Aims & Methods: The aim of the study was to assess the effectiveness of *Lactobacillus reuteri* as an adjunct to macrogole in the treatment of functional constipation in children.
A double-blind placebo randomized controlled trial was conducted in a group of 129 children (57 girls, 72 boys) aged 4.66 ± 1.33 years (mean $\pm$ SD), with functional constipation (average duration: 23 months) who were treated with a poor effect for at least two months prior to the study.
Patients were randomly assigned to one of the two groups: 1. *Lactobacillus reuteri* (1 tablet containing 10^8 CFU) and macrogole therapy or 2. macrogole and matching placebo for 8 weeks.
Results: 121 patients completed the study. The majority (119/121) of patients increased their bowel movements in both groups (59 vs 60, ns.) and there was no statistically significant difference in the number of bowel movements per week at week 8 between the study and the placebo group (7.5 ± 3.3 vs 6.9 ± 2.5, respectively).
Additionally, there were no significant differences between groups in the numbers of patients complaining of pain at defecation (13/47 vs 8/53), abdominal pain (19/41 vs 25/36), withholding stools (15/45 vs 13/48), passing hard stools (7/53 vs 3/58) or large stools (14/46 vs 12/49), fecal incontinence (17/43 vs 11/50). Patients in both groups required similar dose of macrogole per week (265g vs 300g, ns.)
Conclusion: *Lactobacillus reuteri* supplementation was not effective in the treatment of functional constipation in children aged 2-7 years.
Disclosure of Interest: None declared

OP059 HOW DOES PSYLLIUM REALLY WORK IN CONSTIPATION? A DOUBLE-BLIND CROSSOVER STUDY TO EVALUATE ITS IMPACT ON MAGNETIC RESONANCE IMAGING BIOMARKERS

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Introduction: Ispaghula/psyllium (PS) is a recognised treatment for constipation. Its effect is believed to be mediated by its ability to trap water in the lumen although exactly where in the gut this occurs is unclear. Magnetic Resonance Imaging (MRI) can assess whole gut transit(WGT)[1], small bowel free water content[2], colonic volume[3] and colonic chyme T_1 and T_2 - constants of a substance's physical structure that increase with greater fluidity.
Aims & Methods:
Aims: To assess these parameters in patients with functional constipation disorders, and test whether they were sensitive to the effect of PS. Hypotheses: PS would accelerate WGT, and increase luminal water content, T_1 and T_2.
Methods: A double-blind crossover study of adults with functional constipation or constipation-predominant irritable bowel syndrome by Rome III criteria. Intervention: Metamucil Original Coarse Fiber® (P&G, USA) 14g tds, (daily

PS dose 21g). Placebo comparator: Maltodextrin(MD) 14g tds. Treatment periods were preceded by 10 days of usual laxatives, then 8 days without therapy. At 0800 on day 5 of treatment subjects swallowed 5 MRI transit markers. On day 6 MRI scans were taken fasting and serially after a standard test meal for 7 hours, with a final fasting scan on day 7 of treatment. Primary endpoint: Weighted Average Position Score of transit markers 24 hours after ingestion (WAPS24). Score increases with longer WGT. Secondary endpoints: free water content of the small bowel (SBWC) and ascending colon (ACWC); T_1 and T_2 values of the chyme in the ascending colon (AC) and descending colon (DC). Colonic volume (CV) was also measured.

Results: 16 subjects completed both treatment periods. All reported analyses by paired t-test. PS accelerated WGT such that WAPS24 decreased by mean 0.8 ($\pm$1.8, $p = 0.05$, 1-tailed), or 24%. Postprandial SBWC rose markedly with PS: mean SBWC 32.9mL $\pm$16.7 on MD vs. 81.5mL $\pm$41.2 on PS ($p < 0.001$). This was followed by a smaller increase in ACWC ($p < 0.05$). Fasting T_1 values were lower than previously reported in healthy volunteers(HVs) but on PS rose in both the AC ($p < 0.001$) and DC ($p < 0.01$) to values within the normal range. CV increased by 332mL (95%CI 214-451, $p < 0.001$), or 48%. Table 1 shows the distribution of key parameters in previous studies[1,3,4] of HVs alongside data in constipation on MD and on PS.

Mean (SD) orMedian (Q25-Q75)	Healthy Volunteers	Constipation subjects on MD	Constipation subjects on PS
WAPS24	0.8 (0-1.6)	3.4 (1.6-4.8)	2.2 (1.5-3.0)
Colonic Volume (mL)	561 (239)	690 (218)	1022 (240)
T_1 AC (secs)	0.77 (0.64-0.92)	0.55 (0.49-061)	0.82 (0.44-1.14)
T_1 DC (secs)	0.55 (0.39-0.85)	0.23 (0.19-0.55)	0.57 (0.32-0.78)

Conclusion: Psyllium decreased WGT while both CV and fluidity of the colonic chyme (T_1) increased. All these measures on placebo were different to prior data in healthy volunteers and showed a significant response to therapy. The sequences used are readily translatable to any MRI scanner in clinical use and show great promise as non-invasive biomarkers for the assessment of constipation and the effect of gut modulators.

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Disclosure of Interest: K. Murray: None declared, G. Major: None declared, C. Hoad: None declared, A. Nowak: None declared, L. Marciani: None declared, A. Silos-Santiago: None declared, C. Kurtz: None declared, J. Johnston: None declared, P. Gowland: None declared, R. Spiller Financial support for research: a collaborative study funded by Ironwood Pharmaceuticals Inc.

OP060 SACRAL NERVE STIMULATION FOR REFRACTORY CONSTIPATION: PRELIMINARY RESULTS OF A MULTICENTER RANDOMIZED CROSS-OVER DOUBLE BLIND STUDY

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Introduction: Uncontrolled studies have reported conflicting results on the benefit of sacral nerve stimulation (SNS) in patients suffering from refractory constipation. We assessed the efficacy of SNS in a multicenter randomized cross-over double blind study.

Aims & Methods: Patients with severe constipation refractory to conservative therapy were included if they had at least 2 criteria among: i) Less than 3 bowel movements (BM) per week, ii) straining to evacuate on >25% of attempts, iii) sensation of incomplete evacuation on >25% of occasions. Response to therapy was defined by a number of BM $\geq$3/wk and/or > 50% improvement in symptoms. Responders to a 3-week temporary stimulation were offered permanent neurostimulator implantation. After a 2-week wash-out period, patients were randomly assigned in a cross-over design with 2 periods of 8-week of active (ON) or sham (OFF) stimulation. The 2 periods were separated by a 2-week wash out period. Patients and investigators were blinded to the stimulation sequence. At the end of the 2 trial periods, all patients were offered to receive active stimulation until the last evaluation at 1 year. Symptoms (Wexner score, Visual Analogic Scale), Quality of Life scale, and tolerability/side effects were assessed before and at the end of each period. Colonic transit time and anorectal manometry were performed at inclusion and at the end of follow-up.

Results: From July 2012 to November 2013, 36 patients (mean (SD) age: 45 years (14), 33 female) underwent a temporary stimulation, the majority of whom (n = 28, 77.8%) had predominant dyschesia. A total of 21 patients (58.3%) were responders, and 20 received permanent stimulation (mean (Standard Deviation) age: 44 years (15), 19 female) (1 patient refused the implantation). Response was obtained in 60% and 55% after ON and OFF stimulation periods, respectively (ITT analysis, missing = failure). During the study period, 3 patients had the stimulator explanted, 2 for infection of the stimulator site, 1 for consent withdrawal (lack of efficacy), and 1 was excluded for non compliance to study protocol. After a 1-year follow-up, 55% of implanted patients (n = 11) remained responders. Median Wexner scores were 20 at inclusion (min-max: 13-28), 15 after the temporary stimulation (min-max: 2-29), and 13.5 at one year (min-max: 3-24, n = 18).

Conclusion: In patients with refractory constipation who responded to temporary SNS, this randomized double-blind study could not demonstrate any significant effect of active stimulation (ON) compared to absence of stimulation (OFF). SNS may be a therapeutic option in a small subgroup of patients: indeed, a positive response 1 year after permanent implantation of the stimulator remained in 30% of the patients initially tested.

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MONDAY, OCTOBER 26, 2015 14:00–15:30
OMIC TECHNOLOGY PROVIDES NEW BIOMARKERS – ROOM E2

OP061 META-ANALYSIS OF 544 GASTRIC CANCER GENOMES IDENTIFIED NOVEL DRIVER GENES AND A PROGNOSTIC MUTATION SIGNATURE

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Introduction: Gastric cancer is not a single entity and its molecular classification is still evolving. Despite a decrease in both incidence and mortality owing to progresses in *Helicobacter pylori* eradication and cancer screening, gastric cancer remains the 7th most common cancer and the 3th leading cause of cancer death worldwide with a 5-year survival rate of 29.6%. Next-generation sequencing studies have identified novel driver genes in gastric cancer but their use in molecular typing and prognostication remains unestablished.

Aims & Methods: To characterize mutational processes operative in gastric cancer and to identify novel significantly mutated genes (SMGs) and prognosticators for patients with gastric cancers, we aggregated somatic mutational profiles and clinicopathological information of 544 gastric cancer patients from previous genomics studies. We further applied nonnegative matrix factorization (NMF) to decipher mutational signatures operative in gastric cancer, MutSigCV to discover new SMGs, and Kaplan-Meier survival and multivariate Cox regression analyses to identify prognostic mutation signatures.

Results: Gastric cancer could be classified into regular- (86.8%; average mutations per Mb: 2.5) and hyper-mutated (13.2%; average mutations per Mb: 33.7) subtypes based on mutation frequency. TpCpW mutations were significantly more frequent and associated with APOBEC expression in regular- but not hyper-mutated gastric cancer despite *APOBEC3B* mRNA levels were comparable. In regular-mutated gastric cancer, twelve reported (*TP53*, *ARID1A*, *CDH1*, *PIK3CA*, *etc.*) and six novel recurrently mutated genes (*FLG*, *COL14A1, BNC2, CNBD1, ITGAV, TP53BP1*) exhibited high mutation prevalence ($\geq$3.0%) and higher-than-expected number of non-silent mutations. Mutational profiling further identified two molecular subtypes in regular-mutated gastric cancer with distinct prognostic outcomes independent of TNM staging and Lauren classification. Genotoxic/oncogenic stress response (58.0%), histone modification/chromatin remodeling (28.9%) and growth factor receptor signaling (25.3%) were frequently altered by somatic mutations in regular-mutated gastric cancer. In diffuse-type gastric cancer, *CDH1* mutation was associated with shortened patients' survival independent of TNM staging.

Conclusion: Meta-analysis of 544 gastric cancer genomes has identified novel driver genes and a mutation signature predictive of patients' survival. *CDH1* mutation is an independent prognostic factor in diffuse-type gastric cancer.

Disclosure of Interest: None declared

OP062 A NOVEL GLYCOMIC-BASED SERUM BIOMARKER (GLYCOCIRRHOTEST) FOR RISK ASSESSMENT OF HEPATOCELLULAR CARCINOMA IN COMPENSATED CIRRHOSIS

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Introduction: Cirrhosis is a major risk factor for the development of hepatocellular carcinoma (HCC) with a yearly incidence ranging from 1 to 8%. EASL and AASLD guidelines recommend systematic screening with liver ultrasound at 6 months interval in cirrhotic patients. A glycomic-based test, called GlycoCirrhoTest (GCT), based on to the respective abundance of bisecting GlcNAc residues and triantenarry glycans on serum proteins, has shown a 79% sensitivity and 86% specificity for the diagnosis of cirrhosis among patients with chronic liver diseases.

Aims & Methods: The aim of the present study was to determine whether serum glycomics are predictive for the risk of HCC development in compensated cirrhosis.

Serum samples of 132 cirrhotic (Child A or B) patients collected between 1995 and 2005 were analysed. Seventy percent suffered of Hepatitis C. In the remaining patients, the cause of cirrhosis was HBV infection, alcohol and autoimmune diseases. Cirrhosis was confirmed by liver biopsy. The patients were followed until the appearance of a HCC, death or liver transplantation. Patients with HCC at the moment of serum sampling and during the first year were excluded. GCT was performed using capillary electrophoreses as previously described by Callewaert et al. (*Nature Medicine* 2004).
Results: After a median follow up of 4 years (IQR: 3.6–8.06), 35 (26.5%) of the patients developed a HCC. Mean follow up in the patients who did not develop HCC was 3.7 years (IQR: 3.4-9.9; ns). We observed a significant increase of the mean baseline GCT value in the patients who developed a HCC during follow up ($p < 0.001$) as compared to those who did not. ROC Curve analysis showed an AUC of 0.716 (95% CI: 0.611-0.820) for the prediction of HCC in the patients with a follow up of at least 1 year. An 0.1 increase in the value of the GCT was associated with a 27% increase in the risk for developing HCC (OR 1.27; 95%CI: 1.098-1.475). An optimal cutoff for the GCT was defined at 1.6 and the hazard ratio for the development of HCC was 3.88 (95% CI: 1.81-8.29) for patients with a baseline GCT above this treshold.
Conclusion: This study suggests that an analysis of the serum protein glycome could generate a useful biomarker for the identification of cirrhotic patients at high risk for the development of HCC up to 4 years before HCC development. GlycoCirrhoTest may help to stratify cirrhotic patients according to the risk of HCC and optimize screening.

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Disclosure of Interest: None declared

OP063 OVEREXPRESSION OF MIRNA221 AND 222 IN CANCER STROMA IS ASSOCIATED WITH MALIGNANT POTENTIALS IN COLORECTAL CANCER

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Introduction: Cancer stroma plays an important role in cancer development. Although a few study were reported on differential miRNA expression profile comparison between cancer stroma and normal stroma, the aberrant expression of miRNA in cancer stroma that related to cancer progression remains unclear.
Aims & Methods: The aims of this study is to investigate the miRNAs associated with liver metastasis in cancer stromal tissue of human colorectal cancer. Using a laser capture microdissection technique, we obtained cancer stromal tissues from primary lesion of 6 colorectal cancer patients with liver metastasis (CRCWLM) and 6 colorectal cancer patients without liver metastasis (CRCWOLM). These samples were analyzed by miRNA microarray to identify differentially expressed miRNAs in cancer stromal tissues of CRCWLM versus CRCWOLM. Results of microarray were further analyzed by quantitative real-time polymerase chain reaction (qRT-PCR). Furthermore, we examined 101 CRC samples whether miRNA expression status in stromal tissue could affect the clinicopathologic factors.
Results: Microarray analysis revealed that miR221 and miR222 were higher expressed in cancer stromal tissue of CRCWLM than in that of CRCWOLM, whereas the 4 miRNAs including miR659, 4470, 4669 and 5703 were lower expressed in CRCWLM. To confirm the microarrays findings, we measured the expression level of 6 miRNAs described as above in stromal tissues of 20 CRCWLM and 20 CRCWOLM, using qRT-PCR. Expression levels of miR221 and miR222 in cancer stromal tissue were significantly higher in CRCWLM than in CRCWOLM, while there was no difference in the expression of 4 down-regulated miRNAs. To examine the clinicopathological utility of stromal miR 221/222 expression in CRC patients, we measured miR 221/222 expression of cancer stroma and cancer cells in 101 CRC samples, using qPCR analysis. qPCR revealed that CRC patients with high miR221 expression level was related to liver metastasis, distant metastasis, venous invasion and shorter overall survival compared to CRC with low miR221 expression level ($P < 0.05$). Similarly, high miR222 expression level was related to liver metastasis, distant metastasis, depth of tumor invasion and shorter overall survival ($P < 0.05$). On the other hand, in cancer cells there is no correlation between clinicopathological factors and expression of miR221 and miR222.
Conclusion: Both miR-221 and miR-222 are two highly homologous microRNAs and many reports indicate that miR-221/222 may function as an oncogene in human cancer as an onco-miR. Our result suggested that overexpression of miR221 and miR222 in cancer stromal tissue is related to the malignant potentials to develop liver metastasis in patients with CRC.
Disclosure of Interest: None declared

OP064 EPIGENOME-WIDE DNA METHYLATION PROFILING IN INFLAMMATORY BOWEL DISEASE

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Introduction: Epigenetic alterations including DNA methylation may provide important insights into gene-environment interaction in complex immune diseases such as inflammatory bowel disease (IBD). Whilst whole tissue methylation changes may provide clinically useful biomarkers, epigenetic changes are cell-type specific. This study aimed to characterise the circulating methylome in IBD, and relate changes seen in whole blood to the methylation profile in separated leucocytes, gene expression data, as well as our previous data in childhood-onset disease.[1]
Aims & Methods: The Illumina 450k array was used to assess whole blood leucocyte DNA methylation at over 485,000 CpG sites across the genome in 240 patients (121 Crohn's disease[CD], 119 ulcerative colitis[UC]) and 191 controls. Whole blood data was analysed after correcting for batch effects and for the cellular composition of the samples. Differentially methylated sites discovered in whole blood were also investigated in immunomagnetically separated leucocytes (CD4+ & CD8+ lymphocytes, CD14+ monocytes). All participants were genotyped using the Illumina Omni Core Exome array.
Results: There were 446 differentially methylated positions (DMPs) meeting epigenome wide significance as defined as a Holm corrected p value of <0.05 (uncorrected $p \leq 1.1 \times 10^{-7}$) in IBD cases versus control. No markers were significantly different between CD and UC.
There were 60 differentially methylated regions (DMRs) with unidirectional methylation change in 3 or more adjacent markers each achieving False Discovery Rate significance of $p < 0.05$. Of these, 5 were significant following more stringent Holm correction for the probes.
There was significant enrichment of methylation alteration around known susceptibility loci.[2] Linear Discriminant analysis using two CpG sites discriminated IBD cases and controls with high accuracy (area under curve 0.87)
Established as well as novel pathways pertinent to disease pathogenesis are strongly implicated. The most significant DMP in whole blood (RPS6KA2 [corrected $p = 1.1 \times 10^{-16}$] was also hypomethylated in monocytes in UC (uncorrected $p = 3.5 \times 10^{-6}$). The most significant DMR, VMP1/miR21 (most significant probe corrected $p = 4.9 \times 10^{-14}$) strongly replicates the same finding in our previous study. The gene encoding Beta-2 Integrin (ITGB2) was a hypermethylated DMR in IBD and more specifically CD (most significant probe corrected $p = 4.3 \times 10^{-4}$) compared with controls. Integration of genetic and epigenetic level data permitted identification of methylation quantitative trait loci.
Conclusion: This is the most detailed characterisation of the epigenome carried out in IBD to date and includes novel data exploring the circulating methylome in UC. The findings strongly validate this approach in complex disease, replicate and expand previous data, and provide clear translational opportunities.

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OP065 COMPREHENSIVE DNA METHYLATION ANALYSIS REVEALS A COMMON TEN-GENE METHYLATION SIGNATURE IN COLORECTAL ADENOMAS AND CARCINOMAS

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Introduction: Microarray analysis of promoter hypermethylation provides insight into the role and extent of DNA methylation in the development of colorectal cancer (CRC) and may be co-monitored with the appearance of driver mutations.
Aims & Methods: Colonic biopsy samples were obtained endoscopically from 10 normal, 23 adenoma (17 low-grade (LGD) and 6 high-grade dysplasia (HGD)), and 8 ulcerative colitis (UC) patients (4 active and 4 inactive). CRC samples were obtained from 24 patients (17 primary, 7 metastatic (MCRC)), 7 of them with synchronous LGD. Field effects were analysed in tissues 1 cm ($n = 5$) and 10 cm ($n = 5$) from the margin of CRC. Tissue materials were studied for DNA methylation status using a 96 gene panel. Expression levels

were assayed using whole genomic mRNA arrays. SFRP1 was further examined by immunohistochemistry. HT29 cells were treated with 5-aza-2' deoxycytidine to analyse the reversal of DNA methylation.
Results: More than 85% of tumor samples showed hypermethylation in 10 genes (*SFRP1, SST, BNC, MAL, SLIT2, SFRP2, SLIT3, ALDH1A3, TMEFF2, WIF1*), whereas the frequency of examined mutations were below 25%. These genes distinguished precancerous and cancerous lesions from inflamed and healthy tissue. The mRNA alterations that were caused by systematic methylation could be reversed by demethylation treatment.
Conclusion: Systematic changes in methylation patterns were observed early in CRC carcinogenesis, occuring in precursor lesions and CRC, often prior to the appearance of sporadic mutations. Thus we conclude that DNA hypermethylation is an early and systematic event in colorectal carcinogenesis, and it can be potentially reversed by systematic demethylation therapy.
Disclosure of Interest: None declared

OP066 DEVELOPMENT OF RECOMBINANT ANTIGEN MICROARRAY FOR AUTOANTIBODY BIOMARKER SIGNATURE ANALYSIS IN GASTRIC CANCER

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Introduction: According to GLOBOCAN data, Gastric cancer (GC) represents fifth most common type of cancer and third most common cause of cancer-related death worldwide. Over 80% of GC cases are detected at late stage when expected 5-year survival ranges from 4 to 20%. Hence, the development of a reliable and simple non-invasive biomarker assay for the early detection of GC among high-risk individuals is of paramount importance. Among other emerging biomarkers, circulating IgG class autoantibodies against tumour-associated antigens (TAAs) have been shown to have promising biomarker qualities for GC detection[1].
Aims & Methods: In our previous studies, we applied T7 phage-displayed antigen microarray (PDAM) technology to identify autoantibody biomarker signatures with relevance to GC. This resulted in the identification of GC-associated biomarker panel with promising diagnostic (AUC = 79%) and prognostic value[1]. Within the current study, in order to obviate the limitations of the PDAM system, we aimed to develop a recombinant TAA microarray that would be applicable for standartized large-scale autoantibody biomarker validation in independent patient and matched control cohorts. The selected GC antigen B cell epitope coding sequences were cloned in pFN19A (HaloTag® 7) T7 SP6 Flexi expression vector, expressed as His-HaloTag fusion proteins in *E. coli* and purified by using Protino® Ni-TED 150 Ni^{2+} columns. For microarray generation, the expressed antigens were printed in duplicate by Q-Array Mini microarray printer (Genetix) onto nickel chelate glass slides (Xenopore). Serum autoantibody signal was detected in 1:200 diluted GC patients' specimens, the protein amount in each spot was determined by using rabbit Anti-HaloTag® polyclonal antibody and respective fluorophore labelled secondary antibodies. Finally, preliminary analytical characteristics of the developed assay (i.e., reproducibility, limit of detection, dynamic range) was determined.
Results: In total, 105 antigen clones having most promising diagnostic and prognostic value for GC were selected for the expression and microarray development – these included clones from 15 Cancer-Testis antigens, 31 known TAAs and 46 novel antigens. According to the Western blot, 85% of the expressed proteins were shown to be soluble, and the obtained seroreactivity data showed that 92% of the expressed antigens retained their B cell epitopes exposed by using this expression system. The lower limit of antibody detection of the microarray platform was determined to be ~100 ng/ml. The dynamic range within the assay was set to be 7,000-15,000 MFI (mean fluorescence intensity) units basing on the linearity of analysed HaloTag and serum reactivity signal ratios. Intra-assay variation was determined to be within the range of 0.11-0.21 (mean 0.14), and inter-assay variation ranged from 0.12-0.36 (mean 0.19).
Conclusion: This study has resulted in the development of a robust platform applicable for serum autoantibody detection against a representative set of GC-associated antigens, which was shown to comply with the analytical and technical prerequisites of the serological assay to be applied for systematic autoantibody biomarker validation.

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Disclosure of Interest: None declared

OP067 PAIRED TRANSCRIPTOMIC AND PROTEOMIC PROFILING ANALYSIS OF THE INTESTINAL MUCOSA IDENTIFIES SIMILAR BIOLOGICAL PATHWAYS IN DIARRHOEA-PRONE IRRITABLE BOWEL SYNDROME

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Introduction: Altered intestinal barrier and mucosal inflammation are physiopathological characteristics in Irritable Bowel Syndrome (IBS). A transcriptomic analysis has previously guided us to identify a strong association between the transcript signature and immune activity and intestinal permeability in diarrhoea-prone IBS (IBS-D). However, a proteomic analysis with a similar strategy has not been performed so far.
Aims & Methods
Aim: To identify the proteomic profile and to assess whether mRNA changes translate into protein in the intestinal mucosa in IBS-D.
Methods: Total RNA and protein were obtained from jejunal mucosal biopsies from healthy volunteers (H; n = 5) and age-matched (range: 21-59 years) non-celiac, naïve IBS-D patients meeting Rome III criteria (n = 8). RNA was analyzed using Affymetrix GeneChip Human Genome HG-U133 Plus 2.0 array. Protein content was analyzed using 2D-difference gel electrophoresis (DIGE). Differential spots from the gel were picked and analyzed using Ultraflex TOF/TOF mass spectrometer. Mass fingerprint data were searched using Mascot algorithm and submitted to Ingenuity Pathway Analysis (IPA).
Results: RNA analysis showed a distinctive gene expression profile in IBS-D compared with H, with differences in canonical pathways and biological networks associated with mast cell function, intestinal permeability and tight junction (TJ) signalling ($P < 0.001$). Protein analysis revealed 139 spots differentially expressed ($P < 0.05$), of which 95 proteins were identified. The most significant pathways and functions associated with proteomic analysis included categories related to intestinal epithelial barrier modulation such as actin cytoskeleton signalling ($P < 0.003$) and caveolar-mediated endocytosis signalling ($P < 0.005$). Paired analysis of gene and protein profiles revealed association with the same canonical pathways, biological functions and disease mechanisms. Cellular assembly and cell-to-cell signalling were the most significant biological functions associated with IBS-D. Moreover, immunological, gastrointestinal and inflammatory diseases were among the most relevant disease mechanism associated with both IBS-D profiles ($P < 0.001$).
Conclusion: Distinctive mucosal proteomic profile in IBS-D patients identifies alterations in immune activation, mitochondrial dysfunction and cytosketelon signalling. Paired gene and protein expression analysis extends our previous results of dysfunctional tight junction signalling with altered cellular assembly and cell-to-cell signalling in IBS-D patients, supporting the loss of intestinal epithelia barrier function as central molecular mechanism in the disease.
Disclosure of Interest: None declared

MONDAY, OCTOBER 26, 2015 14:00–15:30
NEW TECHNOLOGIES IN GI ENDOSCOPY – ROOM E3

OP068 EFFICACY OF THE CRYOBALLOON FOCAL ABLATION SYSTEM FOR THE ERADICATION OF BARRETT'S OESOPHAGUS

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Introduction: Radiofrequency ablation (RFA) is currently the preferred ablation technique for eradication of Barrett's oesophagus (BO). However, this technique has drawbacks, such as the need for large controller units and multiple deployment steps. Cryoablation using the CryoBalloon Focal Ablation System (CbFAS) may be an attractive alternative.The CbFAS is a balloon-based system, which uses nitrous oxide as a refrigerant. It is designed to overcome the drawbacks of RFA, and earlier studies show that the CbFAS is feasible and safe for the eradication of BO. A recent dosimetry study demonstrated that 10 second ablations result in the most optimal effect (i.e., full conversion of BO to neo-squamous epithelium, without compromising safety). However, efficacy of 10 second ablations in a larger group of patients has not been investigated.
Aims & Methods: To assess the efficacy and performance of the CbFAS in patients with flat, dysplastic BO.
In this ongoing multi-centre, prospective, non-randomized trial, up to 40 patients will be enrolled. Eligible patients may have up to 2 BO islands that will be treated with 10-second ablations using the CbFAS.Follow-up (FU) endoscopy with photo documentation and biopsy of the treated area(s) is performed 6-8 weeks post-ablation. Primary outcome parameter is the percentage of completely eradicated BO islands at FU. Secondary outcome parameters are the percentage of BO islands with at least 50% eradication, device performance, and adverse events.
Results: As of May 2015, 16 patients were enrolled and treated (14 male, median BO C3M6). Eight patients (50%) underwent endoscopic resection (ER) of a visible lesion before ablation therapy, containing early adenocarcinoma in 5 patients (62%), HGD in 2 (25%), and LGD in 1 patient (13%). Worst pathology found, either in the ER-specimen or the baseline BO, was LGD in 8 patients (50%), HGD in 3 (19%) and early adenocarcinoma in 5 (31%). Thirteen patients (81%) had circumferential RFA-treatment prior to inclusion in this study.
23 ablations were performed in 16 patients; median procedure time was 15 (IQR 5-35) minutes. Device malfunction occurred in 4/16 (25%) procedures, but this did not hamper completion of the ablation. No adverse events occurred during the procedure. Mild pain was reported by 5 patients (33%) directly after the procedure; 1 patient reported mild pain during swallowing at two days post-procedure.As of May 2015, FU endoscopy was performed in 10 of 16 patients (14 treated areas). No strictures were detected. Complete eradication of BO islands, endoscopically and histologically, was observed in 12/14 (86%) treated areas. No buried glands were found on biopsy. In two patients, residual BO was observed at follow-up endoscopy, and confirmed by the presence of intestinal

metaplasia in biopsies. However, in one of these patients it was observed at the time of the procedure that the BO island was not completely ablated; in the portion of the island that was ablated, the BO was eradicated. In the other patient, residual BO (< 50% of original size) was found after initial –endoscopically complete- ablation of the BO island.
Conclusion: Preliminary results suggest that cryoablation of BO islands using CbFAS during 10 seconds is effective and safe.
Disclosure of Interest: H. Künzli: None declared, D. Schölvinck: None declared, S. Meijer: None declared, K. Seldenrijk: None declared, J. Bergman Financial support for research: Olympus Endoscopy, Cook Medical, Boston Scientific, Gi Solutions Covidien, Erbe, Ninepoint Medical, Consultancy: Gi solutions Covidien, Boston Scientific, Cook Medical, B. Weusten Financial support for research: Cook Medical, Boston Scientific, GI solutions Covidien, C2 Therapeutics, Consultancy: C2 Therapeutics, Boston Scientific

OP069 A RANDOMIZED TRIAL COMPARING BIODEGRADABLE STENT PLACEMENT AND ENDOSCOPIC DILATION FOR RECURRENT BENIGN ESOPHAGEAL STRICTURES (DESTINY STUDY)

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Introduction: Endoscopic dilation is the standard of care for recurrent benign esophageal strictures (RBES). Esophageal stent placement is thought to prolong the effect of dilation and to reduce recurrences, but stents are associated with migration and require removal. Biodegradable (BD) stent placement might preclude these issues.
Aims & Methods: This multicenter, randomized study compared the efficacy and safety of BD-stent (SX-ELLA, Ella-CS, Czech Republic) placement to endoscopic dilation in patients with RBES. Patients with 1-5 previous dilations were randomized to BD-stent placement or dilation. Power calculation estimated a sample size of 66 patients. Primary outcome was the number of endoscopic dilations for recurrent dysphagia within 3 and 6 months post-procedure. Secondary outcomes were time to recurrent dysphagia, time to first dilation, safety and QoL. Dysphagia scores were recorded daily for one month and monthly thereafter for one year.
Results: A total of 32 patients were randomized to BD-stent placement and 34 patients to ongoing dilation. Baseline patient demographics and lesion characteristics were similar between the two groups. Dysphagia scores significantly improved in both groups at 3, 6 and 12 months compared to baseline ($p < 0.001$ for all comparisons). In the BD-stent group, fewer dilations for recurrent dysphagia were required after 3 months (median: 0 [range 0-9] vs. 1 [range 011],$p < 0.001$), and fewer patients required endoscopic dilation (87.5% vs. 43.6%, $p < 0.01$). No differences between BD-stent placement and dilation were observed after 6 months for number of dilations (median: 1 [range 0-13] vs. 2 [range 0-13],$p = 0.40$) or for number of patients requiring dilation at 6 months (38.8% vs. 31.1%, $p = 0.05$) or 12 months (34.5% vs. 24.9%, $p = 0.24$). Time to the first episode of recurrent dysphagia was significantly longer in the BD-stent group compared to the dilation group (median: 95 days vs. 30 days, $p = 0.03$). Safety was not different between the two groups, with 8 procedure-related serious adverse events in each group ($p = 0.90$). Most important serious adverse events included esophageal perforation (n = 2) in the dilation group and fistula formation (n = 2) in the stent group. At 6 months, patients in the BD-stent group scored better on the health state scale (median: 80 vs. 70, $p = 0.03$) and more patients were able to perform normal levels of activity based on the WHO performance score (85.2% vs. 55.8%, $p = 0.04$), compared to the dilation group.
Conclusion: BD-stent placement in patients with RBES prolonged time to recurrent dysphagia and was associated with a higher QoL compared to ongoing endoscopic dilation, while safety parameters were not different. These results suggest that BD-stent placement can be considered at an early stage in the treatment algorithm of RBES.
Disclosure of Interest: D. Walter: None declared, M. van den Berg: None declared, M. Hirdes: None declared, F. Vleggaar: None declared, A. Repici: None declared, P. Deprez: None declared, B. Viedma: None declared, L. Lovat: None declared, B. Weusten: None declared, R. Bisschops: None declared, E. O'Leary Conflict with: Employee for Cook Research Incorporated, J. van Hooft Financial support for research: Cook Medical, P. Siersema Financial support for research: Cook Medical

OP070 FULL-THICKNESS PERORAL ENDOSCOPIC MYOTOMY (POEM) FOR THE TREATMENT OF SIGMOID-TYPE ACHALASIA: A COMPARATIVE STUDY OF CONVENTIONAL AND MODIFIED POEM

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Introduction: POEM treatment of Sigmoid-type esophagus, especially of type S2, is a big challenge due to the technically demanding procedures and high incidence of complications.
Aims & Methods: This work is aimed to explore the feasibility of POEM in treatment of S-type achalasia and to provide experiences in prevention of gas-related complications by using a modified POEM method.A total of 23 S-achalasia patients from August 2011 to June 2014 in our department were included in the present study. Among those patients, six patients including one S2-achalasia underwent conventional full-thickness POEM; while seventeen patients including three S2-achalasia adopted an modified full-thickness POEM with operation changes in a) Creating tunnel entry by longitudinal incision combining with bilaterally perpendicular dissection; b) presetting tunnel routes by endoluminally submucosal injection of dye solution during tunnel creating process; c) increasing the width of the submucosal tunnel. Procedure-related parameters and adverse events, symptom relief and manometry outcomes were collected before and during periodical follow-up.
Results: All the S-achalasia patients have successfully undertaken either conventional or modified full-thickness POEM. The overall treatment success was achieved in 95.6% (22 of 23 cases) during follow-up. The overall mean lower esophageal sphincter pressures (15 of 23 cases) were 38.91 ± 5.83 mmHg and 12.38 ± 3.76 mmHg before and after treatment ($P < 0.01$). The mean Eckardt score decreased from 6.67 ± 1.97 to 0.50 ± 0.55 ($P < 0.001$) by conventional method, and from 7.47 ± 1.67 to 0.76 ± 0.75 ($P < 0.001$) by modified method. No significant differences were shown in the operation time, mytomy length, pre- and post-treatment values of symptom scores between two methods. Yet compared to conventional method, modified POEM decreased gas-related complications from the occurrence rate of 100% (6 of 6 cases) to 11.8% (2 of 17 cases).
Conclusion: POEM is feasible, safe and effective in treatment of S-type achalasia, including S2. Modified POEM method could prevent occurrence of gas-related complications. Yet further experiences and long-term results are warranted.

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Disclosure of Interest: None declared

OP071 INDIVIDUALIZED CHOICE OF SUCTION METHOD INTO APPLICATION CAP OF OVER-THE-SCOPE CLIP SYSTEM: COMPARISON OF SIMPLE SUCTION VERSUS TWINGRASPER IN MULTICENTER EXPERIENCES

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Introduction: The efficacy of over-the-scope clip (OTSC) for GI defects has been described. A successful key of OTSC depends on secure suction into the application cap of target lesion. The suction method includes three methods; simple suction (SS), twingrasper (TG) accessory device, and Anchor device. It seems unclear what kind of suction method should be applied to the target lesion with how type of characteristics.
Aims & Methods: The aim of this study was to investigate better choice of suction methods by comparing SS versus TG in the management of GI defects. The retrospective comparative study at 5 medical centers involved 56 consecutive patients with OTSC placement, dividing into two groups: 14 cases in SS-Group or 42 in TG-group. The primary outcomes were technical (TSR) and clinical success rate (CSR), procedure time, complication rate. Secondarily, the TSR and CSR regarding each parameters; indications, maximum defect size (D, mm), duration from onset, and the combined parameters in each indications were compared.
Results: Significant differences were observed between the two groups in only mean procedure time (SS, 5.9 vs.TG, 14.1 min). The CSR of SS with D≦10, immediate or acute in refractory bleeding was 100%, suggesting better situation of convenient SS. The CSR, 78.6% of SS despite technical success (TSR, 100%) had a tendency to decrease due to delayed leakage, compared to TG (TSR, CSR; 88.1%), revealing that TG assist is desirable for leak and fistula with defect of whole layer. However, OTSC using TG had some limitations in situations with D > 20, chronic, refractory bleeding and fistula.
Conclusion: Individualized choice of the suction method in OTSC system plays the most important role for OTSC success. Considering the size of defect, and

duration from onset in each indications may contribute to the improvement of OTSC success.

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Disclosure of Interest: None declared

OP072 A COMPARISON OF TWO FULL-THICKNESS ENDOSCOPIC CLOSURES: OVER-THE-SCOPE-CLIP (OTSC) VERSUS KING CLOSURE (ENDOLOOP) IN A RANDOMIZED LONG-TERM EXPERIMENTAL STUDY

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Introduction: There are several tools for endoscopic closure of gastrointestinal perforations. We have shown that both over-the-scope-clip (OTSC) and KING closure (endoloop + clips) are safe and effective and provide full-thickness closure but OTSC clip demonstrated inferior histological short-term outcomes [1].
Aims & Methods: To compare long-term effectiveness and macroscopic and histologic quality of healing of perforation closed with OTSC or KING closure. The main outcomes were the effectiveness, complication rate and histological response.
We conducted a randomized experimental study with 16 minipigs (average weight 43.2 ± 11.2 kg). A standardized perforation was performed on the anterior sigmoid wall using a needle knife followed by a 2 cm balloon dilation. KING closure (n = 8) was attained by approximation of an endoloop fixed to the margins of perforation with endo-clips. OTSC method (n = 8) was executed by deploying nitinol OTSC (OVESCO) clip over the defect. Pigs underwent a control rectoscopy 8 months after the perforation closure to assess the macroscopic quality of healing. Then, autopsy was performed and the rectosigmoid was sent for histopathological assessment.
Results: All closures were completed successfully without air leaks. The duration of closure was similar in both techniques (OTSC 17.8 ± 7.6 min vs. KING 19.6 ± 8.8 min). We found one small polyp-like formation (6.3%) in the KING group at autopsy. All other closures (93.7%) were healed with a flat scar without the presence of any foreign material or signs of leakage. Microscopically, no inflammatory or other changes were observed after KING closure. In the OTSC group, however, ulcers involving lamina muscularis mucosae were present in 2 pigs (25%), cryptal abscesses in 3 pigs (38%) and significant neutrophil accumulation in 7 pigs (88%). Giant cell granulomas, bridging, dysplasia or abundant scarification were not observed in either group.
Conclusion: Both OTSC closure and KING closure offer a long-term reliable seal of perforations without stenosis or fistulas. KING closure provides histologically superior healing.

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2. Supported by a grant IGA NT-13634-4.

Disclosure of Interest: None declared

OP073 EFFECTIVENESS AND SAFETY OF ENDOSCOPIC RESECTION FOR RECTAL NEUROENDOCRINE TUMORS ACCORDING TO DIFFERENT RESECTION METHODS: A KASID MULTI-CENTER STUDY

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Introduction: Most rectal NETs can be treated by endoscopic resection because they are diagnosed at a small and early stage. However, optimal therapeutic methods have not been elucidated to date.
Aims & Methods: We are aimed to evaluate the effectiveness and safety of endoscopic resection for rectal NETs according to different resection methods through conducting a large, multicenter study. Patients with endoscopically resected rectal NETs, from January 2000 to November 2011 in 15 university hospitals were included in this study. Endoscopic resection methods were classified into three groups; (1) endoscopic mucosal resection (EMR) including conventional EMR methods; (2) modified EMR (mEMR) including EMR using a transparent cap (EMR-C), EMR using a ligation device (EMR-L), and precut EMR; (3) endoscopic submucosal dissection (ESD). End outcomes were determined by assessing resection margin status and complications.
Results: Of a total of 573 patients with rectal NETs, the mean age at diagnosis was 49.6 ± 11.6 years (male:female ratio = 1.4:1). The mean tumor size was 6.0 ± 3.3 mm (range 1.0 – 22.0 mm). Tumors were resected using conventional EMR (n = 369), EMR-L (n = 68), EMR-C (n = 41), precut EMR (n = 19), and ESD (n = 74). When classified into three groups, the tumor size was 6.2 ± 3.2, 4.7 ± 2.7, and 7.3 ± 3.9 mm in EMR, mEMR, and ESD group, respectively ($p < 0.001$). As for resection margin status, the complete resection rate of mEMR and ESD was superior to that of EMR ($p < 0.001$). However, in the overall complication rate including bleeding and perforation, there was no significant difference between groups.
Conclusion: On the basis of our results, as for en bloc resection and resection margin status, mEMR and ESD shows significantly superior efficacy compared to conventional EMR.
Procedure-related complications are independently associated with incomplete resection and deep invasion beyond submucosa, but not with treatment method.
Disclosure of Interest: None declared

MONDAY, OCTOBER 26, 2015 14:00–15:30
NASH: FROM BENCH TO BEDSIDE – ROOM E5

OP074 INCIDENCE AND RISK FACTORS FOR NON-ALCOHOLIC FATTY LIVER DISEASE IN AN URBAN, ADULT SRI LANKAN POPULATION – A COMMUNITY COHORT FOLLOW-UP STUDY

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Introduction: We previously reported a community prevalence of 33% for NAFLD in an urban, adult Sri Lankan population. We also found a significant association between patatin-like phospholipase domain containing 3 *(PNPLA3)* gene rs738409 polymorphism, and susceptibility to NAFLD in the same population, after testing 10 selected single nucleotide polymorphisms (SNPs) in a case-control study.
Aims & Methods: The aim of this study was to assess the incidence and risk factors for NAFLD in this population after seven years of follow-up. The study population consisted of 42-71-year-old adults, originally selected by age-stratified random sampling from electoral lists from Ragama, Sri Lanka. The target population was screened initially in 2007 and subsequently invited back for re-evaluation in 2014. On both occasions they were assessed using a structured interview, clinical and anthropometric measurements, liver ultrasound, and biochemical and serological tests. NAFLD was diagnosed on established ultrasound criteria for fatty liver (two out of three criteria: increased echogenecity of the liver compared to kidney and spleen, obliteration of the vascular architecture of the liver and deep attenuation of the ultrasonic signal), safe alcohol consumption (Asian standards: <14 units/week for men, <7 units/week for females) and absence of hepatitis B and C markers. Non-NAFLD controls were defined as subjects who did not have any of the ultrasound criteria for NAFLD. We also performed an updated case-control study to investigate associations of selected genetic variants with incident NAFLD [SNPs: *PNPLA3* (rs738409), *LYPLAL1* (rs12137855), *GCKR* (rs780094), *PPP1R3B* (rs4240624) and *NCAN* (rs2228603), *APOC3* (rs2854117 and rs2854116), *ADIPOR2* (rs767870) and *STAT3* (rs6503695 and rs9891119)].
Results: Of the 2985 original study participants, 2155 (72.2%) (1244 women and 911 men; mean age 59.2 years [SD, 7.7]) participated in the follow-up assessment. 1322 [mean age 58.9 years (SD, 7.6), 483 (53.0%) men and 839 (67.4%) women] had NAFLD. Out of 795 [466 (58.6%) women] participants who did not have NAFLD in the original study, 365 [226 (61.9%) women, mean age 58.6 years (SD, 7.9)] had developed NAFLD after 7 years, giving an annual incidence rate 6.6%. On multivariate analysis, increased waist circumference [OR 1.96(1.30 – 2.97), p = 0.001], BMI > 23 kg/m^2 [OR 2.93(1.99 – 4.30), $p < 0.001$] and raised plasma triglycerides (TG) [OR 1.49(1.03 – 2.13), p = 0.03] were independently predictive of incident NAFLD in this cohort, while raised BP and reduced

HDL, were not. In the updated association study involving 1310 cases and 427 controls, we found borderline association with NAFLD at two of the 10 candidate loci: rs4240624 at *PPP1R3B* and rs738409 at *PNPLA3* (one-tailed P = 0.044 and 0.033, respectively).
Conclusion: In this community cohort follow-up study in an urban, adult population in Sri Lanka, the annual incidence of NAFLD was 6.6%. Incident NAFLD was associated with features of the metabolic syndrome, and showed tendency of association at *PNPLA3* and *PPP1R3B* gene polymorphisms.
Disclosure of Interest: None declared

OP075 THE RECEPTOR TYROSINE KINASE MERTK IS INVOLVED IN THE HEPATIC FIBROGENESIS IN NAFLD

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Introduction: NAFLD comprises a spectrum of disease states, from steatosis (fatty liver) to non-alcoholic steatohepatitis (NASH) followed by progression to fibrosis, cirrhosis and hepatocellular carcinoma (1,2). Several genetic factors involved in NAFLD severity and progression have been identified through genome-wide association studies (GWAS) but their determination is still not sufficient to accurately predict the risk of progression of NAFLD. Mertk is a receptor tyrosine kinase with oncogenic properties that is often over-expressed or activated in various malignancies (3). In a recent GWAS study a SNP of Mertk (rs4374383 G > A) has been associated with fibrosis severity in patients with chronic hepatitis C (4), but currently there is no evidences on the involvement of Mertk in the hepatic fibrosis process.
Aims & Methods: Aim of this study was to assess the possible role of Mertk in the fibrogenic process in NAFLD. Genetic analyses were performed on specimens from patients, who underwent liver biopsy for suspected NASH without severe obesity. Human HSC were isolated from livers and cultured on plastic. The inhibitor used was UNC569 (5) C57BL6/J mice were treated with CCl4 for 6 weeks. Balb/C mice were fed with a methionine and choline deficient (MCD) diet for 8 weeks. Intrahepatic gene expression was assayed by qPCR.
Results: We found that Mertk rs4374383 AA genotype is associated with a lower prevalence of clinically significant fibrosis in patients with NAFLD and this polymorphism is associated with a decreased expression of Mertk. In murine models of hepatic fibrogenesis, we observed an increased hepatic expression of Mertk. In hepatic stellate cells (HSC) Mertk was found to be highly expressed and stimulation with a specific ligand, GAS6, resulting in a time-dependent activation of ERK1/2 and an enhancement of cell migration. Inhibition of Mertk induced apoptotic cell death of HSC. Finally analysis of the mRNA levels in liver specimens from patients with NAFLD, presenting different degree of liver fibrosis, showed that Mertk expression correlates with the score of fibrosis observed.
Conclusion: These data strongly suggest that Mertk could play an important role in fibrogenesis process and additional studies are needed to characterize this pathway in the pathogenesis of NAFLD.

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Disclosure of Interest: None declared

OP076 DUAL TARGETING OF MICRORNA-21 AND FXR AMELIORATES NAFLD PATHOGENESIS IN MICE

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Introduction: Non-alcoholic fatty liver disease (NAFLD) pathogenesis remains incomplete and effective therapeutic approaches are urgently needed. We and others identified microRNAs (miRNA/miRs) as novel pathogenic factors in NAFLD. In addition, nuclear receptors (NRs), namely peroxisome proliferator-activated receptors (PPARs) and the farnesoid X receptor (FXR) are currently under scrutiny as promising therapeutic targets for non-alcoholic steatohepatitis (NASH). In that regard, interim results from the NIH-funded FLINT clinical trial showed that obeticholic acid (OCA), a potent FXR agonist, has significant beneficial effects on NASH-induced liver damage.
Aims & Methods: In this study, we aimed to: 1) elucidate the role of miR-21 during NAFLD pathogenesis in mice, including modulation of PPARα, a miR-21-direct target; and 2) evaluate the therapeutic potential of a dual NR-targeting approach, namely activation of PPARα and FXR through miR-21 inhibition and OCA administration, respectively. C57BL/6 wild type (WT; n = 24) and miR-21 knockout (KO; n = 24) mice were fed either a standard diet (SD; n = 12) or a fast food diet (FF; n = 12) for 25 weeks. Six animals from each group were fed with OCA 10 mg/kg/day (provided by Intercept Pharmaceuticals, Inc.). In parallel, human liver biopsies were obtained from morbid obese NAFLD patients at different disease stages (n = 28). Liver samples were processed for histological analysis and quantification of miR-21 and pro-inflammatory cytokine expression by qRT-PCR, as well as NRs protein levels by immunoblotting.
Results: Our results showed that, after 25 weeks, WT FF-fed mice displayed increased liver/body weight ratio, macrovesicular steatosis and inflammatory infiltrates. Expression levels of TNF-α, IL-6, TLR4, IL-1β and NLRP3 were increased, consubstantiating steatohepatitis. Further, WT FF-fed mice exhibited increased miR-21 levels and decreased expression of the miR-21 target PPARα, a correlation also found in patients, and further increasing from steatosis to less and more-severe NASH. WT FF + OCA-fed animals displayed decreased steatosis and, interestingly, lower levels of miR-21 compared with WT FF-fed mice. In turn, KO FF-fed mice exhibited significantly reduced liver inflammation, as well as steatosis severity, in parallel with increased PPARα, comparing with WT FF-fed mice. Importantly, improvement of these histological, biochemical/metabolic and inflammatory parameters was augmented in KO FF + OCA-fed mice.
Conclusion: In conclusion, our results indicate that miR-21 downregulation, likely leading to increased PPARα, together with FXR activation by OCA, strongly ameliorate NASH in mice, highlighting the therapeutic potential of novel dual-targeting therapies for human NAFLD. (Supported by PTDC/BIM-MEC/0873/2012, SFRH/BD/88212/2012, SFRH/BD/91119/2012 and SFRH/BD/104160/2014, FCT, Portugal).
Disclosure of Interest: None declared

OP077 CXCL10 MEDIATES THE IMPAIRMENT OF AUTOPHAGOSOME-LYSOSOME SYSTEM THROUGH LYSOSOME DYSFUNCTION IN STEATOHEPATITIS

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Introduction: Autophagosome-lysosome system plays a crucial role in non-alcoholic steatohepatitis (NASH) progression. We recently demonstrated that chemokine CXCL10 is a key inflammatory mediator in NASH development. However, it is uncertain whether CXCL10 regulates autophagosome-lysosome system in the development of NASH.
Aims & Methods: We aim to delineate the underlying mechanism of autophagosome-lysosome impairment in CXCL10 induced NASH. The role of CXCL10 in autophagosome-lysosome system was investigated using CXCL10-knockout (KO) and C57BL/6 wild type (WT) mice. The effect of CXCL10 inhibition on autophagic flux was illustrated in C57BL/6 WT mice and hepatocytes (AML-12 and HepG2) administered with neutralizing anti-CXCL10 or control monoclonal antibodies (mAb). Lysosome function was assayed by LysoTracker Red staining and protein expression of lysosomal membrane glycoproteins. Mitochondrial function was monitored by flow cytometric analysis of MitoTracker staining and reactive oxygen species (ROS) detection.
Results: Impaired autophagic flux as indicated by accumulation of p62 and LC3-II proteins was significantly more pronounced in WT mice with severe steatohepatitis than in CXCL10-KO mice with mild steatohepatitis. Concordantly, autophagic flux impairment could be restored by CXCL10 inhibition using neutralizing anti-CXCL10 mAb both in AML-12 hepatocytes with steatohepatitis changes induced by methionine and choline-deficient medium and in HepG2 hepatocytes treated with palmitic acid. CXCL10 inhibition successfully restored autophagic flux not only in hepatocytes but also in mouse livers with steatohepatitis. Interference with autophagosome-lysosome fusion by bafilomycin A1 abolished the effect of anti-CXCL10 mAb in AML-12 cells with steatohepatitis, indicating the impairment of autophagic flux at the late stage by CXCL10. LysoTracker Red staining further demonstrated that anti-CXCL10 mAb treatment in AML-12 cells could restore lysosome acidification. The impaired lysosome function was further confirmed by reduced protein expression of lysosomal membrane glycoproteins (LAMP-1 and LAMP-2) in mice with genetic CXCL10 deletion and pharmacological CXCL10 inhibition. Moreover, CXCL10-induced autophagosome-lysosomal impairment was associated with ROS production, mitochondria dysfunction, polyubiquitinated proteins accumulation and endoplasmic reticulum stress.
Conclusion: We demonstrate for the first time that CXCL10 inhibits autophagic flux in the pathogenesis of steatohepatitis through eliciting lysosome dysfunction. CXCL10-induced lysosome impairment promotes experimental

steatohepatitis through mitochondria dysfunction and ubiquitinated protein accumulation.
Disclosure of Interest: None declared

OP078 GALECTIN-9 SUPPRESSES NONALCOHOLIC STEATOHEPATITIS-ASSOCIATED HEPATOCELLULAR CARCINOMA

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Introduction: Non-alcoholic steatohepatitis (NASH) is one of the most common causes of chronic liver disease and is considered to be a causative factor of cryptogenic cirrhosis and hepatocellular carcinoma (HCC). So far, various kinds of drugs have been used for the treatment of NASH, but these trials resulted in poor outcomes. Galectin-9 (Gal-9), a soluble β-galactoside-binding animal lectin, attenuates the inflammation via negative regulation of Th1-mediated immune responses. However, little is known about the effect for liver inflammation, and hepatocarcinogenesis.
Aims & Methods: The aim of this study is to determine therapeutic effects of Gal-9 during NASH-associated HCC using Stelic Animal Model (STAM) mice, a validated animal model for NASH-associated HCC, and Gal-9 knockout mice. Four-week-old male STAM were divided into 2 experimental groups and fed as follows: 1) high-fat diet (HFD) (control group); 2) HFD injected with 90 μg/mouse/day of mouse galectin-9 three times a week (Gal-9-treated group). After 12 weeks, mice were sacrificed and blood samples, livers, and bone marrow were collected. Samples were subjected to clinical parameters, histological study, mRNA and protein expressions for multiple genes. We also performed same procedure for Gal-9 knockout mice.
Results: Gal-9 significantly decreased transaminases and alkaline phosphatase. Histological examination revealed marked reduction of steatosis, ballooning, and inflammation in Galectin-9-treated group. In addition, mice treated with Gal-9 developed smaller area of liver fibrosis following fibrosis-related mRNA up-regulations. Furthermore, as for bone marrow derived macrophages, TNFα and CD14 were up-regulated in Gal-9 knockout mice as compared to those in control mice ($P < 0.05$). Moreover, Gal-9 significantly inhibited total number and size of HCC.
Conclusion: Gal-9 improved the clinical and histological development of NASH and reduced the number and size of HCC. Thereby, Gal-9 might be a potential therapeutic target for the treatment of NASH-associated HCC.

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Disclosure of Interest: None declared

OP079 PREDICTIVE VALUE OF FATTY LIVER INDEX FOR NON-ALCOHOLIC FATTY LIVER DISEASE: A POPULATION BASED STUDY

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Introduction: Fatty liver index (FLI) is a simple measure calculated based on body mass index (BMI), waist circumference (WC), and triglyceride (TG) and gamma glutamyl transferase (GGT) levels. The primary aim of this study is to determine the predictive performance of this index in the diagnosis of nonalcoholic fatty liver disease (NAFLD).
Aims & Methods: The data of approximately 5900 subjects, 16 years of age or older, participating in a baseline cohort study was used in the present study. Univariable and multivariable logistic regression analyses were conducted to determine the association between FLI and NAFLD. To determine the predictive performance of FLI in the diagnosis of NAFLD, ROC analysis was performed by which the optimal cutoff points of FLI were also determined based on calculated maximum values of the Youden index.
Results: The prevalence of NAFLD was shown to be 39.5% among men and 43.6% among women in this study. FLI was strongly associated with NAFLD, so that a one unit increase in FLI increased the chance of NAFLD 0.059% (OR = 1.059, [95%CI = 1.053-1.063]). Although FLI displayed accurate performance in the diagnosis of NAFLD (AUC = 0.868 [95% CI = 0.858 - 0.879]), its performance showed a lack of precision regarding WC (p-value = 0.2676). The optimal cutoff points of FLI in the diagnosis of NAFLD were 46.9 in men (sensitivity = 0.823, specificity = 0.775, Youden index = 0.598) and 53.7 in women (sensitivity = 0.824, specificity = 0.771, Youden index = 0.595).
Conclusion: FLI was shown to be an acceptable predictive measurement in the diagnosis of NAFLD; however, WC as a simple and more accessible index revealed a similar performance.
Disclosure of Interest: None declared

MONDAY, OCTOBER 26, 2015 14:00-15:30
NOVEL APPROACHES TO COLORECTAL CANCER - ROOM E6

OP080 DELTA-LIKE 4 INHIBITION HAS A CUMULATIVE EFFECT WITH ANTI-EGFR THERAPY ON APCMIN/+ MOUSE TUMOR INITIATION

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Introduction: Colorectal cancer (CRC) is the third most common malignancy and mutations in the *Adenomatous polyposis coli (Apc)* gene are needed for the initiation of the hereditary CRC familial adenomatous polyposis (FAP) syndrome and most sporadic CRC (Fearnhead, Wilding et al. 2002). One of the strategies to treat CRC is the anti-epidermal growth factor receptor (EGFR) therapy (Vokes and Chu 2006). Notch signalling is another important pathway in CRC development (Qiao and Wong 2009) and it has been demonstrated that Delta like 4 (Dll4)/Notch is a key regulator of tumor angiogenesis (Liu, Fan et al. 2014). There is a cross talk between Notch and EGFR signaling in several types of cancer (Dai, Ma et al. 2009). However this was never demonstrated in CRC.
Aims & Methods: Our aim was to confirm the effect of Dll4 inhibition in the $Apc^{Min/+}$ mouse model of CRC (Yamada and Mori 2007) and to evaluate if the combination of anti-Dll4 and anti-Egfr therapies seemed beneficial in this setting. For that we tested the dominant-negative fusion protein Dll4-Fc alone and in combination with the anti-Egfr tyorsine kinase inhibitor erlotinib hydrochloride in the $Apc^{Min/+}$ model.
Results: We found that in the $Apc^{Min/+}$ model, besides the known role on angiogenesis, Dll4 seems to have an additional effect maintaining the proliferative state and inhibiting the differentiation of tumor-initiating cells. Furthermore Dll4-Fc associated to an anti-Egfr therapy had a cumulative effect inhibiting the tumor initiation and an additional role inhibiting the $Apc^{Min/+}$ tumor volume. Moreover anti-Egfr therapy led to Notch activation, while Dll4-Fc inhibited Egf/Egfr pahtway in the tumors.
Conclusion: Our results indicate that Dll4 inhibition, and mainly the association of anti-Dll4 therapy with anti-Egfr treatment, should be considered to treat CRC at initial stages and as chemoprevention on patients predisposed to this disease such as FAP patients.

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Disclosure of Interest: None declared

OP081 GRP78 HETEROZYGOSITY IN THE INTESTINAL EPITHELIUM PROTECTS AGAINST ADENOMA FORMATION

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Introduction: In the intestinal epithelium, differentiation of healthy stem cells is required for normal organ function. Perturbed stem cell differentiation underlies tumorigenesis. We have previously shown that endoplasmic reticulum (ER) stress, by knockout of the critical chaperone *Grp78*, results in forced differentiation of intestinal epithelial stem cells and may thereby protect against tumorigenesis. ER stress-induced stem cell differentiation occurs through activation of the unfolded protein response (UPR). However, since no stem cells remain upon deletion of *Grp78*, this situation is incompatible with normal organ function. Previously, *Grp78* heterozygosity has been used to induce moderate levels of ER stress. We set out to determine the phenotype of heterozygous deletion of

intestinal epithelial *Grp78*. In addition, this model enables long-term recombination and analysis of intestinal tumorigenesis.

Aims & Methods: For inducible heterozygous deletion of *Grp78*, we crossed $Grp78^{fl/+}$ mice with inducible intestinal epithelium specific *Cre deleter* mice ($Ah1^{Cre}$ or $Villin^{CreERT2}$) to obtain $Grp78^{fl/+}$ animals with heterozygous recombination in intestinal epithelial cells (IEC; $Grp78^{fl/+(IEC)}$). For adenoma studies, we used heterozygous intestinal epithelium specific deletion of tumor suppressor gene *Apc*, which results in development of multiple adenomas throughout the intestine and colon ($Apc^{fl/+(IEC)}$). To monitor recombination efficacy, we crossed *LacZ* reporter alleles into all mice. Upon staining with X-gal, all recombined cells become blue.

Results: We first analyzed the phenotype of $Grp78^{fl/+(IEC)}$ animals and *Grp78* wildtype littermate controls during homeostasis. Counting X-gal stained sections, recombination in all animals was excellent with >95% of crypts recombined. Compared to controls, proliferation in $Grp78^{fl/+(IEC)}$ animals was unaltered, as judged by BrdU incorporation. Additionally, gene-expression analysis by means of quantitative RT-PCR for intestinal epithelial stem cell markers showed no change in *mRNA* levels of stem cell markers *Lgr5*, *Olfm4* or *Ascl2* compared to controls. We found no changes in the expression of a set of UPR target genes showing that heterozygous deletion of *Grp78* has no observable phenotype in a situation of homeostatic epithelial turn over. We next analyzed adenoma numbers in $Grp78^{fl/+}$-$Apc^{fl/+(IEC)}$ animals and $Apc^{fl/+(IEC)}$ controls. After 100 days, $Grp78^{fl/+}$-$Apc^{fl/+(IEC)}$ animals had a marked reduction in adenoma burden compared to $Apc^{fl/+(IEC)}$ mice (1.43 vs. 3.33; $P = 0.0054$).

Conclusion: Heterozygous deletion of *Grp78* from the intestinal epithelium results in unaltered proliferation. Maintenance of stemness in these animals is not affected as judged by RNA expression of stem cell markers. However, adenomagenesis is markedly reduced in compound heterozygous $Grp78^{fl/+}$-$Apc^{fl/+(IEC)}$ animals. These results show that induction of moderate levels of ER stress by perturbation of a single *Grp78* allele results in protection against intestinal tumorigenesis without affecting the healthy stem cell pool.

Disclosure of Interest: None declared

OP082 DELTA-LIKE 4/NOTCH SIGNALING BLOCKADE INHIBITS THE DEVELOPMENT OF IBD-ASSOCIATED COLORECTAL CANCER IN MOUSE MODEL

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Introduction: Colorectal cancer (CRC), one of the most frequent cancers, can develop as a complication of inflammatory bowel diseases (IBD) (Mattar, Lough et al. 2011). The Notch pathway plays a central role in intestinal homeostasis and in CRC development (Miyamoto and Rosenberg 2011). We know that Dll4/Notch signaling is a key regulator of tumor angiogenesis (Liu, Fan et al. 2014). However a putative role for Dll4 in the development of IBD-derived CRC (colitis associated cancer or CAC) has yet to be addressed.

Aims & Methods: Our objective was to analyze Dll4/Notch expression and the effect of Dll4/Notch inhibition in IBD and in CAC. We assessed the expression of Dll4 and other Notch pathway members by immunohistochemistry and the effect of Dll4 inhbition using genetical ($Dll4^{+/-}$) and pharmacological (Dll4-Fc) strategies in the azoxymethane plus dextran sodium sulphate (AOM + DSS) IBD-associated CRC (CAC) mouse model (Neufert, Becker et al. 2007).

Results: Dll4/Notch expression was strongly detected in IBD and in CAC. The inhibition of Dll4 led to a significant reduction in the average number and volume of tumors by several mechanisms. Specifically, Dll4 blockade promoted immature and dysfunctional tumoral angiogenesis and apoptosis and inhibited tumor proliferation. Additionally, it decreased the number of Leucine-rich G-protein coupled Receptor 5 (Lgr5) positive tumor stem cells and promoted Paneth and goblet cell differentiation. Furthermore the observed inhibition of carcinogenesis was associated with reduced colitis and tumor inflammation by decreasing the number of immune cells (macrophages, dendritic cells, neutrophils and helper and cytotoxic T cells) and the expression of important inflammatory mediators, such as *iNos*, *Cox-2*, *Tnf-α*, *Il-6, Il-17a, Ifn-γ* and *Il-4*. Dll4 inhibition also decreased the expression of the CAC promoter *Nfkb2,* upregulated the CAC inhibitor *Tgf-β,* increased the number of regulatory T cells and inhibited the proinflammatory M1 macrophage polarization in the tumors.

Conclusion: Our findings show that additionally to the known Dll4 blockade action on angiogenesis, it also seems to inhibit CAC initiation and progression through its effect on reducing inflammation and promoting stem cell differentiation. Furthermore, we believe that this therapy could be also useful to treat IBD and therefore to prevent CRC initiation.

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Disclosure of Interest: None declared

OP083 MEK5/ERK5 SIGNALLING CONTROLS COLON CANCER CELL SENSITIVITY TO 5-FLUOROURACIL THROUGH A P53 DEPENDENT MECHANISM

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Introduction: We have recently shown that MEK5 and ERK5 expression is increased in human colon adenomas and adenocarcinomas, and that ERK5 expression correlates with tumor stage progression. Moreover, ERK5 has been suggested to play a role in the suppression of p53 function. In turn, p53 is known to be a major determinant of the balance between apoptosis and cell cycle progression following exposure to 5-fluorouracil (5-FU), the most widely used chemotherapeutic agent for colon cancer treatment. Thereby, we hypothesized that MEK5/ERK5 signalling inhibition could sensitize colon cancer cells to 5-FU-induced cytotoxicity through a p53-dependent mechanism.

Aims & Methods: In the present study, we aimed to investigate the role of MEK5/ERK5 signalling in colon cancer cell proliferation and sensitivity to 5-FU. For this purpose, HCT116 and SW620 cell lines expressing a constitutively active (CA) or a dominant negative (DN) form of MEK5 were produced by lentiviral transduction, followed by sorting of stably transduced cells. Alternatively ERK5 activity was blocked in HCT116 p53 wild-type ($p53^{+/+}$) and null ($p53^{-/-}$) isogenic cell lines using the pharmacological inhibitor XMD8-92.

Results: Our results demonstrate that CAMEK5 increased cell proliferation ($p < 0.05$), as well as KRAS expression ($p < 0.01$), in both HCT116 and SW620 cells. In turn, 5FU exposure markedly decreased the levels of endogenous KRAS/MEK5/ERK5 expression and/or activation ($p < 0.05$). In the HCT116 model, DN-MEK5 increased cell death following 5-FU exposure, associated with increased caspase-3/7 activation and apoptosis ($p < 0.05$). Conversely, CA-MEK5 reduced 5-FU-induced cytotoxicity and apoptosis ($p < 0.05$). Moreover, DN-MEK5 increased the expression of p53 ($p < 0.05$) and its transcriptional targets p21 and Puma ($p < 0.01$). Interestingly, ERK5 inhibition by XMD8-92 increased the response of HCT116 $p53^{+/+}$ cells to 5-FU ($p < 0.05$), but failed to sensitize HCT116 $p53^{-/-}$ cells to the cytotoxic effects of this chemotherapeutic agent, suggesting a p53-dependent mechanism mediating 5-FU sensitization following ERK5 inhibition. Finally, ERK5 inhibition by XMD8-92 increased the antitumoral effects of 5FU in a HCT116 subcutaneous xenograft model ($p < 0.05$).

Conclusion: Overall, our results indicate that MEK5/ERK5 pathway overactivation may contribute to CC aggressiveness and chemoresistance, suggesting ERK5-targeted inhibition via siRNA, miRNA or small-molecule inhibitors may provide a promising therapeutic approach for CC treatment.

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Disclosure of Interest: None declared

OP084 SUCCESSFUL SELECTIVE ERADICATION OF COLORECTAL CANCER CELLS BY ADENOVIRUS-BASED DELIVERY OF TOXINS

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Introduction: *K-Ras* gene mutation is an early event in the development of colorectal cancer (CRC) and occurs in ~50% of CRC cases. We propose a strategy that exploits the Ras hyperactive pathway, rather than inhibiting it as was tried and failed many times. We have previously reported that recombinant adenovirus, carrying a pro-apoptotic gene under the regulation of Ras-responsive elements (Ets/AP1), suppressed the growth of cancer cells displaying hyperactive K-Ras (*Biomed Pharm,* 2005, *Cancer Gene Ther,* 2012, *Exp Cell Res,* 2012). TA systems are evolutionarily successful entities that are prevalent in lower organisms and play important roles in a diverse range of cellular activities

Aims & Methods

Aim: To establish a tight control and improved ras responsive element based on the bacterial MazEF system.

Methods: Efficient vectors for cancer-directed gene delivery were constructed and cloned into a ''first generation'' ΔE1/ΔE3 human type-5 adenoviral-vector. Virus particles were produced, their titer was calculated by the End-Point Dilution Assay (EPDA) and their potency was tested. Cell death was measured qualitatively by using the fluorescent microscopy and colony formation assay, and was quantified by MTT. FACS analysis using annexin V and RedDot2 dyes was performed for measuring apoptosis and dead cells, respectively. *In vivo* tumor formation was measured in xenograft model. Ad-Py4-SV40-MazEF and

Ad-ΔPY4-CMV-MazEF viruses (1×10^9pfu) or PBS were administrated intraperitoneal twice with a 3-day interval between injections.
Results: Adenovirus therapy induced massive cell death, in a dose-dependent manner; 73% with a titer of 10 MOI in cells with activated K-Ras as compared to 22% in tumor cells having the WT K-Ras. The cytotoxic effect was confirmed qualitatively by colony formation assay. In the absence of K-ras-responsive DNA element increase expression of MazE, the anti-toxin, protected normal cells from any possible internal or external leakage of the system and confirmed the selectivity, specificity and safety of the targeting system. FACS analysis confirmed massive cell death, 55% apoptosis and 82% dead cells, following infection with the full toxin-antitoxin encoding viruses. Control viruses lacking the K-ras responsive element a modest toxicity was seen (18% and 10%, respectively). Impressive tumor shrinkage was demonstrated *in vivo* following treatment with Ad-Py4-SV40-MazEF-encoding adenovirus (61%) without any toxic or side effects. Ad-ΔPY4-SV40-MazEF treated mice (control group) tumor volume was reduced only by 27% ($P < 0.05$). No growth inhibition was seen following injection of PBS.
Conclusion: A proof-of-concept for a novel cancer gene therapy by exploiting aberrant K-Ras hyperactive pathway was successfully demonstrated. The lack of toxicity holds promise for effective and safe therapy of human cancers carrying K-Ras mutations.
Disclosure of Interest: None declared

OP085 CONTRIBUTION OF MIRNA-143 AND MIRNA-145 TO CETUXIMAB-MEDIATED CELLULAR CYTOTOXICITY IN COLON CANCER CELLS

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Introduction: Only 10-20% patients with metastatic colorectal cancer benefit from cetuximab treatment. miRNAs, regulators of gene expression, have been associated with differential chemosensitivity in numerous cancer types. miR-143 and miR-145 are reported as downregulated in colon cancer, and their forced expression promotes apoptosis and suppresses tumorigenesis. In this context, we hypothesise that miR-143 and miR-145 may play a role in modulating cell sensitivity to cetuximab-induced apoptosis.
Aims & Methods: We aimed to evaluate the effect of miRNA-143 and miRNA-145 overexpression in the sensitivity of colon cancer cells to cetuximab-mediated cellular cytotoxicity, and its role in cetuximab-induced apoptosis. We produced miR-143, miR-145 and empty vector control overexpressing cell lines in KRAS mutant HCT116 cells, and evaluated viability and proliferation of cells exposed to cetuximab. Further, cetuximab-mediated cellular cytotoxicity was evaluated using the xCELLigence system and LDH assays, in cells exposed to cetuximab, and/or peripheral blood mononuclear cells (PBMCs) isolated from human healthy donors as effector cells. Apoptosis was detected by Guava Nexin flow cytometry assay, evaluation of nuclear morphology following Hoechst staining, and by caspase-3/7 activity.
Results: Our results show that miR-143 and miR-145 overexpression sensitized HCT116 colon cancer cells to cetuximab, resulting in 40% reduction of cetuximab IC_{50}, compared to control ($p < 0.01$), and also reduced cell proliferation and migration ($p < 0.05$). Overexpression of miR-143 and miR-145 triggered cetuximab-mediated cellular cytotoxicity ($p < 0.01$) by increasing apoptosis, displaying increased nuclear fragmentation, caspase-3/7 activation and PARP cleavage ($p < 0.01$). Following rituximab (anti-CD-20 antibody) and PBMCs treatment, no antibody dependent cellular cytotoxicity was seen in HCT116-derived cells ($p < 0.01$). In addition, overexpression of miR-143 negatively regulated Bcl-2 protein, which was further reduced upon treatment with cetuximab and PBMCs in cells overexpressing miR-143 and miR-145 ($p < 0.01$). Further, Bcl-2 silencing reduced HCT116 cell viability with a concomitant increase in cell death and cetuximab-mediated cellular cytotoxicity, compared to control siRNA ($p < 0.05$). Moreover, inhibition of granzyme B, a serine protease involved in effector cell-mediated granule secretory pathway, abrogated cetuximab-mediated cellular cytotoxicity, reducing caspase-3/7 activity in HCT116-derived cells ($p < 0.01$). In turn, caspase inhibition reduced the cytotoxic effect of PBMCs and cetuximab in HCT116 cells overexpressing miR-143 and miR-145 ($p < 0.01$).
Conclusion: Collectively, restoration of miR-143 and miR-145 could sensitize cancer cells to cetuximab by stimulating cells for apoptosis induced by cetuximab-mediated cellular cytotoxicity.
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Disclosure of Interest: None declared

MONDAY, OCTOBER 26, 2015 14:00–15:30
OBESITY: POTENTIAL SOLUTIONS – ROOM B3

OP086 IMPACT OF A 2-WEEK VERY LOW CALORIE DIET ON FATTY ACID SENSING AND TRANSPORT, INCRETIN HORMONES AND LIPID PROFILE IN MORBIDLY OBESE HUMANS

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Introduction: Human obesity is associated with increased expression of the fatty acid (FA) transporter CD36 in the small intestine but reduced expression of the G-protein coupled FA receptor GPR119 (Little et al. *AJP* 2014). We previously showed that a two-week very low-calorie diet (VLCD) reduced expression of small intestinal sweet taste receptors and glucose transporters in the morbidly obese (Nguyen et al. *EUGW* 2014, abstract).
Aims & Methods: This study examined the effects of VLCD on small intestinal FA sensors and CD36, as well as incretin hormones, lipid profile and body weight in the morbidly obese. 10 non-diabetic, morbidly obese subjects (2M:8F; 45 ± 3yrs, BMI: 46 ± 3kg/m^2) were studied before and after a 2 week VLCD (750kcal/day). On each occasion, endoscopic duodenal biopsies were collected at baseline to assess relative expression of CD36, free FA receptors (FFAR) 1, 2, 3 and 4 transcripts by QT-PCR. Blood glucose and plasma concentrations of glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), and insulin were also measured over 270 mins following an intraduodenal (ID) glucose infusion (30 g over 30 min). Insulin resistance was assessed by HOMA-IR score.
Results: Expression of CD36 ($-22 \pm 7\%$; $P = 0.03$), body weight (-5.6 ± 0.5kg, $P < 0.001$), plasma low density lipoprotein (LDL: -4.8 ± 2.1 μM; $P = 0.001$) and triglycerides (-36.3 ± 11.8μM; $P = 0.10$), as well as ID glucose-stimulated insulin (-4.6 ± 0.4; $P = 0.03$) and GIP (-4.6 ± 0.4; $P = 0.03$) were lower after 2 weeks VLCD, but plasma high density lipoprotein (HDL: $+45.2 \pm 8.5$μM; $P = 0.02$) was increased. There were no differences in the expression of FFAR 1, 2, 3, and 4, or ID glucose-stimulated plasma GLP-1 concentration after VLCD. The reduction in CD36 expression correlated with the reduction in plasma insulin ($r = 0.61$; $P = 0.04$) and HOMIR score ($r = 0.57$, $P = 0.05$), whilst the changes with plasma GIP correlated positively with the changes in body weight ($r = 0.72$; $P = 0.01$), plasma LDL ($r = 0.63$; $P = 0.03$) and inversely with HDL ($r = -0.67$; $P = 0.02$).
Conclusion: This study is the first to show that dietary intake can alter transcriptional control of the small intestinal FA transporter CD36 in morbidly obese subjects. Reduced CD36 expression after VLCD was linked to improved insulin resistance, while the reduction in plasma GIP may be important in mediating the improvement in lipid profile and body weight.
Disclosure of Interest: None declared

OP087 A RANDOMIZED CONTROLLED MULTICENTER STUDY OF AN INCISIONLESS OPERATING PLATFORM FOR PRIMARY OBESITY (POSE) VS. DIET-EXERCISE ALONE: THE MILEPOST STUDY

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Introduction: ***Pose***™ is a minimally invasive procedure used to treat Class I and II obesity. During the procedure, an endoscopist or bariatric surgeon per-orally places full-thickness plications in the gastric fundus and distal body to modify gastric capacity and function. The effect of these full thickness plications is believed to reduce fundal accommodation, accelerate the passage of food from fundus to antrum, and alter antral motility, thus slowing total gastric emptying. By so doing, the patient experiences a feeling of fullness sooner and may stay full longer. The purpose of this study was to compare safety, satiety, and weight loss outcomes of subjects undergoing ***Pose*** plus diet and exercise to those following diet and exercise alone.
Aims & Methods: A prospective, multi site, open label, randomized controlled trial was conducted in 3 EU countries. Following Ethics approval, 44 subjects (mean age 38) were enrolled and randomized with baseline BMIs between 30 to 40 in a 3:1 (treatment: control) ratio. The treatment group received ***Pose*** with diet and exercise guidance. The control group received diet and exercise guidance only. Following the procedure, diet was advanced to full solids over 4-6 weeks to allow time for suture plication healing. The control group was instructed to follow the same diet progression up through 6 weeks post randomization. After 6 weeks, all subjects were counseled to follow a diet that provides a specified maximum number of calories (1500-1800) with a targeted amount of protein and minimum quantity of liquids throughout the duration of the study. Both groups were followed at regular intervals (1 week post-procedure or randomization and at 1, 2, 3, 6, 9, and 12 months. Primary outcome measures were: change in mean % total body weight loss (TBWL) (6 and 12 months post randomization) and changes in liquid gastric capacity from baseline at 2, 6, and 12 month time points. To evaluate changes in capacity, a validated satiety test was employed to measure the volume of nutritional drink ingested by the subject and time to reach satiation. At the 12 month time point the control subjects can choose active treatment if they have remained in the study and complied with the follow-up visit schedule.
Results: Groups were comparable (BMI 36.2 treatment vs 37.1 control). There was a significant reduction in mean %TBWL in treatment 12.5% ($n = 31$) versus control 4.6% ($n = 9$) at 6 months ($p < .003$). Gastric capacity change is statistically significant for the treatment group between baseline and 6 months ($p < .001$) but not for the control group ($p = .103$). There were no serious adverse events related to device or procedure.
Conclusion: ***Pose*** provides a safe and superior weight loss solution over diet and exercise alone. The significant reduction in gastric capacity tolerated at 6 months in the treatment group provides ongoing evidence to support how ***Pose*** can affect satiety through durably impacting gastric anatomy and function.
Disclosure of Interest: R. Turro Financial support for research: USGI Medical, J. W. Greve Financial support for research: USGI Medical, K. Miller Financial support for research: USGI Medical

OP088 GASTRIC MUCOSAL DEVITALIZATION PROMOTES WEIGHT LOSS AND IMPROVES METABOLIC PROFILE: A POTENTIAL ENDOSCOPIC OBESITY THERAPY

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Introduction: The gastric mucosa is increasingly recognized as an important regulator of hunger and food intake. This is evidenced by studies demonstrating that the effects of vertical sleeve gastrectomy (VSG) are independent of gastric restriction and weight loss. Therefore, could a method of selectively ablating the gastric mucosa be a potential metabolic therapy?

Aims & Methods

Aims: To investigate whether gastric mucosal devitalization can affect weight, lipid metabolism and glucose homeostasis in a diet induced rat model of obesity.

Methods: Four week old male Sprague-Dawley rats received a high fat diet (HFD) for 11 weeks to induce a previously validated obesity phenotype. Rats were randomized into 3 groups: APC, VSG and sham. A rat model of gastric mucosal devitalization was developed by opening and mobilizing the stomach and using argon plasma coagulation (APC) to ablate 80% of the gastric mucosa. VSG was accomplished by performing a J-shaped resection of 80% of the stomach. Sham rats received a laparotomy and mobilization of the stomach. HFD was resumed at day 2 ad libitum for another 54 days.

Results: APC rats had a significant reduction in body weight as well as visceral and subcutaneous adiposity compared with sham rats. Furthermore, APC rats had a significant reduction in triglycerides and total cholesterol (Table 1). Total free fatty acid levels were significantly reduced in APC compared with sham rats. Fasting glucose, fasting insulin and insulin resistance (HOMA-IR) were significantly reduced in APC compared with sham rats (Table 1). We found that compared to sham, APC rats had a significant lowering of daily food intake. Energy expenditure (assessed by body temperature measurement) was similar between the APC and sham rats. The aforementioned findings were also seen when VSG was compared with sham rats (Table 1). Therefore, these results indicate that a therapy selectively targeting the gastric mucosa can reduce weight, decrease food intake, improve lipid metabolism and improve glucose homeostasis in the absence of gastric restriction.

8 weeks post op	Sham N = 20	APC N = 20	VSG N = 20	P
Body weight [g]	646 ± 32	509 ± 56 *	571 ± 29 *	0.023
BMI [g/cm2]	0.81 ± 0.02	0.72 ± 0.05 *	0.76 ± 0.02 *	0.036
Fat mass visceral [g]	25.5 ± 8.8	9.9 ± 5.4 *	12.8 ± 6.8 *	ns
Fat mass subcutaneous [g]	16.1 ± 2.2	8.9 ± 3.94 *	12.3 ± 2.0 *	ns
Triglyceride [mmol/L]	1.67 ± 0.99	0.71 ± 0.25 *	0.86 ± 0.52 *	ns
Total Cholesterol [mmol/L]	3.82 ± 1.29	2.24 ± 0.38 *	2.11 ± 0.4 *	ns
LDL Cholesterol [mmol/L]	1.15 ± 0.82	0.95 ± 0.31	1.02 ± 0.38	ns
Total Free Fatty Acids [mmol/L]	1.03 ± 0.23	0.68 ± 0.10 *	0.81 ± 0.11 *	0.047
Food Intake [g/d]	22.7 ± 0.41	18.6 ± 0.33 *	20.3 ± 1.95 *	0.015
Fasting glucose [mmol/L]	7.4 ± 0.29	6.8 ± 0.16 *	6.8 ± 0.3 *	ns
Fasting Insulin [ng/mL]	1.93 ± 0.66	0.76 ± 0.48 *	0.67 ± 0.24 *	ns
HOMA-IR	2.9 ± 1.0	0.8 ± 0.4 *	0.7 ± 0.3 *	ns

Conclusion: Gastric mucosal devitalization using APC results in a significant reduction in weight and improvement in metabolic profile. We propose that a minimally invasive procedure, such as endoscopic gastric mucosal devitalization, be investigated as a potential new therapy for obesity.

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OP089 INTRAGASTRIC BALLOON: A BRAZILIAN MULTICENTRIC STUDY OF 3545 CASES

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Introduction: The intragastric balloon has been used for more than 10 years in Brazil as an endoscopic method for assisting weight loss, and alongside multidisciplinary team support, the results have been satisfactory.

Aims & Methods: To assess the efficacy and complications of the weight loss with IGB in patients seen at the 5 private centers. A total of 3545 patients with IGB implanted from 2009 to 2014 were analyzed from a prospective fed databank. A liquid filled IGB with a volume in-between 620 to 700 ml was used. Initial BMI started at 27 kg/m2 (as approved by Brazilian health authorities) and were followed up by a multidisciplinary team during implant. IGB maximum period implant was 08 months. Statistical analysiswas performed according to sex and degree of excess weight (overweight and grade I, II and III). Data were analyzed using Student t-test, and andTukey post-test. The level of significance was set at $p < 0.05$.

Results: 205 patients (5.78%) were excluded from the analysis: 110 (3.1%) due to early removal, 39 (1.1%) due fail on weight loss or weight gain, 56 (2.2%) due to incomplete data. There were also spontaneous hyperinflation on 0.34% (n = 12) and balloon spontaneous deflation or leakage in 0.62% (n = 22). Incidence of complications not leading to removal were 5.95% Complications other happened as fungal contamination in in 4.54% (n = 161); WernickKorsakoff syndrome 0.05% (n = 2) and pregnancy during implant period on 0.39% (n = 14). The incidence of complications with IGB removal was 0.028% (n = 1): gastric perforation and upper digestive bleeding. On the 3340 remaining patients, 2271 (68%) were women and 1069 (32%) were men. Mean age was 35.72 years. The patients showed a significant weight loss, with a significantly lower final BMI (28.58 ± 7.14 kg/m2; range: 18.69-37) than the initial BMI (34.83 ± 5.13 kg/m2; range: 27-76.12) Percent EWL was higher in the overweight group (142.69%EWL), followed by obesities grades I (78.72%), II (61.51%) and III (47.13%) sequentially.

Conclusion: The intragastric balloon has been established as an valid endoscopic therapeutic option for weight loss, especially in patients with overweight and obesity grades I and II.

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Disclosure of Interest: None declared

OP090 THE FIRST PROCEDURELESS GASTRIC BALLOON: A PROSPECTIVE STUDY EVALUATING SAFETY, WEIGHT LOSS, METABOLIC PARAMETERS, AND QUALITY OF LIFE

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Introduction: Traditional gastric balloons for weight loss require endoscopy for placement and removal. Elipse™ (Allurion Technologies, Wellesley, MA USA) is the first procedureless gastric balloon. The balloon is swallowed, resides in the stomach for 3 months, and is then excreted.

Aims & Methods: The objectives of this study were to assess the safety of Elipse™ and to measure its effects on weight loss, metabolic parameters, and quality of life in up to 50 patients. We report the complete results of the first 8 patients treated at the time of abstract submission.

Each patient swallowed one Elipse™ device which was filled with 550mL of filling fluid through a thin delivery catheter that was then removed. Each device was designed to remain in the stomach for 3 months and then reproducibly open and pass during the 4th month. Weight was measured every 2 weeks, and metabolic parameters were assessed at baseline and at trial exit. The Impact of Weight on Quality of Life-Lite (IWQOL-Lite) questionnaire was administered at baseline and trial exit to measure the effects of weight loss on Physical Function (PF), Self-Esteem (SE), Sexual Life (SL), Public Distress (PD), Work (W), and Overall (O).

Results: Eight patients were enrolled with a mean BMI of 34.3 kg/m^2. All 8 patients successfully swallowed the Elipse™ device. As expected with balloon therapy, all patients experienced nausea and vomiting during the first 48 hours. There were no other adverse events. At 3 months, weight loss was statistically significant. The mean percent total body weight loss was 6% (range: 2.4% - 9.7%, $p < 0.01$) and mean percent excess weight loss was 25.4% (range: 6.5% - 47.3%, $p < 0.01$). All 8 balloons were uneventfully excreted in the stool. Mean waist circumference and hemoglobin A1c (HgbA1c) were reduced by 6cm

($p < 0.01$) and -0.15% ($p < 0.05$), respectively. Improvements were also seen in triglycerides, HDL, LDL, ALT, and AST. At trial exit, IWQOL-Lite mean scores improved across all domains: +10.5, +14.4, +1.9, +9.6, +6.9, and +9.1 for PF, SE, SL, PD, W, and O, respectively. An improvement of greater than 7.7 in any domain is considered statistically significant.
Conclusion: This study demonstrates clinically significant weight loss with Elipse™, the first procedureless gastric balloon. The weight loss was similar to that seen in prior studies of endoscopically placed balloons. There were no serious adverse events. In addition, Elipse™ therapy led to a significant improvement in waist circumference, HgbA1c, and overall quality of life.
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OP091 OPTIMAL TIMING FOR ENDOBARRIER RE-IMPLANTATION: AN EXPLORATORY STUDY

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Introduction: EndoBarrier (EB) therapy involves the endoscopic placement of a removable, impermeable liner that anchors in the duodenum and bypasses the first two feet of the upper bowel, replicating features of gastric bypass. Clinical data has demonstrated weight loss and improvements in glucose control after 12 months of EB therapy in obese subjects with or without type 2 diabetes mellitus. The feasibility of repeat EB treatment is often questioned.
Aims & Methods: This study aimed to determine the feasibility of a potential EB re-implant with evaluation of optimal timing for re-implantation. Subjects were eligible ($n = 21$) for re-implant if they completed 12 months of initial EB treatment. Upper-endoscopy was performed at explant and prior to re-implant to evaluate the feasibility of re-implantation. Lanza scale was used to grade the mucosal injury observed by upper endoscopy.
Results: 19 subjects (mean age 38.5 yrs, mean BMI 37.2 kg/m^2, mean body weight 93.4 kg, 73.7% non-diabetic) underwent endoscopic evaluation after the initial EB was explanted. All subjects had duodenal pseudopolyps; 6/19 subjects had a Lanza score of 2 or less, and one subject had a score of 3 (6 to 10 erosions).
Of the 13 subjects suitable for re-implant at 8 months, 12/13 subjects had pseudopolyps and 9/13 subjects had no visible mucosal injury. 11/13 subjects were successfully re-implanted. At 12 months, among the 8 subjects remaining to be re-implanted, all had pseudopolyps and all but one subject (score of 4) had no visible mucosal injury. These 8 subjects were successfully re-implanted.
With a 12 month time lapse between the initial explant and re-implant, all subjects (8/8) completed sequential EB therapy with no early device removal. With an 8 month time lapse between the initial explant and re-implant, 45% (5/11) of subjects had early device removal. The early device removal in 5 subjects was due to abdominal pain (2), device migration (2), and GI bleed (1). Four of five subjects required hospitalization.
Regardless of the wait time between initial and second implant (8 months vs 12 months), subjects benefited from EB re-implantation by renewed weight loss (mean weight loss 6.5 ± 1.1 kg, mean percent excess body weight loss 30.1 $\pm 23.1\%$). Furthermore, the implant procedure time trended to be less for subjects who waited 12 months as compared to 8 months (20.4 ± 10.6 mins vs. 29.2 ± 14.3 mins, respectively, $p = 0.06$).
Overall, adverse events (AEs) were classified as either mild (84%) or moderate (16%), with the majority of AEs related to GI symptoms.
Conclusion: This exploratory study suggests sequential EB placement is feasible with careful interim assessment. The optimal timing for re-implantation after the initial EB treatment appears to be approximately 12 months, but these findings warrant additional clinical evaluation.
Disclosure of Interest: N. Quezada: None declared, F. Pimentel Financial support for research: GI Dynamics, Inc., E. Chiquette Conflict with: Employee, P. Wenten Conflict with: Consultant, K. Malomo Conflict with: Employee, A. Escalona Financial support for research: GI Dynamics, Inc., D. Maggs Conflict with: Employee

MONDAY, OCTOBER 26, 2015 15:45–17:15
LONG-TERM MEDICAL MANAGEMENT OF IBD – ROOM A2

OP092 EVOLUTION AFTER ANTI-TNF DRUG DISCONTINUATION IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE (IBD): A MULTICENTER LONG-TERM FOLLOW-UP STUDY

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Aims & Methods: 1) to assess the risk of relapse after anti-TNF discontinuation; 2) to identify the factors associated with relapse; 3) to calculate the response rate to re-treatment with the same anti-TNF after relapsing, and 4) to evaluate the safety of re-treatment with these drugs.
Retrospective, observational, multicenter study. Crohn's disease (CD) or ulcerative colitis patients who had been treated with anti-TNFs and in whom these drugs had been withdrawn after having achieved clinical remission were included
Results: 1,055 patients were included (50% women, mean age 42 years, 69% CD). The cumulative incidence of relapse was 44% (95%CI = 41-46%): 15% at 6 months, 24% at 1 year, 38% at 2, 46% at 3, and 56% at 5 years after anti-TNF withdrawal. The incidence rate of relapse was 18% per patient-year (95%CI = 17-20%). In the multivariate analysis, the variables associated with a higher risk of relapse were younger age at anti-TNF discontinuation (HR = 0.9, 95%CI = 0.97-0.99), treatment with adalimumab (ADA) (vs. infliximab) (HR = 1.3, 95%CI = 1.02-1.6), and the elective discontinuation of anti-TNFs (HR = 1.7, 95%CI = 1.1-2.6) or the discontinuation of anti-TNFs due to adverse events (HR = 1.9, 95%CI = 1.2-2.9) (vs. top-down strategy). The treatment with IMMs (vs. no treatment) after anti-TNF discontinuation was associated with lower risk of relapse (HR = 0.7, 95%CI = 0.6-0.9). 69% of patients who relapsed were re-treated with the same anti-TNF; 75% of them achieved remission at the end of follow-up; 11% presented adverse events, all mild.
Conclusion: The incidence rate of relapse after anti-TNF drug discontinuation was 18% per patient-year. The predictive factors for relapse were the lack of IMM maintenance treatment after anti-TNF is stopped, younger age, treatment with ADA, and the elective discontinuation of anti-TNFs or the discontinuation of anti-TNFs due to adverse events. Re-treatment of relapse with the same anti-TNF was effective and safe.
Disclosure of Interest: None declared

OP093 LONG-TERM OUTCOME AFTER INFLIXIMAB WITHDRAWAL FOR SUSTAINED REMISSION IN CROHN'S DISEASE

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Introduction: The long-term outcome of Crohn's disease (CD) patients after infliximab (IFX) withdrawal is not well established. The aim of this study was to describe the long-term outcome of the patients previously included in the STORI trial studying infliximab cessetion in patients with sustained corticosteroid-free remission on IFX and antimetabolites.
Aims & Methods: Clinical notes of the patients included in STORI were retrospectively reviewed. The following clinically significant events were recorded: need for surgery, active perianal lesions, treatment modification including need for corticostereroids, infliximab, adalimumab or other biologic.
Results: 17/20 GETAID centres involved in the STORI trial participated in this retrospective study, representing 94/115 STORI patients. Long-term data were available in 85/94 (9 patients lost to follow up, including 5 early relapsers in STORI). Median follow-up from STORI inclusion was 79 months. A medical treatment was restarted in 64 (85%) patients after a median time of 29 months (IFX in 54, Adalimumab in 9, steroids in 1); eleven (13%) patients underwent surgical resection after a median of 59 months (before resuming any medical treatment in 6 patients); nine (11%) developped perianal lesions after a median of 55 months (after resuming anti-TNF in 6 cases). At maximal follow up, 13 hadn't experienced any significant event and 32 were still under IFX or Ada without surgical resection.
Conclusion: The vast majority of patients stopping IFX for sustained remission under antimetabolites + IFX had to restart a treatment over the long term. Almost one quarter develop tissue damage (surgical resection and perianal fistula). A controlled trial is necessary to properly assess benefits and risks of this strategy.

Reference

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Disclosure of Interest: None declared

OP094 OPTIMIZATION OF THIOPURINE THERAPY IMPROVES REMISSION RATES AFTER CESSATION OF ANTI-TNFA IN CROHN'S DISEASE

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Introduction: Biologics are effective in treating Crohn's disease but are expensive. Also, many patients develop immune responses or experience effect loss. Studies have shown remission rates at 12-months of 51-67%[1,2] when halting biologic treatment in patients in clinical remission.

Thiopurines (azathioprine (AZA) or 6-mercaptopurine (6-MP) are used to maintain remission but lack of efficacy and intolerance are common problems. Optimizing thiopurine therapy with measurements of metabolites and initiation of combination therapy with allopurinol (ALLO) improves efficacy and decreases intolerance.

In this study on patients with Crohn's disease in clinical remission, we optimized thiopurine treatment prior to cessation of anti-TNFα (infliximab (IFX)/adalimumab (ADA)), and evaluated remission rates at 6- and 12-months follow-up.

Aims & Methods: Physicians were instructed how to optimize thiopurine treatment using measurements of metabolite levels and combination therapy. When the patients had reached a level of 6-thioguaninenucleotide of 150-200 pmol/$8x10^8$ and were in clinical remission (Harvey Bradshaw Index (HBI) < 5), biologics were discontinued. During follow-up, relapses, defined as the need to restart of biologics, were recorded. Data on remission or relapse was obtained six and twelve months after stopping biologic therapy.

Results: 32 patients with luminal Crohn's disease had their thiopurine therapy optimized, were in clinical remission, and discontinued biologics. At inclusion, the median (IQR) age was 34 years (26-41), median disease duration was 7.2 years (3.8-12.5), median durations of biological therapy before discontinuation were 1.7 years (1.2-3.2 (IFX)) and 1.5 years (1.3-4.8 (ADA)). We found a median 6-TGN of 205 pmol/$8x10^8$ (178-261), MeMP 1124 pmol/$8x10^8$ (171-1156), and fecal calprotectin 100 mg/kg (30-158). 1(3%) patient received 6-MP, 3 (9%) 6-MP/ALLO, 16 (50%) AZA, and 12 (38%) AZA/ALLO.

97.0% (31/32) were in clinical remission six months after stopping biologic treatment, and 90.0% (26/29) patients were in remission after twelve months. Three patients had not yet completed one year follow-up.

We did not find any predictive risk factors for relapse (disease duration, length of biological therapy, smoking, fecal calprotectin, leucocytes, C-Reactive Protein or hemoglobin).

Conclusion: In this study, optimizing thiopurine treatment prior to stopping biologic treatment leads to at least 30% higher remission rates than shown in other studies with non-optimized patients.[1,2] No predictive factors for relapse were identified. Optimization has previously been shown to decrease side effects and intolerance. It is possible that optimizing thiopurine therapy in patients with Crohn's disease might alter the disease prognosis and decrease the need of biological therapy. Prospective studies will further clarify the future position of thiopurine optimization in IBD therapy.

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Disclosure of Interest: None declared

OP095 ADJUNCTIVE ALLOPURINOL IN THIOPURINE NON-RESPONDERS OPTIMISES 6TGN AND IMPROVES CLINICAL OUTCOMES IN IBD: THE MULTICENTRE, PROSPECTIVE, DOUBLE BLIND, DOSE-RANGING AAA STUDY

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Introduction: 15% of IBD patients who do not respond to azathioprine (AZA) or mercaptopurine (MP) are shunters. They preferentially metabolise MP to 6-methylmercaptopurine (6MMP) instead of the efficacious 6-thioguanine nucleotides (6TGN).

Aims & Methods: This multicentre, prospective, double-blind, dose-ranging, randomised trial aims to show that low-dose allopurinol–thiopurine achieves steroid-free clinical remission and minimises toxicity; and to compare outcomes of allopurinol 50 vs 100mg. Inclusion criteria were: clinically active or steroid-dependent IBD; thiopurine shunters with 6TGN <260pmol/$8x10^8$ RBCs and 6MMP:6TGN ratio ≥ 20; total leucocyte count $\geq 3.5x10^9$/L. Patients were randomised to a blinded dose of 50 or 100mg allopurinol and 25% of their screening thiopurine dose. Thiopurine doses were then optimised, aiming for 6TGN >260. The primary endpoint was steroid-free clinical remission after 24 weeks (SFR24) using the Harvey Bradshaw Index and the Simple Clinical Colitis Activity Index. An intention-to-treat analysis was performed.

Results: 73 patients were enrolled: 46 had Crohn's disease and 27 ulcerative colitis. Mean doses for AZA reduced from 164mg at screening to 67mg at week 24 and 6MP from 88mg to 45mg (both $p<.001$). Significantly greater thiopurine dose reductions were seen in the 100mg allopurinol arm than the 50mg arm (63-65% vs 35-53% reduction, $p=0.006$ and 0.008). 39 patients [53% (95% CI 42–65)] achieved SFR24 with no difference in rates of SFR24 between 50 and 100mg arms ($p=.913$). 6TGN increased from 177 ± 14 to 402 ± 16 ($p<.001$). 6MMP decreased from 9949 ± 485 to 1235 ± 547 ($p<.001$) and 6MMP:6TGN ratio fell from 64 to 4 ($p<0.001$). There was no significant difference in 6TGN between allopurinol arms, however mean 6MMP was significantly higher in the 50mg arm (1987 vs 483, $p=0.023$). Hepatitis decreased with ALT improving from 52 ± 6U/L to 27 ± 6U/L ($p<.001$). 26 of 32 patients (81%) were able to cease steroids ($p=.011$). Total leucocyte count decreased from mean $7.1x10^9$/L to $5.9x10^9$/L ($p<.001$). Only two transient episodes of mild leucopenia occurred in 1 patient, resolving with a reduced thiopurine dose. Significant reductions in faecal calprotectin occurred in steroid dependent CD patients from mean 864ug/g to 122ug/g ($p=.043$). Significant reductions in CRP occurred in UC patients from mean 6.1mg/L to 3.6mg/L ($p=.019$). 15 serious adverse events occurred; 2 (dental abscess and perianal abscess) were possibly related to the drug combination.

Conclusion: Allopurinol-thiopurine combination safely and effectively optimises 6TGN and concurrently reduces 6MMP. Optimisation of thiopurine metabolites improves disease outcomes without additional toxicity. No clinically significant differences were seen between allopurinol groups. It has been prospectively validated as a therapeutic intervention for IBD patients who are shunters.

Disclosure of Interest: None declared

OP096 FIRST EXPERIENCE OF SWITCHING BETWEEN ORIGINATOR AND BIOSIMILAR INFLIXIMAB IN PAEDIATRIC INFLAMMATORY BOWEL DISEASE PATIENTS

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Introduction: Inflammatory bowel disease incidence in children is on the rise. In relative to more cases biological treatment is needed. Recently, biosimilar infliximab (IFX) was authorized in European Union what may lead to switching patients. First experiences of such switch are described.

Aims & Methods: 32 paediatric patients with diagnosis of Crohn Disease (CD) and 7 of Ulcerative Colitis (UC) from 3 academic hospitals who were switched from originator to biosimilar infliximab (Remsima) were included in the study. Patient characteristics, disease severity (PCDAI for CD; PUCAI for UC), laboratory values (CRP, ESR, platelet count, haemoglobin level) was recorded. Mean, median and range values were calculated. Adverse events were recorded before and after the switch.

Abstract number: OP096

	Originator INF start	At 2nd last originator INF infusion	At last originator INF infusion	At switch (before 1st biosimilar infusion)	Before 2nd biosimilar infusion	Before 5 biosimilar infusion
Week	-	W -16	W -8	W 0	W +8	W +32
No. patients	32	32	32	32	32	18
PCDAI	47,8(52,5;2.5-65)	7,4(3.8;0-32,5)	7(5;0-30)	8,8(5;0-35)	7.2(5;0-30)	7,1(5;0-42,5)
CRP	1,4(0.9;0-6,5)	0.6(0.3;0-2,3)	0.6(0.4;0-3,8)	0.6(0.3;0-3,8)	0.6(0.3;0-2,1)	0.6(0.2;0-2,3)
ESR	28(23;3-80)	14(9;2-63)	15(10;2-59)	14(9;1-63)	14(8;0-75)	10(7; 1-35)
Platelets	389(392; 169-630)	302(305; 112-543)	299(288; 171-635)	304(282; 183-804)	325(315; 175-854)	294(272; 152-493)
Hb	12,3(12.3;10.3-14.4)	13,1(13.3;10.4-16,7)	13,1(12.9;10.3-15.6)	13.1(13.1;10.4-16.4)	13.3(13.3;11.2-16,4)	13(12,3; 9,8-15,8)

Results: Mean age of patients at diagnosis of CD was 11.2y (2.7-15.3), of UC patients was 12.3y (8.5–14.8). Mean time from CD diagnosis to the start of current biological treatment was 1.8y (range:1 week–5y) and from UC 1.7y (median 0.55y, range 0.5-4.8y). Mean number of originator IFX infusions before the switch to biosimilar in CD group was 9.9 (8; 4-29); in UC 5.1 (5;1-12). At originator IFX qualification patients mean PUCAI was 42.9 (median 45, range 10-65). CRP, ESR, platelet count were elevated for 1,5,4 patients, respectively. PUCAI decreased for all patients after first dose: 12.5 (10; 0-35). At switch mean PUCAI was 16.4 (20; 0-30). CRP, ESR, platelet count were elevated for 3,2,2 patients, respectively. Before 2 and 4 dose of Remsima mean PUCAI was 11 (0; 0-40) and 2 (0;0-5), respectively.
For CD patients data before and after switch were presented in the Table as mean(median; range).
There was no infusion reactions observed in CD group after originator of biosimilar INF treatment. In UC group during first biosimilar IFX dose infusion-related reactions (skin erythema) was observed for 2 patients, which was not observed for the originator. Antihistaminic treatment caused resolution of symptoms and the full dose of IFX was delivered. The occurrence of sporadic mild adverse events did not differ before or after switching and was consistent with IFX molecule safety profile.
Conclusion: Switching form originator to biosimilar infliximab in children with CD seems to be safe.
Disclosure of Interest: None declared

OP097 ANTI-REMICADE ANTIBODIES CROSS-REACT WITH THE BIOSIMILARS REMSIMA AND INFLECTRA IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Introduction: Remicade (INN-infliximab, IFX) has proven to be effective in inducing and maintaining remission of Crohn's disease and ulcerative colitis. The link between the serum trough concentration and the clinical outcome has been demonstrated repeatedly and has led to the introduction of therapeutic drug monitoring (TDM) for treatment optimization. In September 2013, the European Medicines Agency issued the marketing authorisation of a biosimilar of Remicade, CT-P13, under trade names Remsima and Inflectra.
Aims & Methods: 1) To evaluate binding of a panel of 55 mouse monoclonal antibodies, generated toward Remicade, to Remsima and Inflectra; 2) to quantify biosimilars in the Ridascreen IFX monitoring assay (R-Biopharm); 3) to compare titers of the antibody response of patients that developed anti-Remicade antibodies toward Remsima and Inflectra.
The reactivity of a panel of monoclonal antibodies, including MA-IFX6B7 and MA-IFX10F9, toward the biosimilars was tested using a sandwich ELISA and mixed model analysis was used to determine dissimilarity between Remicade and the biosimilars. Schuirmann's two one-sided *t*-test (TOST) was used to analyse the similarity between the detection of biosimilars and Remicade in the Ridascreen IFX monitoring assay using four quality control samples. Bridging assays to determine anti-biosimilar antibodies were developed according to the protocol of the bridging ELISA of Remicade using MA-IFX10F9 as calibrator.[1]
Serum of 18 patients previously treated with Remicade was analysed for anti-drug antibodies toward Remicade, Remsima and Inflectra using their respective bridging ELISA.
Results: Using mixed model analysis, no evidence for different reactivity of IFX6B7 and IFX10F9 toward Remsima and Inflectra versus Remicade was found ($p > 0.05$). TOST demonstrated an equally well quantification of the biosimilars and Remicade in the Ridascreen IFX monitoring assay. Quantification of anti-IFX antibodies in serum of patients treated with Remicade revealed highly correlated titers toward the biosimilars as compared to Remicade (Spearman $r = 0.9963$, $p < 0.0001$).
Conclusion: This study describes an assay to perform TDM of the IFX biosimilars. TDM provides a basis for personalised dosing based on predictive models, an approach which is expected to further increase cost efficacy. We have demonstrated that anti-drug antibody titers toward Remicade correlate with titers toward Remsima and Inflectra.

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Disclosure of Interest: A. Gils Lecture fee(s): MSD, Janssen Biologicals, Conflict with: license of infliximab ELISA to apDia, T. Van Stappen: None declared, E. Dreesen: None declared, R. Storme: None declared, S. Vermeire Financial support for research: MSD, Abbvie, Lecture fee(s): MSD, Abbvie, Takeda, Falk, Tillotts, Consultancy: MSD, Abbvie, Takeda, Falk, Ferring, Shire, Galapagos, Hospira, Mundipharma, Genetech/Roche, Pfizer, Celgene, P. J. Declerck Lecture fee(s): Abbvie, Amgen, Celltrion, Hospira, Merck-Serono, Novo Nordisk, Roche, Pfizer., Consultancy: Abbvie, Amgen, Celltrion, Hospira, Merck-Serono, Novo Nordisk, Roche, Pfizer.

OP098 UPPER GASTROINTESTINAL BLEEDING SECONDARY TO PEPTIC ULCER DISEASE – CAN WE CONTINUE TO REDUCE ITS INCIDENCE?

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Introduction: In the last decades the incidence of Peptic Ulcer Disease (PUD) progressively decreased in the western world, but it still remains as an important factor of morbidity and mortality. The reduction allowed by the improvement of socio-economic conditions and the decrease in incidence of *Helicobacter pylori* infection, was partially outweighed by the advanced age of patients and the iatrogenic effect of modern medicine.
Aims & Methods: (1) To assess the number of potentially preventable hospitalizations due to upper gastrointestinal bleeding secondary to PUD; (2) identification of the factors that led doctors to prescribe proton pump inhibitors (PPIs) in clinical practice; (3) and the accordance with the current guidelines for gastroprotective therapy.
Retrospective analysis of all patients admitted to our center between 2009 and 2013, with upper gastrointestinal hemorrhage secondary to endoscopically proven PUD. According to the guidelines of the American College of Gastroenterology and the American Heart Association for gastroprotective therapy, patients were divided into low and high-risk groups. Demographic, comorbidities and medication data were recorded. From published studies, we assumed the 50-85% potential effect of PPIs in preventing hemorrhage secondary to PUD.
Results: We identified 348 patients (high-risk:133), with a mean age of 72 years, a male sex preponderance ($n = 249$) and a mean age adjusted Charlson comorbidity index of 5. The percentage of patients doing antiaggregation was 35% (dual antiaggregation: 14%); non-steroidal anti-inflammatory: 24%; anticoagulation: 13% and corticosteroids: 5%; 18% of patients had past history of PUD. PPIs were identified in 14% of patients, however only 26% of the patients in the high-risk group were doing gastroprotection. Although it was not statistically significant ($p = 0.065$), we identified a trend for concomitant gastroprotection prescription if the factor that led the patient to belong to the high-risk bleeding group was an initial prescription from a hospital doctor, instead of one from a general practitioner (21% versus 10%). In 30% of patients, the factor for belonging to the high-risk group was self-medication. Assuming that all high-risk patients should do gastroprotection, it was estimated that about 49-83 admissions could be prevented (14-24% of admitted patients).
When analyzed the factors that led doctors to prescribe gastroprotective therapy, the only variable that was statistically associated and in agreement with the current guidelines was antiagregation plus antiagregation/ anticoagulation ($p = 0.027$; $OR = 2.64$). In univariate analysis, other statistically associations were identified (not in line with current guidelines): age ≥ 65 years, anticoagulation, use of cox-2 inhibitors, aspirin and clopidogrel, but in the multivariate analysis, the only variable associations that prevailed were anticoagulation ($p = 0.001$; $OR = 3.48$) and clopidogrel ($p = 0.000$; $OR = 6.71$).
Conclusion: The high percentage of self-medication and the low obedience to the current guidelines (especially in general practitioners), led that up to 25% of hospital admissions secondary to peptic ulcer hemorrhage could be preventable.
Disclosure of Interest: None declared

OP099 INTERNATIONAL, MULTICENTRE PROSPECTIVE STUDY COMPARING RISK SCORING SYSTEMS FOR PATIENTS PRESENTING WITH UPPER GASTROINTESTINAL BLEEDING

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Introduction: Several risk scoring systems have been developed for the assessment of patients with upper gastrointestinal bleeding (UGIB). However, only few of these have been externally validated in international studies.
Aims & Methods: We compared the ability of five risk scoring systems to predict: 1. Need for hospital-based intervention or mortality, 2. Rebleeding within 7 days, 3. Length of hospital stay (LOS), and 4. 30-day mortality.
We performed a prospective study on consecutive patients presenting with UGIB at six centres in United States, Scotland, England, Denmark, Singapore, and New Zealand over 12 months. Using area under receiver operating characteristics curves (AUROC) we compared the discriminative abilities of the pre-endoscopic scores: Glasgow Blatchford score (GBS), AIMS65, and admission Rockall score (ARS) and the post-endoscopic scores: the full Rockall (FRS) and PNED scores to predict outcome.
Results: 3171 patients were included. Median age was 65 years, and 58% were male; 45% needed hospital-based intervention or died, 5% rebled, median LOS was 3 days, and mortality was 7%. In the prediction of need for intervention, or death, GBS had the highest discriminative ability (AUROC 0.89) when compared to AIMS65 (AUROC 0.70; $p < 0.0001$), PNED (AUROC 0.70;

$P < 0.0001$), FRS (AUROC 0.69; $P < 0.0001$) and ARS (AUROC 0.69; $P < 0.0001$). The PNED was best (AUROC 0.85) at predicting rebleeding, compared with GBS (AUROC 0.71; $P < 0.0001$), FRS (AUROC 0.62; $P < 0.0001$), AIMS65 (AUROC 0.62; $P < 0.0001$), and ARS (AUROC 0.62; $P < 0.0001$). All risk scores had poor discriminative abilities for predicting LOS > 3 days (all AUROCs < 0.70). PNED (AUROC 0.80) and AIMS65 (AUROC 0.79) had better discriminative abilities for mortality than ARS (AUROC 0.76; $P < 0.02$), FRS (AUROC 0.72; $P < 0.03$), and GBS (AUROC 0.70; $p < 0.0001$). All of these findings were consistent across all sites.

Conclusion: This large international study shows that GBS has the best accuracy for predicting need for hospital-based intervention or mortality. PNED and AIMS65 are best at predicting 30-day mortality. Apart from PNED (which includes data on rebleeding) all scores were poor at predicting rebleeding, and no score could accurately predict LOS.

Disclosure of Interest: None declared

OP100 WEEKEND ADMISSION INCREASES MORTALITY OF UPPER GASTROINTESTINAL BLEEDING PATIENS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: Upper gastrointestinal bleeding (UGIB) mortality has remained stable in recent years despite advances in endoscopic and pharmacological treatment. The studies identify factors such as severity of the bleeding, advanced age and high comorbidity as predictors of mortality. However, the finding of additional modifiable factors associated with mortality could allow establish measures to reduce mortality in UGIB. The "weekend effect" is defined as an increased mortality rate in patients presenting to hospitals on the weekend.

Aims & Methods: To evaluate if admission weekend increases rebleeding, the need for surgery and mortality in UGIB by performing a systematic review and meta-analysis.The search was conducted in PubMed and ISI Web of Knowledge (until February 2014) to identify studies comparing mortality in patients with UGIB admitted on weekend versus weekday admission. We used a model of fixed and random effects with odds ratio (OR) to determine differences for rebleeding, need for surgery and mortality. Publication bias was assessed using the method of Egger and Macaskill. Heterogeneity between studies was analyzed using the statistical I2, Q and Tau 2. The quality of the publications was evaluated using the STROBE statement criteria.

Results: Seventeen studies including 1,038,106 patients met the inclusion criteria. Compared to patients admitted on weekdays, patients with UGIB admitted on weekends had higher mortality (OR 1.12; 95%CI:1.07-1.18) and higher rates of surgical intervention (OR 1.18; 95%CI:1.11-1.26. However, weekend admission did not significantly increased rebleeding rates: (OR:1.23; 95%CI:0.98-1.53). The subgroup analyses evaluating variceal and non-variceal upper gastrointestinal bleeding separately found that Weekend admission increased mortality (OR:1.14; 95CI%(1.07-1.21)and the need for surgery (OR:1.23; 95%CI:1.07-1.4) but not rebleeding (OR 1.10 (95%CI 0.73 -1.67) in non-variceal upper gastrointestinal bleeding. Regarding variceal upper gastrointestinal only the mortality was significantly elevated (OR1.06; 95%CI:1.00-1.12).

Conclusion: Patients with UGIB admitted on the weekend show worse outcomes in terms of mortality and need for surgery than those admitted on a weekday. As the rebleeding rate is not increased, our study may suggest that poorer management of comorbidities due to the lower level of staffing and the decreased intensity of care provided in hospitals during the weekend may account for this finding.

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Disclosure of Interest: None declared

OP101 TITLE: THE EFFECT OF OFF-HOUR HOSPITAL ADMISSION ON MORTALITY FOR PATIENTS WITH UPPER GASTROINTESTINAL HEMORRHAGE: A SYSTEMIC REVIEW AND META-ANALYSIS

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Introduction: Controversies abound upon the impact of non-office hour admission on clinical outcomes for patients with upper gastrointestinal hemorrhage (UGIH). This study aimed to evaluate the relationship between off-hours admission and clinical outcomes for UGIH.

Aims & Methods: We conducted literature search on Medline, Embase, Scopus, and Cochrane until November 2014. All manuscripts or abstracts that reported the association between hospital admission time and outcomes for patients with UGIH would be identified without restriction to language and study design. We used the Newcastle-Ottawa scale to determine the quality of the included studies. Clinical outcomes included mortality, time to receive endoscopy, length of hospital stay, need for surgery, rebleeding rate, and length of hospital stay were assessed. A randomized effect model was used for the meta-analysis. Heterogeneity was evaluated by calculating I2 statistic and Q test.

Results: We recruited 16 studies with an average of 7.81 points on quality scale into the meta-analysis, including 519,521 cases of UGIH. Patients with UGIH who were admitted during off-hours had a significantly higher mortality (OR 1.08, 95% CI 1.03-1.12). Moreover, those with non-variceal UGI bleeding had significantly increased risk of mortality when admitted during off-hours (OR 1.08, 95%CI 1.03-1.15; OR 1.07, 95%CI 1.02-1.12). However, for studies conducted in hospitals where there was an off-hours endoscopist on-call rota, the mortality rate for patients admitted during off-hours became insignificant (OR 1.10, 95%CI 0.89-1.36). Patients in the off-hour group were less likely to be treated by early endoscopy with 24 hours after admission (OR 0.74, 95% CI 0.63-0.86).

Conclusion: Patients with non-variceal UGI bleeding and admitted during off-hours had significantly higher mortality, while this impact can be offset among hospitals with on-call endoscopist rota.

Disclosure of Interest: None declared

OP102 WHAT ARE THE RISKS OF UPPER GASTROINTESTINAL BLEEDING AMONG PEOPLE OVER THE AGE OF 65 WHILE BEING PRESCRIBED NSAIDS OR ASPIRIN? A POPULATION BASED COHORT STUDY FROM ENGLAND

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Introduction: Limited knowledge exists on the impact of interactions between hazardous prescriptions on the risk of upper gastrointestinal bleeding (UGI).

Aims & Methods: This study aims to precisely determine the population level absolute rates of UGI bleeding associated with NSAID/aspirin use in relation to interactions with other drugs and comorbidities. Our study population consisted of individuals over the age of 65 years registered within primary care data (Clinical Practice Research Datalink – CPRD) linked to secondary care data (Hospital Episode Statistics-HES) between 1998 and 2010. NSAIDs/Aspirin exposure was defined in a time varying manner. The absolute rate (AR) of UGI bleed among those exposed to NSAIDs/aspirin was calculated and compared to those not exposed to NSAIDs/aspirin using a Cox regression model adjusted for PPI use. We then stratified by the presence of comorbidities and any exposure to drugs previously known to be associated with UGI bleed (anticoagulants, clopidogrel, steroids, SSRI and anti-cirrhotic drugs).

Results: Our study population consisted of 376,586 individuals of whom 39% received an NSAID or Aspirin prescription at least once during the study period. Overall there were 8,410 UGI bleeds and the risk of GI bleed associated with NSAIDs/Aspirin exposure was 208 per 10,000 person-years (Table 1; 95% Confidence Interval (CI) 192-226). This corresponded to a 1.5% absolute excess risk and a 3-fold risk relative (95%CI 3.04-3.60) compared to those not exposed to NSAIDs/Aspirin. These estimates remained broadly similar when stratified by comorbidity and receipt of other prescriptions known to increase UGI bleed risk.

Table 1: Absolute rate of GI bleed per 10,000 and hazard ratio by drug use stratified by NSAIDs exposure

Variable	NSAIDs exposed			NSAIDs unexposed			HR (adjusted)*	95% CI		Rate difference
	Rate	95% CI		Rate	95% CI					
Overall rate	208.3	192.2	225.8	55.6	54.6	56.9	3.31	3.04	3.60	152.7
Male	241.0	215.8	269.2	64.9	62.9	67.0	3.26	2.92	3.65	176.1
Female	180.6	160.6	203.1	48.5	47.0	50.1	3.36	2.98	3.80	132.1
No Comorbidity[1]	169.4	150.6	190.5	46.8	45.4	48.2	3.30	2.92	3.73	122.6
At least 1 comorbidity[1]	312.0	254.9	381.9	81.8	77.0	86.9	3.62	2.93	4.46	230.2
≥2 comorbidities[1]	244.2	214.5	278.6	68.5	65.9	71.3	3.20	2.78	3.67	175.7
No prescriptions[2]	170.9	152.9	191.1	46.9	45.6	48.2	3.29	2.93	3.69	124
At least 1 prescription[2]	226.9	194.0	265.3	74.7	71.3	78.3	2.90	2.46	3.41	152.2
≥ 2 prescriptions[2]	265.1	306.2	433.0	115.9	108.8	123.4	2.98	2.48	3.59	149.2

*HR adjusted for age, gender, comorbidity and concurrent PPI use when not stratified by those variables [1]Ulcer, varices, UGI cancer, GI neoplasm, angiodysplasia, Cirrhosis, Gastric/oesophageal/duodenitis, Mallory Weiss Syndrome, H-pylori, Alcohol consumption, Crohn's disease, liver failure, Ascites, Portal hypertension, Encephalopathy, Ascetic complications [2]Anticoagulant, Clopidogrel, Coxib, SSRI, Anti-cirrhotic drugs and oral steroids.

Conclusion: During exposure to NSAIDs/aspirin individuals have a 1.5% per annum excess absolute rate of UGI bleed compared to those unexposed to these drugs, corresponding to an estimated number needed to harm per NSAIDs/Aspirin prescription of 67. The excess risk remains broadly similar when stratified by comorbidities and other drugs previously associated with GI bleed suggesting limited interaction between them.
Disclosure of Interest: None declared

OP103 MAINTENANCE OF ANTITHROMBOTIC THERAPY POST ENDOSCOPY FOR ACUTE UPPER GASTROINTESTINAL BLEEDING IS ASSOCIATED WITH IMPROVED CLINICAL OUTCOMES

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Introduction: Antithrombotic drugs (antiplatelets and anticoagulants) are often stopped following acute upper gastrointestinal bleeding (AUGIB). In the UK, NICE (National Institute of Health and Care Excellence) have recently advocated resuming aspirin after AUGIB,[1] but their position on non-aspirin antithrombotics is less clear.
Aims & Methods: We aimed to assess if maintenance of antithrombotic therapy following AUGIB correlated with improved clinical outcomes. We identified patients on antithrombotic therapy who underwent gastroscopy for suspected AUGIB at University Hospital Birmingham whilst on antithrombotic therapy between May 2013 and November 2014 and performed follow-up until March 2015. Clinical outcomes were measured after endoscopy and discharge, and included cause-specific mortality, thrombotic events, rebleeding, and any adverse event (any of the above). Exclusion criteria included failure of haemostasis, death <24 hours of endoscopy, and end of life care. Patients were stratified according to whether antithrombotics were maintained or discontinued. Data comparisons were performed using Fisher's Exact and *t*-test, with Kaplan-Meier analysis to estimate follow-up outcome. *p*-values (two-tailed) were significant if <0.05.
Results: 132 patients were included for analysis, of which 118 survived until discharge. Antithrombotic use consisted of aspirin monotherapy (43%), oral anticoagulants (27%), dual antiplatelet therapy (DAPT) [16%], thienopyridine monotherapy (10%), and other (4%). Antithrombotic maintenance, defined as resumption within 72 hours of endoscopy or prior to discharge, was observed in 51%. Older age, aspirin monotherapy and peptic ulcer disease were significant predictors of antithrombotic discontinuation, whereas DAPT use and warfarin use for metallic heart valve were significant predictors of maintenance. Mean follow-up after discharge was 286 days. The overall mortality rate was 22%, with in-hospital mortality of 11%. Our rebleeding rate over this follow-up period was 8.2%. Overt bleed-related mortality ($n=3$) was overshadowed by cardiovascular mortality ($n=16$) [$p=0.005$]. Mortality during inpatient AUGIB (33%) was significantly higher than those admitted with AUGIB (14%). Discontinuation of antithrombotic therapy post endoscopy was associated with increased thrombotic events (RR 5.5, $p<0.001$), reduced rebleeding (RR 0.5, $p=0.35$), and increased incidence of any adverse event (RR 2.1, $p=0.005$). Discontinuation post discharge was associated with reduced survival ($p=0.03$), increased thrombotic events ($p=0.01$) and any adverse event ($p=0.006$). Discontinuation of aspirin monotherapy was observed in 67%, but did not reach significance for thrombosis ($p=0.24$) or adverse outcome ($p=0.15$). However, thrombotic events were significantly higher in the discontinued oral anticoagulant ($p=0.01$) and non-aspirin monotherapy subgroups ($p=0.002$).
Conclusion: In our patient group, mortality from thrombotic causes following AUGIB is high. Maintenance of antithrombotic therapy, including non-aspirin regimens, appears to be associated with improved thrombotic outcomes and reduced mortality.

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Disclosure of Interest: None declared

MONDAY, OCTOBER 26, 2015 15:45-17:15
ADVANCES IN CAPSULE ENDOSCOPY AND ENTEROSCOPY - ROOM E1

OP104 MAGNETICALLY ASSISTED CAPSULE ENDOSCOPY IN THE UPPER GASTROINTESTINAL TRACT: A RANDOMISED TRIAL OF CONTROL AND PREPARATION

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Introduction: Delayed gastric emptying can be a significant factor in incomplete small bowel capsule endoscopy (SBCE). This has been addressed by using prokinetic agents, albeit with the need for cannulation or intramuscular (IM) injections and the small risk of adverse drug reactions. Recently a manoeuvrable small bowel (SB) capsule has become available using a handheld magnet to control movement. In this study we have compared this technique with a standard protocol to determine if control using a magnet can be demonstrated by the achievement of a readily definable and in terms of small bowel examination, a clinically useful end point: entry into the duodenum.
Aims & Methods: Single centre, randomised controlled trial involving 122 patients attending for SBCE using MiroCam Navi (Intromedic, Seoul, Korea) between February 2014 and February 2015. Patients were randomised to either the standard (control) group or the steerable capsule (intervention) group. The control group were mobilised for 30 minutes after ingestion of the capsule, followed by IM metoclopramide 10mg if the SBCE had failed to enter the SB. The intervention group ingested a gastric distention volume of 1000mls of water with 5 drops of simethicone prior to SBCE. Positional change and magnetic steering was used to manipulate the SBCE into the duodenum. If unsuccessful after 30 minutes, the patient transferred to the standard protocol. Outcome measures: gastric transit time (GTT), capsule endoscopy completion rate (CECR), gastric visibility and distention (as measured on a 1-4 scale). Secondary outcome measures: first pyloric image, relationship of body habitus to GTT and CECR and patient comfort scores. For the primary outcome measures; 60 patients per group were required to achieve 80% power, assuming a completion rate of 70% for the control protocol, improving to 90% with the intervention. Ethics: 13/YH/0358
Results: 122 patients were recruited (61 to each group: 34 men, mean (SD) age 49.6 ± 17.8 years, range 20-85 years). 2 patients were excluded due to gastric retention of the capsule. GTT was longer in the intervention group but this did not reach statistical significance (median 23 vs 51 minutes Mann-Whitney $U=1487$, $p=0.116$). There was no significant difference in CECR between the two groups (χ^2 $p=0.395$). Gastric mucosal clarity and distention were significantly better in the intervention group ($p<0.0001$ and $p<0.0001$ respectively). Similarly the first pyloric image was seen significantly sooner in the intervention group ($p=0.029$), suggesting that magnetic control hastens capsular transit to the gastric antrum but is unable to impact upon duodenal passage. Examining the intervention sub-group: no correlation between body mass index (BMI) or waist-hip ratio (WHR)and GTT was demonstrated ($r=0.002$ and $r=5.98$ respectively). Similarly no significant difference between WHR ($p=0.938$) or BMI ($p=0.507$) and CECR was noted.
Conclusion: Magnetic steering of a small bowel capsule is unable to overcome pyloric contractions to enhance gastric emptying. However mobility, image clarity and distention within the gastric cavity was significantly better in the intervention group, suggesting that with further improvements this technique could potentially be harnessed to enable capsular examination of the gastric cavity.
Disclosure of Interest: None declared

OP105 SMALL BOWEL IMAGING IN CROHN'S DISEASE: MEASURING THE TRUE ACCURACY OF PROXIMAL AND DISTAL SMALL INTESTINAL DISEASE ACTIVITY USING TOTAL ENTEROSCOPY IN PATIENTS WITH ESTABLISHED AND SUSPECTED CROHN'S DISEASE

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Introduction: Small bowel imaging, such as MR enterogprahy (MRE), CT enterography (CTE), and capsule endoscopy (CE) are used not only for detecting small intestinal (SI) Crohn's disease (CD), but also for assessment of mucosal healing; however, previous studies have relied on ileocolonoscopy alone as the reference, not taking into account the full length of the SI.
Aims & Methods: The aim of this study was to assess the accuracy of SI imaging using total enteroscopy (TE) as the gold standard. This is a single-center retrospective chart review of patients with established and suspected CD status post TE via double balloon enteroscopy (DBE) and small bowel imaging. CD activity was defined as positive if $\geq$1:aphthous lesion, small ulcer, large ulcer, ulcerated mucosa, and/or stenoses. For imaging, CD was defined as presence of wall thickening, increased contrast enhancement, or hyperemia, and/or presence of stenoses. Disease location was defined as proximal (duodenum to proximal ileum) or distal (proximal ileum to terminal ileum). Using TE as the gold standard, sensitivities, specificities, positive predictive values (PPV) and negative predictive values (NPV) were calculated.
Results: 2146 DBEs were performed between 2004-2014 with 611 TEs achieved in 337 patients; 71 TEs were achieved in one direction. 55 patients (M36:F19, 51yo) identified with CD (30 suspected and 25 established) underwent 109 DBEs for 58 TEs. 11 DBEs required balloon dilation. 2 DBEs were performed for capsule retrieval. There were 0 perforations, pancreatitis. 18 patients underwent CE with a median Niv score of 5.5. CTE, MRE, and SBFT compared to other imaging modalities, such as CT and MRI, detected CD activity with 66.7% vs 47% sensitivity, and stenoses were detected with 50% vs 62% sensitivity. On the other hand, CE detected CD activity with 75% sensitivity and 50% specificity, and stenoses were detected with 83% sensitivity and 100% specificity. When evaluating the proximal vs distal SI, MRE, CTE, and SBFT had 42% vs 63% sensitivity. Alternatively, the PPV for proximal vs distal CD for CE was 100% vs 70.8%. Because of TE there was maintenance of therapy in 7, escalation of therapy in 10, resection/lysis of adhesions in 4, IBS in 6, de-escalation of therapy in 2, symptom improvement post balloon dilation in 3, diagnosis of CD in 18,

CD ruled out in 5, and other concomitant diagnoses in 7 (celiac sprue, NSAID enteropathy, carcinoid, Meckel diverticulum).

Table1: Diagnostic Accuracy of CTE/MRE/SBFT for Small Intestinal CD

	sensitivity	specificity	ppv	npv	lr	p-value
all crohn's disease activityn = 42	0.6667	0.2083	0.3871	0.4545	0.8421	0.4832
stenosesn = 32	0.5000	0.4091	0.2778	0.6429	0.8462	0.7120

Conclusion: CTE/MRE/SBFT sensitivities for SI CD activity are lower than expected, and may not be as reliable as TE in assessing isolated small intestinal CD activity. Additionally, in comparison, CE has overall excellent accuracy for total small intestine. However, both modalities were less sensitive for detecting proximal SI CD, and deep enteroscopy could be preferred.
Disclosure of Interest: N. Mann Lecture fee(s): Given Imaging, Consultancy: Given Imaging, L. Jamil: None declared, S. Lo: None declared

OP106 COLOR-BASED SEGMENTATION OF CAPSULE ENDOSCOPY IMAGES FOR AUTOMATED LESION SIZE MEASUREMENTS

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Introduction: Accurate & objective measurement of the size of gastrointestinal (GI) lesions in capsule endoscopy (CE) is essential. Currently, measurement is based on subjective estimations relative to the diameter of the bowel lumen. Color carries important information for lesion discrimination[1]; we developed a novel color-based CE image segmentation method & evaluated its capacity for lesion size measurement.
Aims & Methods: Images of GI lesions (various types/sizes) with MiroCam® (IntroMedic® Co., Seoul, South Korea) - available online from **KID** database (*Dataset 1*)[2]. Size reference standards were made by manual annotation. Automatic image segmentation was performed by Simple Linear Iterative Clustering (SLIC), capable of grouping pixels of similar color into contiguous clusters of pixels (regions), called superpixels[3]. The algorithm uses the CIE-Lab color space representation instead of the standard RGB used in CE[1]. The components of this space represent lightness (L), the quantity of red ($a > 0$) or the quantity of green ($-a > 0$), the quantity of yellow ($b > 0$) or the quantity of blue ($-b > 0$) of a pixel. The superpixels are clustered using the k-means algorithm into three clusters using chromatic information only from component a. The method considers that a user specifies a point belonging to an abnormal image region of interest (ROI). Thereafter, the method estimates from each neighboring superpixel of the selected superpixel i.e. the one containing the selected point, the dissimilarities (Euclidean distances) of the color feature vectors composed of the mean values of a and b, with: a) the respective vectors of the selected superpixel (d1); and b) the mean of the respective vectors obtained from all superpixels that do not belong to the cluster of the selected superpixel (d2). Then the neighboring superpixel is considered to belong to the abnormal region of interest if d1.
Results: The algorithm was evaluated for the segmentation of 7 different types of GI lesions. Accuracy of the measurements was assessed comparing the area of the lesion (as identified by the method) with the reference standard area of each lesion. Average accuracies obtained for the measurement of angioectasias, aphthae, chylous cysts, lymphangiectasias, polypoid lesions, stenoses, and ulcers were 98.6%, 92.8%, 94.3%, 99.1%, 80.0%, 82.9%, and 94.8%, respectively. Comparatively, using the well-known color space proposed by Ohta (I1I2I3) for image segmentation instead of CIE-Lab[1] the results were lower; 97.1%, 92.1%, 92.6%, 97.8%, 75.2%, 78.8%, 91%, respectively. Due to color dependency, in cases where the abnormal ROI has observable color variations, our method presents lower accuracy.
Conclusion: A novel method for accurate size measurement of lesions in CE is proposed & evaluated on a publicly available dataset of CE images; overall accuracy of approx. 92%. These results call for the development of a novel measurement tool embedded in the CE reading software.

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Disclosure of Interest: None declared

OP107 EVALUATION FOR THE CLINICAL EFFICACY OF COLON CAPSULE ENDOSCOPY IN THE DETECTION OF LATERALLY SPREADING TUMOR

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Introduction: With the advancement of technology used in PillCam COLON 2 capsule endoscopy (CCE2), there have been marked improvements in diagnostic rates for CCE2 in the detection of colonic polyps and colorectal cancer. However, a limited data have been reported about laterally spreading tumor (LST) in the colorectum.
Aims & Methods: This study compared CCE2 with optical colonoscopy (OC) for the detection of LST. We performed a prospective, single-academic center study comparing CCE2 with OC (the gold standard for comparison) in a cohort of patients with LSTs by diagnostic OC performed within 3 months prior to CCE2 at Hiroshima University Hospital. Patients underwent an adapted colon preparation, and colon cleanliness was classified into inadequate and adequate. We focused on the sensitivity and the specificity of CCE2 for detecting LST. All LSTs were resected by endoscopic resection and confirmed histopathological diagnosis. The recorded capsule videos were reviewed by the 2 independent investigators without any information of patients and OC. LSTs were dived into LST-granular type (LST-G) and LST-non granular type (LST-NG) based on detailed observation during chromoendoscopy with indigo carmine dye spraying as previously reported.
Results: A total of 21 LSTs (7 LST-Gs and 14 LST-NGs) in 30 patients (mean age, 59.5 years) were included in the study. The average size of LST was 27 ± 15 mm (10-60 mm) in diameter. Histopathological diagnosis of LST was as follows; tubular adenoma (TA) 12 cases (57%), sessile serrated adenoma/polyp (SSA/P) 4 (19%) cases, Tis carcinoma 1 case (5%), and T1 carcinoma 4 cases (19%). The existed location of LSTs was cecum 1 case (5%), ascending colon 6 cases (29%), transverse colon 6 cases (29%), descending colon 1 case (5%), sigmoid colon 3 cases (13%), and rectum 4 cases (19%). The capsule was excreted within 10 hours after ingestion and before the end of the lifetime of the battery in 100% of the patients. The colon cleanliness was adequate in all cases (100%). The sensitivity and specificity of CCE2 for detecting LSTs were 81% and 100%, respectively. For detecting LST-G, the sensitivity and specificity of CCE2 were 71% and 100%, respectively. For detecting LST-NG, the sensitivity and specificity of CCE2 were 86%and 100%, respectively. The 4 false-negative cases of CCE2 were 1) LST-G, 18mm, cecum, TA, 2) LST-G, 20mm, sigmoid colon, TA, 3) LST-NG, 25mm, transverse colon, SSA/P, and 4) LST-NG, 20mm, transverse colon, SSA/P, respectively.
Conclusion: The use of CCE2 allows visualization of the LST in most cases, however its sensitivity for detecting LST (especially located in the transverse colon or SSA/P) is low as compared with the use of OC.
Disclosure of Interest: None declared

OP108 CAPSULE ENDOSCOPY IS SUPERIOR TO MULTIDETECTOR CT SCAN FOR EVALUATION OF SMALL BOWEL DISORDERS: A META-ANALYSIS

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Introduction: Capsule endoscopy and multidetector CT scan are diagnostic tools for evaluation of small bowel (SB) disorders, including obscure GI bleeding (OGIB). Studies comparing the diagnostic yield of these tests for SB lesions have shown conflicting results.
Aims & Methods
Aims: The aim of this study was to compare the diagnostic yield of capsule endoscopy (CE) and multidetector CT scan (MDCT) for small-bowel (SB) lesions using meta-analysis.
Methods: We performed a recursive search of studies comparing CE with MDCT for evaluation of SB disorders. MDCT in different studies included CT angiogram (CTA), CT enterography (CTE) or CT enteroclysis (CTEC). Data on diagnostic yield of CE and MDCT for small bowel lesions were extracted, pooled, and analyzed. Odds ratio (OR) and 95% confidence intervals (CIs) using pooled data for the yield of CE and MDCT for SB lesions were calculated using a random effects model (REM) for analyses since several of the outcome measures had significant heterogeneity. Funnel plots and Galbraith plots were consulted to determine potential publication bias, and all study results were determined to be appropriate for combined analysis
Results: Ten studies compared CE and MDCT (CTE-4 studies, CTEC-3 studies, CTA-2 studies, and both CTA and CTE-1 study) in patients with suspected SB disorders, including OGIB, Crohn disease or SB tumor. The SB findings on CE and MDCT were confirmed on deep enteroscopy, surgery, or mesenteric angiogram in 9 studies (this information was not provided in 1 study). The pooled overall yield for SB findings was significantly higher with CE (49.7%; n = 409) compared with MDCT (29.7%; n = 461) (odds ratio 1.96; 95% CI 1.14-3.37; REM). Seven studies compared CE and MDCT in patients with OGIB (73% with overt OGIB based upon data from 5 studies). The pooled overall yield was significantly higher with CE (50.4%; n = 329) than MDCT (32%; n = 350); (OR 2.17; 95% CI 1.13-4.18; REM). Ten studies reported vascular, inflammatory lesions and polyps/tumors; the pooled overall yield of CE (12.4%; n = 409) was significantly higher than MDCT (3.4%; n = 461) only for vascular lesions (OR 3.38; 95% CI 1.68-6.78; REM). The pooled overall yield of CE and MDCT for inflammatory lesions was 12.9% (n = 409) and 8.4% (n = 461), respectively (OR 1.61; 95% CI 0.93-2.80; REM).

The pooled overall yield of CE and MDCT for polyps/tumors was 13.6% (n = 409) and 15.1% (n = 461), respectively (OR 0.85; 95% CI 0.57-1.28; REM).
Conclusion: CE has a significantly higher yield than MDCT for SB lesions in patients with suspected SB disorders, including OGIB. Among the SB lesions, CE has a significantly higher yield than MDCT for only vascular lesions. There is no difference between the tests for detection of inflammatory lesions or tumors/polyps. CE should therefore be considered the first test of choice for SB evaluation. MDCT may be indicated in patients with a contraindication for CE, and those with a negative CE but high clinical suspicion for a SB lesion.
Disclosure of Interest: S. Pasha Financial support for research: Covidien, Capsovision, Consultancy: Covidien, R. McLemore: None declared, A. Hara: None declared, M. Crowell: None declared, J. Leighton Financial support for research: Covidien, Capsovision, Consultancy: Covidien, Olympus

OP109 MONITORING AND ENDOSCOPIC TREATMENT OF SMALL INTESTINAL POLYPS IN PEUTZ-JEGHERS SYNDROME: A 12-YEARS FOLLOW-UP

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Introduction: Small intestinal polyps screening in Peutz-Jeghers (PJ) syndrome has evolved during the last decade since new non-invasive technologies have arisen such as capsule endoscopy (CE), MR enterography (MRE) or CT enterograhy (CTE). Polypectomy during double balloon (DBE) or spiral enteroscopy (SE) has become the first line treatment, replacing push enteroscopy (PE), and surgery is less frequently needed.
Aims & Methods: Our aims were: 1/ to describe diagnostic yields of CE and imaging techniques for small intestine polyps screening and 2/ to evaluate therapeutic yield of DBE or SE in PJ syndrome. We conducted a retrospective study based on a cohort of PJ syndrome patients followed-up in a French tertiary center within a specialized network. Between 2002 and 2014, 23 patients (M/F = 14/9, mean age = 35 years old (8-58), history of small intestine surgical resection 17/23 = 74%) with PJ syndrome were followed-up in our center. Small intestinal polyp screening was performed every 2 to 3 years using CE and/or MRE and/or CTE. Endoscopic treatment using mainly DBE or SE was attempted for polyps greater than one centimeter seen during screening. In case of endoscopic treatment failure, or incomplete treatment, surgical enteroscopy or surgical resection was performed.
Results: During a mean follow-up of 62 months (2-132), 21/23 patients (91%) had 39 CE procedures (1.9 CE/patient (1-4)), 13/23 patients (57%) had 21 radiologic exams with CTE (n = 11) or MRE (n = 10) (1.6 exam/patient (1-3)) and 23/23 had 46 small bowel endoscopies (39 per-oral and 7 per-anal) using DBE (n = 29), SE (n = 15) or PE (n = 2) (2 exams/patient, (1-6)). Diagnostic yield for polyp detection was 92% for CE and 90% for both radiologic techniques. Small bowel endoscopic polypectomy allowed the resection of 189 polyps measuring 5 to 60mm (8 polyps/patient (1-45)) and was considered as complete in 17/23 patients (74%). Neither severe bleeding nor perforation was noted. Surgical enteroscopy was performed in 4/23 patients (17%) allowing a supplementary resection of 58 polyps (14 polyps/patient (7-25)), measuring between 5 and 40mm. Surgical treatment by small intestine resection was indicated in 2/23 patients (9%), the first one because of a large jejunal polyp of 6 cm that was not feasible with DBE and the second one because of a recurrence of an anastomotic flat polyp. This actual rate of surgical resection was statistically different from that observed initially in our cohort (9% vs 74%, $p < 0.001$).
Conclusion: CE and small intestine imaging by MRE or CTE have an excellent diagnostic yield (90%) for small bowel polyp screening in PJ syndrome. Endoscopic polypectomy by DBE or SE is sufficient in 90% of cases when combined to surgical enteroscopy. Indication for surgical resection has become very rare, but remains a good alternative for difficult cases or complex post-surgical recurrences.
Disclosure of Interest: None declared

MONDAY, OCTOBER 26, 2015 15:45-17:15
IRRITABLE BOWEL SYNDROME: WHAT CAN SCIENCE TELL US? - ROOM E4

OP110 EXPLORING THE GENETIC ARCHITECTURE OF IBS THROUGH GWA STUDIES OF > 25,000 INDIVIDUALS FROM GENERAL POPULATION COHORTS

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Introduction: A heritable component of Irritable bowel syndrome (IBS) has been demonstrated, but gene-hunting efforts have so far been scarce. Exploiting its high prevalence, we seek to identify IBS risk genes through genome-wide association studies (GWAS) of general population samples.[1]
Aims & Methods: Following our recent report of the first GWAS of IBS in the Swedish population[2], we are now studying several other population-based cohorts, and aim for later comprehensive meta-analyses. So far, the following cohorts have been included (total N > 25,000): SALT (Sweden), SHIP-trend (Germany), Northern Finland Birth Cohort 1966 (Finland), TwinsUK (UK) and LifeLine-Deep (The Netherlands). IBS cases and asymptomatic controls were identified using epidemiological data and symptom-based Rome III criteria. Upon stringent quality controls (QC), genotype and HapMap2 imputed data for 1.8-6.6 million markers and 823-5,332 individuals from different cohorts were used for association testing with logistic regression under an additive model adjusted for gender.
Results: Association testing comparing IBS cases and controls identified several chromosomal regions providing GWAS signals of suggestive ($P < 5x10-5$) significance in individual cohorts, with large heterogeneity across datasets. Genes from shared pathways map to these regions, including those involved in prostaglandin synthesis, circadian clock, neuropeptide transmitters and others. Meta-analysis of data from these cohorts is under way.
Conclusion: It is a long and winding road to the identification of unequivocal IBS risk genes and associated variants. This requires massive sample size and replication of results across different populations, as well as a conclusive validation of findings in the clinical settings through case-control studies. Our approach holds the promise to overcome these limitations, and through large international collaboration we are gathering the numbers that are ultimately necessary to identify true IBS genetic risk factors with adequate statistical power. Overall, the set of association signals identified in independent GWA studies, and the later meta-analysis with additional incoming datasets, provide the first solid foundation for major follow-up efforts and further replication in independent case-control studies.

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Disclosure of Interest: None declared

OP111 INTESTINAL MICROBIOTA IN PATIENTS WITH IBS - HIGH THROUGHPUT SEQUENCING OF THE MUCOSA AND LUMINAL MICROBIOTA

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Introduction: Alterations in the intestinal microbiota is emerging as an important factor in the pathogenesis of irritable bowel syndrome (IBS). The luminal microbiota (LM) and the mucosal-associated microbiota (MAM) are two distinct ecosystems and are thought to have different metabolic and immunological functions. However, most of the studies investigating the intestinal microbiota in IBS have focused on analysis of fecal samples and the very few studies that investigate the MAM have used samples collected following preparation for endoscopic procedures.
Aims & Methods
Aim: To characterize and compared the intestinal LM and MAM in IBS patients and healthy controls (HC) that did not receive a bowel cleansing.
Methods: Fresh fecal samples and colonic mucosal biopsies were collected from 16 IBS subjects before (fecal) and during (mucosa) a flexible sigmoidoscopy of an unprepared bowel. Characterization of bacterial communities was done using high throughput pyrosequencing of the 16S rRNA gene (V1-V3). Microbial richness and diversity were calculated using the Shannon index of diversity. Normalized percentages of the core microbial taxa (present in ≥25% of samples of either niche) were compared, and adjusted for multiple comparisons using a false discovery rate (FDR) at 0.1.
Results: Similar to what we have recently reported in HC, patients with IBS demonstrated: 1. Significant microbial population differences between LM and MAM (ANOSIM: $R = 0.3$, $P = 0.001$) 2. A significantly tighter clustering in the LM compared to the MAM (average weighted UniFrac distances- 0.26 ± 0.04 vs. 0.42 ± 0.11, $P < 0.001$, respectively) and 3. Higher diversity in the LM compared to the MAM (Shannon diversity index: 4.79 ± 0.5 vs 4.26 ± 0.8, $P < 0.05$) 4. The abundance of dominant phyla in the LM and MAM niches was significantly different: *Firmicutes* (41% vs. 28%, FDR < 0.001, respectively), *Actinobacteria* (20% vs. 12%, FDR < 0.001, respectively) and *Proteobacteria* (11% vs. 20%, FDR < 0.001, respectively).
The abundance of 56 genera differed significantly (FDR < 0.1) between the two niches. All genera belonging to the *Proteobacteria* and *Bacteroidetes* phyla, were more abundant in the MAM compared to the LM in HC and in IBS patients. However, while in HC all six genera of the *Actinobacteria* phylum were more abundant in the LM niche and most (23 out of 34) of the genera of the *Firmicutes* phylum were more abundant in the MAM niche, in IBS patients only a few of the genera of the Actinobacteria (3 out of 9) and *Firmicutes* phyla (6 out of 28) were more prominent in the MAM niche.
Conclusion: The intestinal LM and MAM are significantly different from each other in composition and diversity both in IBS and HC. IBS and HC are different in both LM and MAM. These two microbial niches should be investigated independently in order to better understand the role of the intestinal microbiota in the pathogenesis of IBS.
Disclosure of Interest: None declared

MONDAY, OCTOBER 26, 2015 15:45–17:15
NEW WAYS OF ASSESSMENT IN CROHN'S DISEASE – ROOM E3

OP112 INVESTIGATING THE SMALL BOWEL IN PEDIATRIC CROHN'S DISEASE: PROSPECTIVE COMPARATIVE STUDY BETWEEN SMALL INTESTINE CONTRAST ULTRASONOGRAPHY AND MAGNETIC RESONANCE IMAGING

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Introduction: Small bowel (SB) assessment is a cornerstone for the proper management of pediatric Crohn's disease (CD). Magnetic resonance imaging (MRI) is now considered the gold-standard for the evaluation of SB. However, MRI is an expensive technique, it requires a strong patient's compliance and need a considerable amount of oral contrast to ensure an adequate distension of the intestinal lumen. Small intestine contrast ultrasonography (SICUS) is a, non-invasive and low-cost imaging modality in CD, and it is generally well tolerated by pediatric patients (pts).

Aims & Methods: To compare the diagnostic accuracy of SICUS and MRI in detecting presence, site and extension of SB disease and in assessing stricturing complications in pediatric pts with suspected or known CD. Pts referred to our Pediatric Gastroenterology and Liver Unit for suspected CD or for relapse of a known CD were prospectively enrolled, from January 2012 to December 2014. All pts underwent SICUS, MRI and ileo-colonoscopy according to previously published methods *. The examinations were performed by different operators unaware of the results of other techniques. To allow the comparative study the SB was subdivided into three sections: jejunum, ileum, terminal ileum. The statistic concordance (k) between the two techniques in detecting presence and site of SB lesions was calculated according to Landis and Koch criteria**. For the terminal ileum (TI) sensitivity (SE) and specificity (SP) were assessed too, having ileo-colonoscopy as reference standard. Comparative evaluation of the extension (cm) of disease in the different SB segments was assessed using one-way ANOVA with Kruskal-Wallis post-test.

Results: Sixty-six consecutive pts (median age 13; range 7-18), with suspected (23) or known (43) CD were included. The overall concordance (k) between SICUS and MRI in assessing the presence of SB lesions was high: $k = 0.94$ (ES 0.06; 95%CI 0.8-1). The k for segments was: 0.67 (ES 0.1, 95%CI 0.4-0.8) for jejunuum, 0.91 (ES 0.06, 95% CI 0.76-1) for ileum and 0.91 (ES 0.06; 95%CI 0.8-1) for TI. SE and SP of SICUS and MRI in assessing TI lesions respectively were 98% and 100% and 93% and 92%. One-way ANOVA showed no difference in assessing the extension of lesions between SICUS and MRI in the different SB segments. The k between SICUS and MRI for the presence of SB strictures was 0.62 (ES 0.1, 95% CI 0.4-0.8). SE and SP of SICUS and MRI in detecting strictures of the TI respectively were 100% and 100% and 92% and 87%. MRI provided 7 false positive results, not detected at SICUS nor confirmed at endoscopy.

Conclusion: The diagnostic performance of SICUS is comparable to that of MRI in pediatric CD. Due to its capability to provide a dynamic evaluation of the SB, SICUS is useful in assessing strictures, probably with higher accuracy than MRI. Thus, SICUS might represent a first-line diagnostic tool in pediatric CD, able to reduce costs and to post-pone or even avoid more invasive and expensive investigations.

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Disclosure of Interest: None declared

OP113 DIAGNOSTIC PERFORMANCE OF MR ENTEROGRAPHY IN 'ROUTINE CLINICAL PRACTICE' FOR THE ASSESSMENT OF TERMINAL ILEUM IN CROHN'S DISEASE: MARGINALLY INFERIOR RESULTS WITH A COMPLEMENTARY ROLE

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Introduction: Magnetic resonance enterography (MRE) in Crohn's disease (CD) management has been rapidly growing in importance during recent years. MRE has the advantages of providing high soft tissue contrast, obtaining static and dynamic images, and avoiding ionizing radiation. Prospective studies perfomed in highly academic centers by dedicated radiologists with the state-of-the-art technique yields a diagnostic accuracy of 91%. A systematic review reported per-patient sensitivity and specificity of MRI for the diagnosis of CD as 78% and 85%, respectively.[1]

Aims & Methods: The objective of this study was to evaluate the accuracy of MRE for detecting terminal ileal involvement in CD compared to the gold-standard ileocolonoscopy in the 'real-life setting'. A total of 156 patients (mean age 37 ± 11, 94 male) were included in this study, and underwent both MRE and ileocolonoscopy within a 60-day period. Patients with ileocolonic (n:35) and ileal (n:53) CD constitutes 'terminal ileum affected group'. CD patients without ileal involvement (n:47), and ulcerative colitis patients without backwash ileitis (n:21) constitutes control group (normal terminal ileum). All MRE images were evaluated by on-duty radiologists, and not consulted by an expert working in abdominal MR imaging. Colonoscopic SES-CD (<3 inactive), and MRE simple activity scores (SEAS) were calculated.

Results: MRE showed 75% accuracy (71% sensitivity, 80% specificity, 82% positive predictive value, 67% negative predictive value) for detecting ileal disease in routine clinical practice. MRE was false negative in 23 patients (16%). In two patients with a diagnosis of CD according to MRE findings, colonoscopic biopsies revealed lymphoma and adenocarcinoma. A statistically significant positive correlation was found between MRE SEAS scores and SES-CD scores ($r = 0.412$; $P < 0.01$). For SEAS score, a cut off level of ≥ 2 has the best diagnostic performance for discrimating active from inactive disease (accuracy 75%, sensitivity 77%, specificity 73%).

Conclusion: MRE has marginally inferior diagnostic performance in general practice when compared to results in well-designed studies. Diagnostic performance of MRE seems dependent on the experience of radiologists and state-of-the art technique. False negativity/positivity, and unexpected tissue diagnosis of malignancy in two patients (1%) underlies the importance of ileocolonoscopy, and complementary nature of the cross-sectional imaging.

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Disclosure of Interest: None declared

OP114 A SIMPLE ULTRASONOGRAPIC SCORE FOR THE ACCURATE DETECTION OF INFLAMMATORY ACTIVITY IN CROHN'S DISEASE

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Introduction: Cross-sectional imaging is central in the diagnosis and management of Crohn's disease (CD), an immune-mediated disease of the small and large bowel that often leads to transmural damage. Safe, non-radiation based modalities are preferred, given young age of onset. Ultrasound is accurate in detection of disease activity, however a simple validated score for inflammatory activity is not widely used.

Aims & Methods: The aim of this study was to evaluate the sonographic grey scale parameters that contribute most to disease activity and devise a clinically applicable score. This was an IRB-approved, single-center prospective study evaluating patients with established Crohn's disease treated with adalimumab. Patients were evaluated with ileocolonoscopy (scored using validated indices, Simple Endoscopic Score and Rutgeert's Score) and ultrasound within 2 weeks of endoscopy at time zero and either at 6 or 12 months depending on clinical indication. Clinical indicators (Harvey Bradshaw Index/ HBI) and serologic inflammatory markers (C-Reactive Protein/ CRP) were collected at each time point. The ability of HBI and CRP to predict disease activity was determined by comparison with endoscopy and ultrasonography using Fisher's exact test. An US score was developed based on ordinal logistic regression using a proportional odds model. The final model included only variables with p values ≤ 0.05. Disease severity was classified according to endoscopic score with the most significant grey scale variables weighted to classify individuals into different severity levels. ROC curves were plotted to demonstrate the discriminative and predictive capacity of the scoring system developed.

Results: A total of 63 patients were included, 24 had 2 endoscopic examinations, while 39 had 1, giving a total of 87 US and endoscopic comparisons. The average age was 40.7 years, with 28 females and 35 males. The most common disease distribution was ileocolonic 59% (37/63), with 30% (19/63) having terminal ileal and 8% (5/63) with isolated colonic disease. HBI and CRP were found to have no significant association with endoscopic ($p = 0.188$, 0.156 respectively) or ultrasonographic ($p = 0.138$, 0.273 respectively) findings. Three grey scale parameters were significantly associated with inflammatory activity, including bowel wall thickness ($p = 0.046$) mesenteric inflammatory fat ($p = 0.006$) and lymph nodes ($p = 0.028$). Based on the novel score, the ROC curve for distinguishing patients with inactive or mild disease from those with active disease was 0.89 while distinguishing normal from any activity was 0.81.

Conclusion: A simple sonographic score comprising three parameters can be used to accurately reflect disease activity, as seen on gold standard endoscopy. Thus, ultrasound may be a surrogate to endoscopy to guide disease management and this score may increase standardization of sonographic CD activity measurement across centers.

Disclosure of Interest: None declared

OP115 THE ROLE OF ULTRASOUND ELASTICITY IMAGING IN PREDICTING ILEAL FIBROSIS IN CROHN'S DISEASE PATIENTS

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Introduction: Bowel wall fibrosis is associated with a complicated disease behavior and a reduced efficacy of anti-inflammatory therapies in patients with Crohn's disease (CD). The quantitative assessment of fibrosis severity in CD-affected areas, and their differentiation from inflammatory lesions, can be of great help in clinical decision-making.
Aims & Methods: The aim of the study was to evaluate the feasibility, reliability and reproducibility of Ultrasound Elasticity Imaging (UEI) towards the assessment of ileal fibrosis in patients with CD.
Twenty-three consecutive patients with ileal or ileocolonic CD, elected for surgical resection of the terminal ileum, underwent bowel ultrasound and UEI. Twenty inflammatory CD patients without complications were enrolled as controls. Bowel wall stiffness was evaluated with UEI by means of color scale and quantitative strain ratio measurement. Bowel wall thickness, stratification pattern and vascularization were evaluated at bowel ultrasound. The severity of bowel wall fibrosis and that of acute and chronic inflammation were evaluated on histological sections by both semi-quantitative and quantitative image analysis, and used as a reference standard.
Results: The UEI strain ratio measurement was significantly correlated with the severity of bowel fibrosis at both semi-quantitative and quantitative histological image analysis: it was characterized by an excellent discriminatory ability for severe bowel fibrosis (AUROC: 0.917; 95% CI: 0.788-1.000). UEI strain ratio measurements were characterized by an excellent inter-rater agreement with with ICC at 0.90 (95% CI 0.75-0.96). At multivariate analysis, bowel wall fibrosis resulted the only independent determinant of strain ratio ($R^2 = 0.75$, $p < 0.0001$). The ileal strain ratio of inflammatory CD patients was significantly lower than in operated CD patients with severe fibrosis (1.2 ± 0.6 vs 2.4 ± 0.5, $p = 0.0005$).
Conclusion: The results show that UEI is a reliable highly reproducible technique, which can be complementary to bowel ultrasound examination in CD patients, as it can accurately identify small bowel segments affected by advanced fibrosis, without being influenced by the severity of intestinal inflammation.

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Disclosure of Interest: None declared

OP116 FAECAL CALPROTECTIN IN PATIENTS WITH SUSPECTED SMALL BOWEL CROHN'S DISEASE: CORRELATION WITH SMALL BOWEL CAPSULE ENDOSCOPY

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Introduction: Faecal calprotectin (FC) is a stool biomarker recommended as a simple, non-invasive test to distinguish between inflammatory bowel disease (IBD) and functional bowel disorders. Despite a good correlation with colonic inflammation, FC is felt to be less accurate at identifying small bowel (SB) inflammation. Small bowel capsule endoscopy (SBCE) has a high sensitivity for detecting SB mucosal inflammation. We investigated the correlation between FC and SBCE in patients with suspected IBD.
Aims & Methods: We prospectively correlated the findings of SBCE with FC levels in patients under investigation for suspected IBD. Patient demographics, clinical symptoms, medications and blood parameters: haemoglobin (Hb), albumin, ESR and CRP were collected. SBCE findings including Lewis scores were analysed against FC values and final diagnosis.
Results: 127 patients were included, mean age 42 years (range 18-75 years), 85 female. Presenting symptoms included: a combination of diarrhoea, abdominal pain and bloating (74%), diarrhoea alone (13%), abdominal pain alone (12%), rectal bleeding (1%). Median time from FC measurement to SBCE was 62 days. 12% had a family history of IBD, 14% were current smokers. 6 patients with a diagnosis of colonic pathology were excluded.
Results are presented in the table. Of the 14 patients (23.0%) with FC > 100mg/kg, 14 had clinically significant SB findings (12 SB ulcers, 2 villous atrophy) and mean FC levels 468mg/kg (range 112-1010mg/kg). A definitive diagnosis was made in 10 patients (9 Crohn's disease, 1 NSAID enteropathy), the remaining 10 patients are undergoing further evaluation. FC > 50mg/kg was significantly associated with clinically relevant SBCE findings (χ^2 $p = 0.02$). FC had a sensitivity 81%, specificity 40%, positive predictive value 42% and negative predictive value (NPV) 80%. Receiver operating curve analysis showed an area under the curve (AUC) of 0.626 for FC, similar to CRP (AUC 0.638) but better than ESR (AUC 0.524) and Hb (AUC 0.545). Albumin most closely correlated with an AUC 0.686. Multiple logistical regression showed serum albumin to be the only variable significantly associated with positive SBCE ($p = 0.032$). Lewis score significantly correlated with FC value ($r = 0.793$, $p < 0.05$).

Table 1

FC Level	< 50mg/kg	51-100mg/kg	> 100mg/kg
Total	40	20	61
Normal SBCE	38	16	47
SBCE suggestive of IBD (or coeliac disease)	2	4	14
Definitive diagnosis	1	2	7

Conclusion: With a reasonable sensitivity and NPV, FC could be most effectively utilised to screen out patients where further SB investigation is unnecessary. However, in our series 1 patient with FC < 50mg/kg had SB Crohn's disease. Thus at best, FC can be only be recommended as an adjunct to clinical decision making, when patient factors and other biochemical parameters are also taken into account.
Disclosure of Interest: None declared

OP117 FAECAL CALPROTECTIN MEASUREMENT AND INFLIXIMAB TROUGH LEVELS PREDICT THERAPEUTIC EVOLUTION CD PATIENTS IN CLINICAL REMISSION

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Introduction: The deep remission notion (clinical remission and mucosal healing) is an important objective for patients under treatment. The appearance of inflammation and pharmacological biomarkers could be a non-harmful way of predicting the evolution of Crohn's disease (CD). The aim of our study was to offer a predictive model for relapse in CD patients presenting clinical remission undergoing infliximab (IFX) treatment.
Aims & Methods: It was a prospective monocentric study that included all CD patients on IFX maintenance treatment (5mg/kg) and in clinical remission (CDAI < 150) for at least 16 weeks, between 2011 and 2014. On the day of the IFX infusion, all of these patients underwent a faecal calprotectin assay (Buhlmann technique), a CRP assay and pharmacological assays of IFX (ELISA technique, Theradiag). TLI (> 2µg/ml) and ATI (< 20ng/ml) were considered therapeutic as well as CRP levels < 5mg/l and faecal calprotectin levels < 250 mg/g of stools. All of the patients included were followed up for a minimum of nine months. A CDAI score was calculated at each IFX infusion. A patient was defined in loss of response to IFX (LOR) when the CDAI was above 220, resulting in a change of treatment deemed necessary by the physician (IFX optimisation, change of medical treatment including the use of corticosteroids, surgery).
Results: 119 patients (mean age: 34 +/- 12 years, M:F sex ratio 1.2, mean duration of evolution of the disease 7.8 years) were included. The mean follow-up period was 20.4 months. 17% of the patients were on combotherapy (IFX and azathioprine). During follow-up, 37 patients (31.1%) out of the 119 relapsed, 78% within the first 6 months (mean period: 4.6 months). While the clinical characteristics of the relapsed and non-relapsed patients were similar, a univariate analysis isolated four significant factors predicting LOR: (CRP > 5mg/l ($p = 0.043$), ATI > 20ng/ml ($p < 0.001$), LTI > 2 µg/ml ($p < 0.001$) and calprotectin > 250 µg/g stools ($p < 0.001$)). After logistic regression, two independent factors were linked to a loss of clinical response: LTI < 2µg/ml (OR: 4.34; 95% CI: 1.28-10.7; $p = 0.001$) and faecal calprotectin > 250µg/g stools (OR: 3.5; 95% CI: 1.5-8.7; $p = 0.001$). In light of these results, a training cohort of 55 patients was isolated randomly in order to implement a predictive model for LOR in patients on IFX and in clinical remission. The combination of calprotectin > 250µg/g stools and TLI < 2µg/ml enabled to be predicted LOR in 95% of the cases within 6 months. This model was validated on the test cohort of 64 patients with a PPV of 95% and an NPV of 95%.
Conclusion: In IFX-treated CD patients and in clinical remission, a combination of TLI (< 2µg/ml) and faecal calprotectin (>250µg/g of stools) enable the prediction of clinical recurrence within 6 months in 95% of cases. Intervention studies are needed to assess the impact of treatment modification in this group of patients.
Disclosure of Interest: X. Roblin Lecture fee(s): MSD; Theradiag, G. duru: None declared, L. Clavel: None declared, E. Deltedesco: None declared, J. M. Phelip: None declared, L. Peyrin Biroulet: None declared, S. Paul: None declared

MONDAY, OCTOBER 26, 2015 15:45-17:15
INSIGHTS INTO CHOLESTATIC LIVER DISEASE - ROOM E5

OP118 BILIARY BILE ACID AND PHOSPHOLIPID COMPOSITION IN PSC: EFFECT OF DISEASE SEVERITY AND UDCA THERAPY

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Introduction: Primary sclerosing cholangitis (PSC) is chronic cholestatic liver disease of unknown origin, characterized by inflammation and strictures of intra- and extrahepatic bile ducts, leading to liver cirrhosis and development of biliary dysplasia and cholangiocarcinoma. Several pathogenetic mechanisms has been suggested including the toxic bile acids induced inflammation and fibrosis of biliary epithelium. Ursodeoxycholic acid (UDCA), has widely been used to treat PSC demonstrating amelioration of cholestatic liver enzymes.
Aims & Methods: Aims of the study were to analyze: 1) bile acid, phospholipid and cholesterol content in bile in relation to disease severity in PSC, compared to controls, 2) the effect of UDCA therapy 20mg/kg/day on bile acid composition 3) the patient and disease severity related factors on bile composition.
Patients and methods: The study population consists of PSC patients naïve for UDCA therapy (n = 21), patients on UDCA therapy (n = 154) and controls (n = 27) referred for ERCP for confirming or excluding the diagnosis of PSC or for biliary dysplasia surveillance. During ERC bile sample was aspirated using balloon catheter and immersed immediately in liquid nitrogen (-196°C) and stored in -20°C. The total bile acids, cholesterol and phospholipids were analyzed by gas-liquid chromatography and the content of individual bile acids: deoxycholic (DCA), chenodeoxycholic (CDCA), cholic acid (CA), lithocholic (LCA) and UDCA were analyzed. The amount were expressed as molar percentages (mM%) of total bile acids. Blood samples were drawn at the time of ERCP for analysis of live enzymes. Cholangiographic findings were scored according to the modified Amsterdam score (mAm score).
Results: In total 175 PSC patients with adequate bile sample were included. The mean age of UDCA naïve patients was 34.0 ± 12.9 vs 40.9 ± 12.7 years in UDCA users, and 44.9 ± 14.8 years in controls, p = 0.020. Concomitant IBD was present at 86% vs 71% of patients, respectively. 1) Compared to controls, no differences were found in total bile acid concentration (mM%), or between individual bile acids. Phospholipid concentration were also similar in controls and in PSC patients. 2) UDCA therapy was associated with markedly increased of UDCA in bile (9.7± 19.0 vs. 49.1± 22.2%, p < 0.001), with significant reduction of biliary cholesterol content, while the total bile acid and phospholipid content remained unchanged. Proportion of both the primary bile acids, DCA (13.4 ± 13.1, vs 7.0 ±7.2%, p = 0.00222) and CDCA (31.8 ± 12.3 vs 18.3 ± 8.0%, p < 0.001) were markedly reduced. Of the secondary bile acids, CA mM% dropped from 43.5 ± 16.9 to 23.4 ± 16.1%, p < 0.0001, but LCA remained unchanged. No correlation was found between the disease severity judged by ERC findings (mAm score) and biliary bile acid changes during UDCA therapy. In multivariate analysis colectomy was associated with decrease with LCA (t = -2.63, p = 0.010) and DCA (t = -2.50, p = 0.014) and increase of CA (t = 3.04, p = 0.003).
Conclusion: No differences were found in biliary bile acid or phospholipid composition between controls and PSC patients, suggesting that they do not play significant role in the pathogenesis of PSC. UDCA therapy was associated with significant reduction of primary bile acids, but also with reduction of more toxic secondary bile acids. Disease progression during UDCA therapy did not impact bile acid composition.
Disclosure of Interest: None declared

OP119 ALKALINE PHOSPHATASE (ALP), BILIRUBIN AND THE RISK FOR LIVER TRANSPLANT AND LIVER-RELATED DEATH IN PATIENTS WITH PRIMARY BILIARY CIRRHOSIS (PBC)

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Introduction: Previous work created and validated a predictive model of liver transplant and liver-related death in PBC patients in the UK [Carbone et al, 2015]. Predictors included bilirubin µmol/l; ALP U/l; albumin g/l, platelets per 10^9/l and ALT. Risk was calculated as: = 1 – (0.87^EXP(-0.35*(((ALP/1500)^-0.5)-2.296) – (0.024*(((ALT/500)^-1)-7.901)) + 1.127*(LN(bilirubin/170)+2.62) + 2.954*((albumin/35^-1)-0.851) - 0.532*(platelets/150-1.854)).
Aims & Methods: The aim was to calculate absolute risk reduction (ARR) and number needed to treat (NNT) associated with fixed percent ALP reductions using an algorithm for predicting liver transplant or liver-related death in PBC patients. ALT was set at 120; albumin at 50; and platelets at 150. Bilirubin varied as a function of upper limit of normal (ULN): 17 (1X ULN), 34 (2X ULN) and 51 (3X ULN). Baseline ALP was set at 500, 400, 300 and 200. We applied 20%, 40% and 60% reductions to each baseline ALP level. We calculated 15-year absolute risk (AR), ARR, and NNT.
Results: Baseline risk for liver-related death or liver transplant increased dramatically as a function of bilirubin. Across bilirubin levels, ARRs were higher and NNTs lower at lower baseline ALP. At bilirubin = 34 and ALP = 200, a 40% ALP reduction produced a 10% ARR for liver transplant or death from liver disease; NNT = 10. A 60% ALP reduction lowered risk by 19%; NNT = 5. At baseline ALP = 500, a 40% ALP reduction yielded ARR = 7% (NNT = 14); 60% reduction ARR = 13% (NNT = 8). At a bilirubin of 20, the NNTs at baseline ALP = 500 were 50 (20% ALP reduction), 20 (40% reduction) and 9 (60% reduction).

		Bilirubin 17								
		20% ALP reduction			40% ALP reduction			60% ALP reduction		
Baseline ALP	AR	AR	ARR	NNT	AR	ARR	NNT	AR	ARR	NNT
500	45%	43%	2%	50	40%	5%	20	34%	11%	9
400	43%	40%	3%	33	37%	6%	17	31%	12%	8
300	40%	37%	3%	33	33%	7%	14	27%	13%	8
200	34%	31%	3%	33	27%	7%	14	22%	12%	8
		Bilirubin 34								
500	73%	70%	3%	33	66%	7%	14	60%	13%	8
400	70%	67%	3%	33	63%	7%	14	56%	14%	7
300	66%	63%	3%	33	58%	8%	13	50%	16%	6
200	60%	56%	4%	25	50%	10%	10	41%	19%	5
		Bilirubin 51								
500	87%	85%	2%	50	82%	5%	20	77%	10%	10
400	85%	83%	2%	50	79%	6%	17	73%	12%	8
300	82%	79%	3%	33	75%	7%	14	67%	15%	7
200	77%	73%	4%	25	67%	10%	10	57%	20%	5

Conclusion: These data demonstrate the importance of early intervention in PBC. Preventing bilirubin from rising above ULN had the greatest impact in terms of lowering risk for adverse liver outcomes. The data show similar results for ALP: the greatest reduction in risk for liver transplant and liver-related death resulted from decreasing ALP at lower baseline levels. These results support the need to treat PBC early, to stabilize bilirubin at the lowest level possible and to treat to the lowest achievable ALP.

Reference

1. Carbone M, Sharp SJ, Flack S, Paximadas D, Spiess K, Adgey C, Griffiths L, Lim R, Trembling P, Williamson KD, UK-PBC Consortium. The UK-PBC Risk Scores: derivation and validation of a scoring system for long-term prediction of end-stage liver disease in primary biliary cirrhosis. Under submission.

Disclosure of Interest: M. Carbone: None declared, T. Mayne Financial support for research: Intercept Pharmaceuticals, Shareholder: Intercept Pharmaceuticals, G. Mells: None declared, D. Jones: None declared

OP120 NOVEL PROGNOSTIC MODEL FOR PRIMARY SCLEROSING CHOLANGITIS: THE IMPORTANCE OF INCLUDING LABORATORY VALUES

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Introduction: Primary sclerosing cholangitis (PSC) is a chronic, cholestatic liver disease, without effective drug treatment options. The only curative option is liver transplantation (LT). It is important to be able to make an indication of prognosis, for purposes of patient counseling, management and adequate timing of LT. Many biomarkers of disease progression have been assessed, recent literature indicates the independent prognostic ability of alkaline phosphatase (ALP) over time.
Aims & Methods: Aim of this study was to create a prognostic model consisting of disease phenotypical as well as biochemical variables.
692 PSC patients were identified in a large population based PSC cohort from the Netherlands. Variables of PSC phenotype, biochemistry results and long term follow-up data were retrieved from patient records. Clinical endpoints were development of cholangiocarcinoma, LT, or PSC-related death. Laboratory values were transformed by log transformation, missing values were imputed by multiple imputation. All variables were assessed as potential predictors of survival by univariate analysis. To calculate the prognostic index (PI), Cox proportional hazards model was developed and internally validated with bootstrap.
Results: The median follow-up time was 85 months (range 0-468 months). All phenotypical variables and biochemistry results were considered for the model. After variable selection by LASSO, multivariable Cox models were fitted, and parameters estimated from 20 imputation datasets were averaged. The following formula was created:
PI = 1.374*PSC type(0/1)[1] + 0.023*Age at diagnosis PSC - 2.643*logAlbuminxULN^2 + 2.029*abs(logTrombocytesxULN-0.5)^2 + 0.544*logAspartate aminotransferase(AST)xULN^2 + 0.683*logAlkakaline phosphatase(ALP)xULN^2 + 0.430*logTotal bilirubinxULN^2
1: PSC type: Large duct = 1; Small duct = 0
2: xULN = times upper limit of normal
The PI yielded a c-statistic of 0.7180 (0.7080 after adjusted for optimism with 1000 times bootstrap).

Conclusion: By using a population-based PSC cohort, we were able to create a prognostic model based on PSC type, age at diagnosis PSC, albumin, thrombocytes, AST, ALP and total bilirubin. Internal validation using bootstrap showed adequate performance. The inclusion of biochemistry could facilitate the dynamic prediction of PI over time.
Disclosure of Interest: None declared

OP121 A SURVEY OF DRUG-INDUCED LIVER INJURY (DILI) CASES IN JAPAN

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Introduction: Drug-induced liver injury is an important cause of acute liver injury and the incidence of drug-induced liver injury seems to be increasing with the increase in the numbers of new drugs.
Aims & Methods: We retrospectively surveyed Japanese DILI cases until February 2015 from 25 hospitals.
Results: The total of 234 cases (97 cases of male and 137 cases of female) were distributed between 17 and 84 years old (average 57 years old), and were classified to 154 cases (66%) of the hepatocellular type, 32 cases (14%) with the mixed type and 48 cases (20%) with the cholestatic type according to the type of liver injury. The percentage of the hepatocellular type was increased compared to previous studies. Eosinophilia (>5%) was observed in 62 cases (26%). Drug-induced lymphocyte stimulation test (DLST) was performed in 136 cases (58%), and was positive in 67 cases (49%). According to the diagnostic scale of the Digestive Disease Week (DDW)-Japan 2004 (*Hepatol Res* 2005; 32: 250), 197 cases (93%) were diagnosed as highly probable and 13 cases (6%) as possible. Among DILI cases, 18% occurred within 7 days, 27% occurred within 14 days, 52% occurred within 30 days, 70% occurred within 60 days, 77% occurred within 90 days after starting drug administration. Percentages of causal drugs were as follows; 12% by antimicrobial drugs, 10% by anti-inflammatory drugs, 9% by drugs for the gastrointestinal system and drugs for the psychiatry and neurological system, 8% by anti-cancer drugs and dietary supplements. To clarify whether genetic factors are involved in the susceptibility of DILI, genetic association study was performed using DILI patients and healthy controls. Specific HLA types and several single nucleotide polymorphisms (SNPs) were significantly associated with the susceptibility of DILI on their type (the hepatocellular type, the mixed type, the cholestatic type).
Conclusion: Further storage of DILI cases and DNA samples will accelerate the characteristics of DILI cases in Japan.
Disclosure of Interest: None declared

OP122 HYBRID DRAINAGE USING A NASOBILIARY TUBE FOR TREATING ACUTE CHOLECYSTITIS

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Introduction: Emergency or early laparoscopic cholecystectomy is the standard treatment for patients with acute cholecystitis. However, in cases with hospital situations or because of patients' conditions, conservative treatment with antibiotics, followed by drainage and elective surgery may be performed as an alternative. For such cases, we developed a hybrid gallbladder drainage procedure that facilitates both external and internal drainage in a single session.
Aims & Methods
Aims: To prospectively evaluate efficacy and safety the hybrid gallbladder drainage in acute cholecystitis.
Methods: Patients with mild or moderate cholecystitis diagnosed according to the Tokyo guidelines 2007 (TG07) were enrolled if they wished to undergo elective surgery. The procedure was performed as follows: 1) place the nasobiliary drainage (NBD) tube in the gallbladder under endoscopic guidance, 2) lavage the gallbladder using 100-200 mL saline without removing the scope, 3) insert the guidewire through the NBD tube, 4) remove the NBD tube while measuring the length from the fundus of the gallbladder to the papilla, 5) cut the tube to the measured length, and 6) insert the trimmed tube into the gallbladder for internal drainage. The main outcome measurements were procedural success rate, clinical success rate, complication rate, procedure time, and duration of hospital stay.
Results: In all, 54 patients (median age, 69 years [range, 34-92], male: 27, female: 17) were included. Cholecystitis was mild in 18 patients (33%) and moderate in 36 patients (67%). The procedure was successful in 43 patients (80%). The total time taken for the procedure was a median of 54 min (range, 13-120). The cut length of the NBD tube was 25 cm (range, 17-35). A minor complication of bile leak from the cystic duct occurred in 2 patients (3.7%). The procedure was unsuccessful in 11 patients of the total 54 patients: complications occurred in 2 and the technical failure in 9, all of whom required percutaneous transhepatic gallbladder drainage (PTGBD). Among the 43 patients in whom the procedure was successful, 42 (98%) showed clinical success. Delayed elective cholecystectomy was performed in 48 patients (89%), and recurrent cholecystitis was not observed during the waiting time of a median of 42 days (range 9-138). The median duration of hospital stay was 8 days (range, 2-76). The duration of hospital stay in patients with procedural success was significantly shorter than in those with procedural failure (7 versus 14.5 days, $P < 0.01$).
Conclusion: Hybrid drainage using the nasobiliary tube for acute cholecystitis is efficient and safe. This procedure may be alternative if emergency/early surgery is impossible because of various causes.
Disclosure of Interest: None declared

OP123 POSTOPERATIVE ANTIBIOTIC USE IN THE TREATMENT OF ACUTE CHOLECYSTITIS: A RANDOMIZED, MULTICENTRE, NONINFERIORITY TRIAL

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Introduction: Acute calculous cholecystitis is a common diagnosis in the surgical practice with a clear indication for surgery. Among surgeons, there is no consensus regarding the use of extended antibiotic prophylaxis and it's use is mainly dependent on the clinical condition of the patient, perioperative findings and the surgeon's preference.
Aims & Methods: To determine the effect of extended antibiotics on postoperative infection rate in patients undergoing cholecystectomy, we conducted a multicentre randomized non-inferiority trial. We hypothesized that extended postoperative antibiotic treatment would not decrease the infectious complication rate. Based on a noninferiority margin of 5% and power of 80%, 78 patients were required in each groups. Patients with acute calculous cholecystitis undergoing cholecystectomy were eligible, provided that the APACHE-II score was 6 or less. Study participants were randomly assigned to a single pre-operative prophylactic dose of cefazoline (2000mgs) 15-30 minutes prior to incision (group A), or postoperative antibiotic treatment (cefuroxime 750mgs 3dd and metronidazole 500mgs 3dd intravenously during three days) in addition to a single prophylactic dose (group B). Primary endpoint was the occurrence of postoperative infections (wound infection, intra-abdominal abscess, pneumonia, urinary tract infection). Secondary endpoints were other postoperative complications, hospital stay and total costs. Analysis was by intention-to-treat.
Results: Between 2012 and 2014 a total of 156 patients were randomized in 6 teaching hospitals: 76 patients in group A and 80 patients in group B. Male/female ratio, age and APACHE-II score (average 3.5) were comparable between groups. Primary endpoint occurred in 3 patients (4%) in group A and in 3 patients (3.8%) in group B (RR 1.04, 95% CI 0.22-4.99; $p = 0.99$). Other postoperative complications occurred in 4 and 5 patients respectively (NS).
Conclusion: In patients with mild calculous cholecystitis, extended postoperative antibiotic treatment did not lead to a decrease of infectious complications.
Disclosure of Interest: None declared

MONDAY, OCTOBER 26, 2015 15:45-17:15
NORMAL AND ABNORMAL UPPER GI FUNCTION - ROOM E6

OP124 ANTICIPATORY FEAR MODULATES PERCEPTUAL AND NEURAL RESPONSES TO SUBSEQUENT GASTRIC PAIN IN HEALTH

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Introduction: Malfunction of descending pain modulatory pathways is believed to be playing an important role in the pathophysiology of pain-predominant functional gastrointestinal disorders such as Functional Dyspepsia (FD). Results from studies that combine neuro-imaging techniques with psychophysical methods suggest this 'top-down' modulation of pain transmission is heavily influenced by affective and cognitive psychological processes such as anticipatory fear. However, studies on the effect of anticipation on visceral pain perception are currently sparse, particularly for gastric pain.
Aims & Methods: We aimed to investigate the relationship between anticipatory fear and the subsequent perception of gastric pain, both at behavioural and neural level. We hypothesized a positive association between anticipatory fear and subsequent responses to gastric pain.
Fifteen healthy volunteers (5 men, mean age: 31.8 ± 2.27) participated in this study. Brain responses during cued certain (100% chance of receiving the painful stimulus) and safe anticipation (0% chance of receiving the painful stimulus, control condition) and subsequent gastric balloon distension at individually titrated pain threshold ($certain_{pain}$) or no balloon distension ($safe_{no\_pain}$, control condition) were measured using functional magnetic resonance imaging (fMRI). Ratings of anticipatory fear and pain intensity were collected using visual analogue scales (0-10) during scanning. Robust regression was used to test the association between anticipatory fear and pain intensity ratings. The relationship between anticipatory brain activity and pain intensity ratings and, vice versa, between anticipatory fear ratings and brain responses during the subsequent pain induction were investigated using SPM8 (whole-brain voxel-based analysis with voxel-level threshold of $p_{uncorr} < .005$ combined with a cluster-level threshold of $p_{FWE\text{-}corr} < .05$).

Results: Subjects rated fear significantly higher during certain compared to safe anticipation (3.93 ± 0.59 and 0.35 ± 0.13, respectively). Pain intensity ratings during subsequent pain induction were also higher ($certain_{pain}$: 5.78 ± 0.45; $safe_{no\_pain}$ 0.18 ± 0.06). Average anticipatory fear ratings during certain compared to safe anticipation were positively associated with average pain ratings during $certain_{pain}$ compared to $safe_{no\ pain}$ ($\Delta certain_{pain} - safe_{no\ pain}$) ($\beta = 0.37 \pm 0.23$, $p < .001$). Significant positive correlations of brain responses during certain anticipation with subsequent pain ratings were found in the insula, basal ganglia, anterior, mid- and posterior cingulate cortex , ventrolateral and –medial prefrontal cortex. Vice versa, fear ratings during anticipation were positively correlated with brain activity during subsequent gastric pain in the insula, midcingulate cortex and caudate nucleus.
Conclusion: This study demonstrated for the first time that behavioural and brain responses (at the level of the ''visceral pain neuromatrix'') during anticipatory fear are associated with increased perceptual and neural responses to gastric pain induction. This may explain how (anticipatory) fear impacts on visceral sensitivity and symptom reporting in FD.
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OP125 GPR84 PLAYS A ROLE IN THE PATHOGENESIS OF REFLUX DISEASE

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Introduction: Gastro-esophageal reflux disease (GERD) is one of the most common disorders in gastroenterology. Patients present with or without increased acid exposure indicating a non-uniform etiology. Thus the common treatment with proton pump inhibitors (PPIs) fails to control symptoms in up to 40% of patients.
Aims & Methods: To further elucidate the pathophysiology of the condition and explore new treatment targets, transcriptomics, proteomics and histological methods were applied to a surgically induced sub-chronic reflux esophagitis model in Wistar rats[1,2] after treatment with either omeprazole (PPI) or STW5, a herbal preparation shown to ameliorate esophagitis without affecting refluxate pH. The normal human esophageal squamous cellline HET-1A and human endoscopic biopsies were used to confirm our findings to the G-protein coupled receptor (GPR)84 in human tissue.
Results: Both treatments reduced reflux-induced macroscopic and microscopic lesions of the esophagi as well as known pro-inflammatory cytokines. Proteomic and transcriptomic analyses identified CINC1-3, MIP-1/3α, MIG, RANTES and IL-1β as prominent mediators in GERD[2]. Most regulated cyto-/chemokines are linked to the TREM-1 signaling pathway. The fatty acid receptor GPR84 was one of the most highly up-regulated genes in esophagitis (32.5x) but significantly decreased in treated groups, a finding supported by Western blot and immunohistochemistry in both rat tissue and capsaicin treated HET-1A cells. GPR84 was also found to be significantly up-regulated in patients with grade B reflux esophagitis.
Conclusion: The expression of GPR84 in esophageal tissue and its potential involvement in GERD are reported for the first time. IL-8 (CINC1-3) and the TREM-1 signaling pathway are proposed, besides GPR84, to play an important role in the pathogenesis of GERD.

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Disclosure of Interest: H. Abdel-Aziz Conflict with: employee of Steigerwald Arzneimittelwerk GmbH, M. Schneider: None declared, W. Neuhuber: None declared, A. M. Kassem: None declared, S. Khailah: None declared, H. Gamaleldeen: None declared, A. Khairy: None declared, M. Khayyal: None declared, T. Efferth: None declared, G. Ulrich-Merzenich: None declared

OP126 ENDOSCOPIC STOMACH VOLUME ESTIMATION FOR BARIATRIC ENDOLUMINAL GASTROPLASTY: ANIMAL VALIDATION STUDY

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Introduction: The shape of stomach is variable among individuals and conditions, so estimation of stomach volume is still difficult even though the recent development of various imaging modalities (CT or MRI). We proposed the possibility of endoscopic stomach volume estimation previously (*Digestive Disease Week* 2014, Mo1154). In this study, we aimed to validate the accuracy and value of endoscopic stomach 3D reconstruction and volume estimation using extracted porcine stomachs.
Aims & Methods: Three extracted porcine stomachs were used to test the accuracy of endoscopic stomach volume estimation. First, internal dimensions of porcine stomachs were measured using endoscopic guide-wire. Then, 3D stomach models were reconstructed using 3D graphic software (Cinema4D R12, MAXON Computer, Germany). Stomach volumes were estimated from the reconstructed 3D models and these results were compared with the real volumes measured by filling the stomach with water. Second, we performed bariatric gastroplasty using our novel endoscopic suture device (Endoscopy 45(8): 655-660), aiming to reduce the stomach volume by 30%. In this step, we took advantage of previously constructed 3D stomach model by simulating the most suitable gastroplasty for predetermined volume reduction. After gastroplasy, real volume of deformed stomachs were measured by filling with water.
Results: Stomach volume estimation by endoscopy was relatively accurate (mean error was about 10% of stomach volume). In addition, planned bariatric gastroplasty for predetermined stomach volume reduction by endoscopic suture device was possible with the help of simulation using 3D graphic software, which was not feasible by random suturing.
Conclusion: Endoscopic stomach 3D reconstruction and volume estimation was useful, accurate method, which can be used for the future tailored bariatric treatment.

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Disclosure of Interest: None declared

OP127 THE EXPRESSION OF RECEPTORS FOR NEUROTROPHINS AND NEUROTROPHIC FACTORS IN THE VAGAL AND SPINAL AFFERENT NEURONS INNERVATING THE STOMACH IN THE RAT

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Introduction: TRPV1-positive primary afferent neurons innervating the stomach have chemosensory and/or nociceptive function thus playing an important role in reflex regulation and perception. Neurotrophins and neurotrophic factors are often produced in inflammation and can induce neural plasticity that contributes to reflex dysregulation and pain. However, the neurotrophic regulation of afferent neurons innervating the stomach is incompletely understood.
Aims & Methods: Here we address the hypothesis that the vagal nodose and spinal dorsal root ganglia (DRG) neurons innervating the rat stomach have distinct expression profiles of receptors for neurotrophins and neurotrophic factors. Nodose and DRG neurons retrogradely traced following DiI injection into the stomach wall (along the major curvature) were individually analyzed by single cell RT-PCR. We evaluated the expression of mRNA for receptors TrkA, TrkB, and TrkC for neurotrophins from the NGF family (NGF, BDNF and NT-3, respectively), and the GFL co-receptor subunits GFRalpha1, GFRalpha 2, and GFRalpha 3 for the neurotrophic factors from the GDNF family (GDNF, neurturin and artemin, respectively).
Results: Total 142 nodose and 31 DRG neurons labeled from the stomach in 25 rats were analyzed. 93/142 gastric nodose neurons were positive for TRPV1. The gastric nodose TRPV1+ neurons often expressed receptors consistent with chemosensory function including TRPA1 (11/21), adenosine A1 receptor (13/27), bradykinin B2 receptor (8/21), and serotonin 5-HT3 receptor (11/27). In contrast, gastric nodose TRPV1- neurons that probably have mechanosensory function virtually lacked these receptors. The gastric nodose TRPV1+ neurons nearly uniformly expressed TrkB (23/27), often expressed GFRalpha1 (10/18) and occasionally expressed GFRalpha2 (6/18) and TrkA (8/27), but essentially did not express GFRalpha3 (2/27) and TrkC (0/45). In comparison, the gastric DRG TRPV1+ neurons expressed more frequently TrkA (17/18, $p < 0.01$ vs. nodose) and GFRalpha3 (11/18, $p < 0.01$), slightly less frequently TrkB (10/18, $p < 0.05$) and similarly GFRalpha1 (11/18). Gastric DRG neurons occasionally expressed TrkC (5/18), but almost never GFRalpha2 (1/18). In TRPV1-negative populations the receptors for neurotrophins and neurotrophic factors were poorly expressed in gastric nodose TRPV1- neurons (only TrkB and GFRalpha2 were occasionally detected), but the expression of TrkA, TrkB and GFRalpha1 in gastric DRG TRPV1- neurons was largely similar to that in gastric DRG TRPV1+ neurons.
Conclusion: The vagal nodose and spinal DRG neurons innervating the rat stomach differentially express mRNA for multiple receptors for neurotrophins and neurotrophic factors. Gastric nodose and DRG TRPV1-positive neurons differ in the expression profile of neurotrophins and neurotrophic factors. While the majority of gastric nodose neurons will be influenced by BDNF through TrkB, the majority of gastric DRG neurons will be influenced by NGF through TrkA. A proportion of both gastric nodose and DRG neurons will be influenced by GDNF through GFRalpha1, but only the gastric DRG neurons will be influenced by artemin through GFRalpha3.

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Disclosure of Interest: None declared

OP128 ACTIVATION OF GASTRIC BITTER TASTE RECEPTOR BY QUININE HYDROCHLORIDE EFFECTS ON INTRAGASTRIC PRESSURE PROFILES AND NUTRIENT TOLERANCE IN HEALTHY VOLUNTEERS

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Introduction: Bitter taste receptors are expressed in the stomach and the duodenum but their function is unclear.
Aims & Methods: We conducted a single-blind crossover trial in healthy volunteers (HVs) who were administered 10 μmol/kg QHCl or placebo intragastrically 30 min before the experimental protocol started.
Drinking test (DT): 10 HVs (age 28 ± 3; BMI 22 ± 1) were asked to drink a nutrient drink (ND; 30% fat, 42% carbohydrate, 28% protein) (15mL/min) until maximum satiation. Satiation was scored every 5 minutes on a 0-5 scale.
Intragastric pressure (IGP) and nutrient tolerance: A high-resolution manometry (HRM) probe was placed via the nose till the duodenum in 12 HVs (age 34 ± 1; BMI 22 ± 2; protocol 1). ND was intragastrically infused (60mL/min) until maximum satiation, when it was stopped. Satiation score was scored every minute. Thereafter, IGP was measured for 4 hours.
Gut peptides: To analyze plasma levels of gut peptides, blood samples were collected before treatment, before the ND infusion, every 15 min for the first hour after the ND and then every 30 min till the end.
IGP was measured as average pressure over 5 channels in the fundus; 5 minutes before ND start was taken as baseline. All data are expressed as mean $\pm$ SEM. Outcomes were compared with paired t-test (ND tolerance, total area above the curve (AAC) and max IGP drop during ND infusion), or mix-model analysis (hormones).
Results: *DT*: The amount of ND tolerated was significantly inhibited by QHCl (721.5 ± 93.4 ml) compared to placebo (846 ± 88.5 ml) ($p = 0.04$). Satiation scores after QHCl tended to be higher ($p = 0.09$).
IGP and nutrient tolerance: During the intragastric ND infusion, the IGP decreased initially and gradually increased thereafter both after placebo and QHCl. After QHCL, the max IGP drop (7 ± 1 mmHg vs. 3 ± 1 mmHg $p = 0.03$) and the AAC of the IGP drop (64 ± 12 mmHg*min vs 11 ± 1 mmHg*min, $p = 0.01$) were significantly suppressed, consistent with inhibition of gastric accommodation. Post-prandial IGP profiles did not differ between the two treatments. Satiation scores tended to be higher after QHCl ($p = 0.06$), and the volume of ND ingested at maximum satiation was significantly lower after QHCl (805 ± 82 vs 660 ± 56 ml, $p = 0.05$).
Gut peptides: Both GLP-1 and motilin plasma levels did not differ between both conditions.
Conclusion: Intragastric administration of QHCl inhibits gastric accommodation and decreases nutrient volume tolerance. These effects do not seem to be mediated by altered GLP-1 or motilin release. The mechanism involved in this action, and its application in the treatment of obesity, warrant further study.
Disclosure of Interest: None declared

OP129 NA+/CA2+ EXCHANGER 2-HETEROZYGOTE KNOCKOUT MICE DISPLAY INCREASED RELAXATION IN GASTRIC FUNDUS

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Introduction: The movements of the contents of the gastrointestinal tract rely on the coordinated contractions and relaxations of the smooth muscles that surround each specialised region. For contraction and relaxation to occur, the intracellular Ca^{2+} concentration must be altered upward and downward. The Na^+/Ca^{2+} exchanger (NCX) is a plasma membrane transporter involved in regulating intracellular Ca^{2+} concentrations.
Aims & Methods: We focused on Ca^{2+} movement through NCX, especially NCX2, on gastrointestinal tract motility because Ca^{2+} homeostasis is central to the regulation of smooth muscle function. To obtain further insight in the physiological roles of NCX2 in gastrointestinal motility, we used an organ tissue bath system to characterize motor function of circular smooth muscle segments from the gastric fundus.
Results: We initially investigated the expression and localization of NCX2 in the gastric fundus of WT using immunofluorescent staining. Strong immunoreactivity of NCX2 was observed within the myenteric plexus layers. Immunoreactivity of NCX2 was observed in the longitudinal and circular muscle layers as well as in the myenteric plexus layers. Electrical field stimulation (EFS) induced a rapid relaxation that showed during the stimulus, and a sustained relaxation, that persisted after the end of the stimulus. We found that the amplitudes of EFS-induced rapid relaxation and sustained relaxation after EFS were greater in NCX2 heterozygote mice (NCX2 HET) than in wild-type mice (WT). In the experiments in which inhibitor of nitric oxide synthase was added following the EFS, NCX2 HET exhibited no EFS-induced rapid relaxation similar to those of WT. In the experiments in which PACAP antagonist was added following the EFS, furthermore, sustained relaxation after EFS in NCX2 HET was similar in amplitude to that of WT. Because there is expression of NCX2 in circular smooth muscles as well as in neurons of the myenteric plexus layers, we determined whether NCX2 deficiency affects relaxation in response to NO and PACAP in smooth muscle cells. NCX2 HET demonstrated magnitudes of NOR-1-induced and PACAP-induced relaxations were similar to those of WT. Therefore, we can exclude the possibility that the NCX2 deficiency of smooth muscle cells enhances their sensitivity to NO and PACAP.
Conclusion: In this study, we demonstrate that NCX2 expressed in the neurons regulates the motility in gastric fundus.
Disclosure of Interest: None declared

MONDAY, OCTOBER 26, 2015 15:45–17:15
ENDOSCOPIC SUBMUCOSAL DISSECTION IN THE UPPER GI TRACT – ROOM B3

OP130 EFFICACY OF ENDOSCOPIC SUBMUCOSAL DISSECTION WITH DENTAL FLOSS CLIP TRACTION FOR GASTRIC EPITHELIAL NEOPLASIA: A PILOT STUDY

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Introduction: Providing appropriate tension to the lesion and securing a stable view of the submucosal layer are important to accomplish a successful endoscopic submucosal dissection (ESD). Dental floss clip traction (DFC), a new traction method, is expected to reduce the difficulty of ESD [1].
Aims & Methods: The objective of this pilot study was to investigate the efficacy of DFC for gastric ESD.
From August to November 2014, a total of 95 patients with 104 gastric epithelial neoplasms underwent DFC ESD (DFC group) at a cancer referral center. Historical controls treated by conventional ESD (control group) were individually matched to cases with a 1:1 ratio by the location of the lesion, the presence of ulcer findings, the resected specimen size, and the proficiency of the operator (trainee / expert). The outcomes of the procedure in two groups were then compared.
DFC was performed as follows: after circumferential mucosal incision, the clip tied with a dental floss was applied to the edge of the lesion. The anchored dental floss was continuously pulled per-orally with a gentle manual traction.
Results: The mean (SD) procedure time was 43 ± 24 minutes in the DFC group and 52 ± 30 minutes in the control group ($P < 0.01$). Fewer lesions in the DFC group needed more than 80 minutes compared with the control group (3 cases vs 16 cases, $P = 0.01$). There were no significant differences in adverse events between the groups. Perforation and delayed bleeding occurred in 1 lesion (1%) and 4 (4%) in the DFC group, and 3 (3%) and 9 (9%) in the control group, respectively. En bloc resection was achieved in all cases. No significant difference was found in regard to the curability of ESD between the groups.

Table: Results of DFC ESD

	DFC (n = 104)	Controls (n = 104)	P value
Procedure time, mean $\pm$ SD, min	43 ± 24	52 ± 30	< 0.01
Procedure time $\geq$80min, n	3	16	0.01
Adverse events, n			
Perforation	1	3	0.31
Delayed bleeding	4	9	0.36
Damage of specimen, n	0	0	-
En bloc resection, n	104	104	-
HM+	0	0	-
VM+	3	4	0.17
Curability, n			0.84
Curative resection	88	87	
Noncurative resection	16	17	

HM, horizontal margin involvement; VM, vertical margin involvement

Conclusion: DFC efficiently reduced the procedure time of ESD without increasing adverse events. DFC is helpful for a quick and safe ESD.

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Disclosure of Interest: None declared

OP131 COMPARISON OF O-TYPE HYBRIDKNIFE TO CONVENTIONAL KNIFE IN ENDOSCOPIC SUBMUCOSAL DISSECTION FOR GASTRIC MUCOSAL LESIONS: A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL

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Introduction: Endoscopic submucosal dissection (ESD) has been accepted as a minimal invasive alternative to surgery for localized superficial gastrointestinal neoplasms recently. However, the procedure remains to be technically challenging and time consuming. A new dissecting knife with partially insulated tip has been recently developed with built-in injection capability.
Aims & Methods: The purpose of this study was to investigate whether the efficiency of ESD procedure could be improved with this new device. A total of 78 patients, who underwent ESD with gastric mucosal lesions including flat type polyps, adenoma or early gastric cancer, were randomly assigned to either ESD with O-type HybridKnife or conventional ESD knives without waterjet. Procedure time and related factors of ESD were analyzed.
Results: ESD procedure time was 43.0 (Interquartile range, IQR 27.0 - 60.0) minutes in HybridKnife group compared to 60.5 (IQR 44.0 - 86.3) minutes in the control group ($P = .001$). There was no difference in the clinical outcome and the adverse event rate. The former demonstrated more favorable results in lesions ≤ 4 cm of specimen size ($P \leq .0001$) and when located in the distal stomach ($P = .001$), also in lesions with fibrosis ($P = .008$). Multivariate regression analysis showed that O-type Knife ($P \leq .0001$), specimen size ($P \leq .0001$) and fibrosis ($P \leq .0001$) were independent predictors of procedure time.
Conclusion: The O-type HybridKnife yields faster procedure time compared to the conventional knives in gastric ESD with a similar safety profile.

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Disclosure of Interest: None declared

OP132 FURTHER EXPANDED INDICATIONS OF ENDOSCOPIC RESECTION FOR EARLY GASTRIC CANCER IN ELDERLY PATIENTS

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Introduction: Early gastric cancers (EGCs) are increasingly encountered in elderly patients, and endoscopic resection (ER) is expected to cover a larger part of the treatment of EGCs in the elderly as it is a less invasive procedure than surgery. However, the widely accepted ER indications stated in the Japanese gastric cancer treatment guidelines, in which ER is indicated only for EGCs with nominal risk of lymph node metastasis (LNM), may be too strict for elderly patients. Management of elderly EGC patients, including the selection of ER or surgery, should be done taking their life expectancy into consideration; this way of thinking could lead to more expanded ER indications for them.
Aims & Methods: The aim of this study was to examine further expanded ER indications in elderly EGC patients (aged $\geq$80 years) based on the data on the risk of LNM in EGC and the overall survival in the elderly. We obtained the LNM risk data from our large retrospective study of 3,131 EGCs undergoing gastrectomy with lymphadenectomy at our institution between 1997 and 2013. These cases were analyzed for the percentage of positive LNM according to the conditions of tumor size, depth, histological type, ulcerative finding (UL), and lymphovascular involvement (LVI). The overall survival rates of the elderly were calculated at the Division of Surveillance, Center for Cancer Control and Information Services at our institution on the basis of the abridged life tables for Japan in 2013.
Results: The percentage of positive LNM in each EGC subgroup in the 3,131 cases, stratified by tumor size, depth, histological type, UL, and LVI, varied considerably from 0% to >50%, even among the noncurative subgroups according to the current guidelines. The 5-year overall survival rates of 80-, 85-, and 90-year-old Japanese were as follows: male, 69.5, 53.1, 34.9%; female 83.7, 69.4, 49.3%, respectively. Several EGC subgroups, for which the upper limit of 95% confidence interval (CI) of the percentage of positive LNM was lower than the 5-year total mortality of 80-year-old females (16.3%), were extracted as follows in addition to the current guidelines' curative subgroups: a) size >3 cm, UL (+), pure differentiated type, depth: mucosa, LVI (−) (positive LNM percentage with 95% CI: 0%, 0–2.9), b) size $\leq$2 cm, UL (+), pure undifferentiated type, depth: mucosa, LVI (−) (4.8%, 3.2–7.0), c) size >2 cm, pure undifferentiated type, depth: mucosa, LVI (−) (5.4%, 3.5–7.8), d) size >3 cm, pure differentiated type, depth: submucosa <500 μm, LVI (−) (1.6%, 0–8.7), e) size $\leq$3 cm, pure differentiated type, depth: submucosa $\geq$500 μm, LVI (−) (5.7%, 2.3–11.5). For elderly populations of older age and/or different sex, more subgroups were extracted in which the upper limit of 95% CI of the positive LNM percentage was lower than the 5-year total mortality.
Conclusion: Considering the extensive variation in LNM risk in EGC according to the lesion characteristics and the overall survival rates of the elderly, it is postulated that ER can be performed as a first-line treatment for more EGC subgroups than are stated in the current guidelines in elderly patients. In addition, after ER, the necessity of surgery can be more properly judged on the basis of the pathological results of the ER specimen and our detailed LNM risk data.
Disclosure of Interest: None declared

OP133 A COMBINATION METHOD OF SUBMUCOSAL TUNNELING ENDOSCOPIC RESECTION AND ENDOSCOPIC FULL-THICKNESS RESECTION FOR THE TREATMENT OF LARGE UPPER GASTROINTESTINAL SUBMUCOSAL TUMORS ORIGINATING FROM THE MUSCULARIS PROPRIA LAYER

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Introduction: Endoscopic full-thickness resection (EFR) can be adequately adopted as an effective treatment for upper gastrointestinal (GI) subumucosal tumors (SMTs) originating from the muscularis propria (MP) layer. However, the skills are more demanding for the endoscopist to seal the wall defect and the risks of GI tract leakage and/or secondary infection further limit the application of EFR. A new procedure, submucosal tunneling endoscopic resection (STER), has been developed to overcome these potential risks via the maintenance of GI tract mucosal integrity. However, the resectable lesion size of STER is limited by the relatively narrow space of the submucosal tunnel. Herein, we used a combination method of STER and EFR for the treatment of large upper GI SMTs originating from the MP layer.
Aims & Methods: Five patients with large upper GI SMTs from the MP layer were included. A submucosal tunnel was created to expose the large tumor as much as possible. EFR was further performed to completely remove the large tumor. Although mucosal perforation was unavoidable due to the large tumor

Abstract number: OP131 Table Univariate analysis of factor related with procedure time

	IT knife	HybridKnife	P value*
Specimen size, Median (mm) (IQR)	40.0 (31.5-50.0)	35.0(30.0-48.0)	*0.866*
Overall median procedure time (min) (IQR)	60.5(44.0-86.3)	43.0(27.0-60.0)	*0.001*
Median procedure time according to locations (min) (IQR)			0.3690.0540.012
U	60.0(33.0-128.5)	43.5(27.5-75.8)	
M	54.0(45.5-95.3)	43.0(27.0-60.0)	
L	64.0(47.5-87.5)	33.0(21.3-43.0)	
Median procedure time according to specimen sizes (min) (IQR)			<0.00010.455
≤40mm	60.0(41.0-84.0)	29.0(21.3-43.0)	
> 40mm	66.0(51.0-99.0)	62.0(43.0-82.0)	
Median procedure time according to fibrosis (min) (IQR)			0.0170.008
No	55.0(38.5-77.5)	37.0(26.5-56.0)	
Yes	63.0(75.0-207.0)	57.5(41.5-66.3)	
Median procedure time according to histology of lesion (min) (IQR)			0.1190.006
Non-Ca	53.0(29.0-79.0)	36.0(23.0-43.0)	
Ca	66.0(47.0-93.0)	43.5(27.8-66.5)	
Median submucosal dissection time (min) (IQR)	34.0(21.0-53.3)	24.0(12.0-38.0)	0.003
Median non-submucosal dissection time (min) (IQR)	26.0(18.0-36.0)	16.0(12.0-27.0)	0.005

U, lower third; M, middle third; U, upper third; Ca, cancerous lesion; Non-Ca, Non-cancerous lesion; IQR, interquartile range.*Due to deviation from normal distribution indicated by Shapiro-Wilk test, Mann-Whitney's U statistic was used to compare medians.

and limited submucosal space, most part of the normal mucosa covering the tumor was protected and the mucosal integrity was easily repaired with several hemostatic clips.
Results: Of the five lesions, 2 were located in the esophagus, 2 in the cardia, and 1 in the gastric antrum. The mean tumor size was 6.6 cm (range 5.0-10.0 cm). The combination procedure was successfully performed in all patients with piecemeal resection of tumors. The operation time ranged from 70 to 180 min (mean, 133.3 min). Mucosal perforations occurred in all cases and were clipped successfully. All complications related to the procedure were successfully managed with conservative treatments. Local recurrence or distant metastasis did not occur during follow-up.
Conclusion: The combination of STER and EFTR is a safe and effective therapeutic strategy for large upper GI SMTs originating from the MP layer. This method can maintain the mucosal integrity as much as possible while achieving completely full-thickness resection of the large tumor.

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Disclosure of Interest: None declared

OP134 LONG-TERM OUTCOMES OF ENDOSCOPIC SUBMUCOSAL DISSECTION (ESD) FOR GASTRIC CANCER INVADED TO THE SUBMUCOSA: A RESULT OF A PROSPECTIVE STUDY OF THE EXPANDED INDICATION OF ESD

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Introduction: ESD is a promising endoscopic treatment for early gastric cancer (EGC) without lymph node metastasis, and an expanded indication of ESD for EGC is proposed including some submucosal cancers (Soetikno R., et al. J Clin Oncol. 23:4490-98, 2005). However, it is not fully reported about long-term outcomes of ESD for them. The aim of this study was to evaluate short-term and long-term outcomes of ESD for submucosal gastric cancers which were recruited in a prospective study regarding the expanded indication of ESD.
Aims & Methods: We previously designed a prospective study in which ESD was applied in patients with differentiated-type EGC up to 30 mm in diameter regardless of ulceration or above 30 mm without ulceration, but definite signs of submucosal invasion. As for cancers invaded to the submucosa diagnosed after ESD, ones less than 500um in depth (SM1) and less than 30mm in size were followed up, and otherwise were advised to be operated on additionally. We assessed short-term and long-term outcomes of ESD for them. Followed-up endoscopic examinations were performed 6 months later, and then every 6 months.
Results: We finally performed ESD in 81 patients with submucosal cancers (SM1; 32, SM2 (deeper invasion than SM1); 49 cases) from April 2006 to March 2013. Cancers were resected en bloc in all patients, and R0 resection were achieved in 72 (89%) patients. The rest, who had all SM2 cancers (range 800-3500μm in depth), had positive vertical margin. In the SM1 cancers, 23 were less than 30mm in size and the patients were followed up. Two of the rest of 9 SM1 patients received surgery. In the 49 patients with SM2, 38 received surgery and the rest refused it. In totally 40 (49%) patients who received surgery, lymph node metastasis were found in 3 patients (7%; all were SM2 cancers more than 2000μm in depth), and the residual cancer were found in 3 patients. In 41 followed-up patients, local recurrence was detected in one (2%) patient, and the subsequent cancer was detected in 8 (20%) patients (median follow-up period 49 months (range 3-106 months)). None of these patients died from gastric cancer, and 7 patients died from other disease.
Conclusion: The short-term and long-term outcomes of ESD for those patients would be preferable. ESD could not only bring accurate diagnosis by en bloc resection, but produce local control of the EGC even in patients with SM2 cancers.
Disclosure of Interest: None declared

OP135 PREVENTION OF BLEEDING AFTER ENDOSCOPIC SUBMUCOSAL DISSECTION FOR GASTRIC NEOPLASMS USING POLYGLYCOLIC ACID SHEETS AND FIBRIN GLUE

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Introduction: For bleeding after endoscopic submucosal dissection (ESD) for gastric neoplasms, no preventive method has been established other than preventive coagulation of visible vessels on the artificial ulcer after ESD or the usage of proton pump inhibitors. We have reported that the endoscopic tissue shielding method with polyglycolic acid (PGA) sheets and fibrin glue can reduce the risk of post-ESD bleeding.
Aims & Methods: The aim of this study is to evaluate the efficacy of PGA sheets and fibrin glue for preventing bleeding after gastric ESD after accumulating more cases. This is a non-randomized historical controlled study. We defined high-risk patients for post-ESD bleeding as follows: 1) those who took antithrombotic drugs regularly; or 2) those expected to undergo large mucosal resection ($\geq$ 40mm). We enrolled patients scheduled to undergo gastric ESD and had above-mentioned risk factors from July 2013 as the study group (Group A). Immediately after ESD we placed PGA sheets on the mucosal defect and fixed them with fibrin glue in the study group. We extracted high-risk patients from those who had undergone gastric ESD at our institution before the enrollment of the first study patient, and defined the group as the historical control group (Group B). The post-ESD bleeding rate was the primary endpoint in comparative analysis.
Results: From July 2013 to October 2014, 98 ESD-induced ulcers in 91 high-risk patients were enrolled in Group A. In Group B, 91 ESD-induced ulcers in 84 consecutive patients were extracted between January 2012 and July 2013. There was a significant difference in antithrombotic drugs use (A: 62 lesions, 63.3%, B: 44, 48.4%; $P = 0.039$), but the other baseline characteristics were not significantly different between the two groups: sex (A: male 86/female 12, B: male 73/female 18; $P = 0.156$); age (A: 71.8 ± 8.2 yrs, B: 73.3 ± 7.9 yrs; $P = 0.229$); Heparin bridging therapy (A: 18 lesions, 18.4%, B: 10, 11.0%; $P = 0.151$); and the diameter of resected specimens (A: 43.7 ± 16.1 mm, B: 48.1 ± 19.7 mm; $P = 0.094$). Perforation did not occur in either group. Post-ESD bleeding occurred in 7.1% of the study group (7 lesions), and 17.6% of the historical control group (16 lesions). There was a significant difference in the post-ESD bleeding rate between the two groups ($P = 0.027$). Multivariate logistic regression analysis also confirmed that applying PGA sheets and fibrin glue was an independent significant factor for decreasing the risk of post-ESD bleeding (Odds Ratio, 0.33; 95% CI: 0.11-0.89, $P = 0.029$). The mean procedural time for applying PGA sheets and fibrin glue was 20.0 ± 9.1 min.
Conclusion: Even after accumulating more cases, this study all the same implied that the endoscopic tissue shielding method with PGA sheets and fibrin glue might be promising for the prevention of post-ESD bleeding.
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MONDAY, OCTOBER 26, 2015 15:45–17:15
ABSTRACTS ON FIRE: HOT TOPICS IN HEPATOLOGY AND PANCREATOLOGY – HOTSPOT

OP136 HEPATIC ARTERY RECONSTRUCTION IS UNNECESSARY AFTER CELIAC ARTERY RESECTION FOR ANY TYPE OF CELIACO – MESENTERIAL ANATOMY

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Introduction: Distal pancreatectomy with celiac artery resection (DPCAR) is widely used for borderline-resectable pancreatic cancer. It is believed that considerable reduction of the liver arterial supply after DPCAR may cause severe liver dysfunction and/or gallbladder necrosis. The necessity of arterial reconstruction is still debated.
Aims & Methods: To study liver collateral arterial supply after temporary occlusion of the common (CHA) and accessory/replaced left hepatic arteries (a/rLHA). Arterial anatomy, diameters of CHA, proper hepatic (PHA), gastroduodenal arteries (GDA) and pancreatoduodenal arcades (PDA) were registered before surgery in 107 consecutive patients with pancreatic body/tail cancer (n32), gastric cancer with pancreatic involvement (n30) and liver tumors (n45) by CT. For DPCAR (n16) these data were obtained after surgery as well. Diameters of peripancreatic arteries and mean systolic blood velocity in hepatic arteries before and after CHA clamping were measured intraoperatively by Doppler ultrasound.
Results: Classical arterial anatomy was identified in 72% and replaced right hepatic artery (rRHA) from the SMA in 12.2% of cases. PDA were not identified before surgery in 20% of cases. Pulse had disappeared in 18 (17%) cases after clamping of CHA and aLHA/rLPA. Collateral arterial blood flow in the liver parenchyma was revealed in all cases. DPCAR led to 1.increase of GDA and rRHA diameters in 1.2-1.5 times; 2. visualization of PDA in all cases as main vessels, whereas they were invisible for CT in 50% before DPCAR.

Conclusion: Hepatic artery reconstruction is unnecessary after DPCAR for any type of arterial anatomy; Doppler ultrasound is the best modality for intraoperative assessment of liver arterial blood supply after DPCAR.
Disclosure of Interest: None declared

OP137 PANCREATIC CYSTIC LESIONS IN LIVER TRANSPLANT RECIPIENTS: PREVALENCE AND OUTCOME

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Introduction: Pancreatic cystic lesions (PCL) are common in the general population and their prevalence increases with age. Pancreatic cystic neoplasia account for more than half of pancreatic cysts. Some of them have malignant potential. Solid organ transplant recipients have an elevated cancer risk due to immunosuppression.
Aims & Methods: The purpose of this study was to investigate the prevalence and course of incidental PCL in liver transplant recipients. We performed a retrospective analysis of imaging findings and medical records of all adult patients who underwent liver transplantation in our center between September 1996 and November 2014.
Results: Nine hundred and sixty-seven orthotopic liver transplantations were performed in 578 males and 389 females (mean age 51 years, range 18-74). PCL were found in 60 patients (6.2%; 26 males, 34 females; mean age 61, range 31-74), with 29 of them diagnosed pre-transplant. The mean size of detected PCLs was 14 mm (range 5-85mm). PCLs were located in the head (35%), body (33%) and tail (15%) of the pancreas, 17% of patients had multifocal PCL. More than 2 PCLs were present in 20 patients (33%). Mean follow-up duration was 51 months. In 10 patients (17%), the size of lesion increased (mean +4mm), however in none of them the progression was clinically relevant. No patient developed symptoms or died from PCL during follow-up. Patients with PLCs were significantly older ($p < 0.001$), more likely to be women ($p < 0.05$) and were more often transplanted for primary biliary cirrhosis ($p < 0.01$) and Alpha1-Antitrypsin Deficiency ($p < 0.001$).
IPMN was suspected in 9 patients (15%, all branch-type). One multifocal IPMN exhibited worrisome features at the time of diagnosis and total pancreatectomy was performed in early post-transplant period.
Conclusion: PCLs are equally frequent in liver transplant recipients compared to general population. Their presence was associated with higher age, female sex, type of liver disease and did not influence patients survival.
Disclosure of Interest: None declared

OP138 LAVAGE VERSUS NO LAVAGE THROUGH PERCUTANEOUS CATHETER DRAINS IN SEVERE ACUTE PANCREATITIS: A RANDOMIZED CONTROL TRIAL

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Introduction: Lavage through peri-pancreatic drains placed after laparotomy has been the standard treatment for patients undergoing surgical necrosectomy in severe acute pancreatitis (SAP). However, it is not known whether large volume lavage given through percutaneous drains (PCDs), placed under radiological guidance, provides further benefits when compared to simple percutaneous drainage only in patients with SAP.
Aims & Methods: Sixty patients of SAP who required placement of PCDs were randomised into 2 groups: group A included 28 patients given high-volume saline lavage through PCD while group B included 32 patients who were managed by PCD drainage alone. Patients in group B who did not improve with drainage alone were transferred to group A and analysed as per protocol. The end-points were improvement of APACHE-II score, reversal of pre-existing organ failure (OF), development of new onset OF, need for surgery and mortality.
Results: The mean duration of PCD placement in group A and B were 24.82 ± 9.62 and 20.00 ± 11.17 days ($p = 0.08$). The mean improvement in APACHE-II scores with intervention was significantly more in group A as compared to group B (3.50 ± 3.40 vs 1.16 ± 3.81, $p = 0.012$). 24/28 (85.7%) patients showed reversal of persistent OF in the irrigation group compared to only 20/32 patients (62.5%) in the control group ($p = 0.023$). There was no statistically significant difference in the development of new onset OF (25% vs 37.5%, $p = 0.299$) and in number of patients requiring surgery (17.8% vs 15.6%, $p = 0.737$) in the two groups. The mortality was less in the lavage group and this difference trended towards significance (18.8% vs 28.8%, $p = 0.37$).
Conclusion: The study showed significant reduction in APACHE-II score and reversal of persistent OF in patients receiving irrigation with PCD as compared to PCD drainage alone. It also showed improvement in survival rates in the irrigation group trending towards significance.
Disclosure of Interest: None declared

OP139 IS RIBAVIRIN ACTUALLY USEFUL FOR GENOTYPE 1 (G1) CIRRHOTIC PATIENTS WHO RECEIVE DAAS COMBINATION? A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS (RCTS)

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Introduction: The use of ribavirin has been suggested to increase SVR12 rates and allow short treatment durations in G1 cirrhotic patients receiving DAAs, especially G1 treatment-experienced (TE) cirrhotic patients. The aim of this meta-analysis was to address this issue and to investigate whether the use of RBV allows 12 weeks duration regimens in TE G1 cirrhotic patients without impairing SVR rates.
Aims & Methods: All phase II and phase III RCTs published or communicated to date which included GI naïve (TN) or TE cirrhotics and contained arms with or without ribavirin and/or compared 12 weeks vs. extended (i.e., 18 or 24 weeks) treatment durations were included. All DAAs regimen were analyzed together. For TN and TE patients, 2 analyses evaluated the ribavirin use (regardless of the treatment duration and for a fixed 12 weeks treatment duration) and 3 analyses evaluated the treatment duration (regardless of, with, or without ribavirin). Another analysis compared 12 wks with RBV vs. 24 wks without RBV. Meta-analyses were performed according to the Der Simonian and Laird method and reported weight-adjusted SVR12 gains.
Results: 10 RCTs including 1307 G1 cirrhotic patients (573 TN, 734 TE) were selected for this meta-analysis. The distribution of DAA combinations was as follows: SIM + SOF (COSMOS, N = 168), 3D Abbvie (TURQUOISE II, N = 380), DCV-TRIO BMS (UNITY 2, N = 202), GPV + EBV (C-WORTHY, N = 253), and LDV + SOF (6 RCTs, N = 496). In G1 TN cirrhotic patients, the use of ribavirin (ΔSVR = +2.45%; 95%CI: -1.27 to +6.16%, NS, N = 411) or an extended duration (ΔSVR = +0.64%; 95%CI :-3.03 to +4.32%, NS, N = 434) did not increase SVR12. In G1 TE cirrhotic patients, the use of ribavirin did not increase SVR12 (ΔSVR = +0.23%; 95%CI :-3.54 to +4.01%, NS, N = 494), even in analyses restricted to 12wks treatment duration (ΔSVR = +1.85%; 95%CI :-3.75 to +7.44%, NS, N = 267). Conversely, extended duration was associated with higher SVR rates (ΔSVR = +6.35%; 95%CI: +1.49 to +11.20%, p = 0.018, N = 532), even with ribavirin use (ΔSVR = +8.26%; 95%CI: +2.29 to +14.23%, p = 0.028, N = 278). The magnitude of SVR gain was similar between the different DAA regimen suggesting that a 18 wks extended duration (as performed in the C-WORTHY study) would be sufficient for other combos. Only four studies (229 patients) compared 12wks + RBV vs. 24wks w/o RBV. Extended duration was associated with a 5.09% SVR gain that did not reach significance, probably because of a type II error and the overweight of the SIRIUS study.
Conclusion: In G1-naïve patients with compensated cirrhosis, ribavirin as well as extending treatment duration are useless. In G1 treatment-experienced patients with compensated cirrhosis, ribavirin does not increase SVR rates but extending treatment duration (18 or 24 wks) significantly increases SVR rates.
Disclosure of Interest: None declared

OP140 2D-SHEAR WAVE ELASTOGRAPHY AS A NON-INVASIVE METHOD FOR PREDICTION OF ESOPHAGEAL VARICES IN PATIENTS WITH LIVER CIRRHOSIS

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Introduction: 2D-SWE might be a valuable, easy to use method for the non-invasive quantification of portal hypertension in patients with liver cirrhosis.
Aims & Methods: The aim of this study was to evaluate the feasibility of 2D-SWE in cirrhotic patients with esophageal varices and the performance of 2D-SWE for predicting the presence of esophageal varices.
The study group included 141 subjects diagnosed with cirrhosis by clinical, biological, ultrasound and/or endoscopic criteria. All subjects underwent 2D-SWE with an AixplorerTM ultrasound system (SuperSonic Imagine S.A., Aix-en-Provence, France). In each patient we performed three liver stiffness measurements in a homogenous color-coded box placed 1-2 cm under the liver capsule, with the patient in supine position, with a mean value expressed in kiloPascals (kPa), as a reliability criteria it was used the standard deviation (SD)/median ratio ≤ 0.10 (1).
Results: The ethiology of the liver cirrhosis was: HCV-38.2%, HBV- 31.5%, HCV and HBV-3.5%, ethanol-21.4% and other ethiologies-5.4%. Esophageal varices were present in 46.8% of cases and significant esophageal varices (grade II and III) in 32.4%. 2D-SWE had similar feasibility in patients with and without esophageal varices: 89.2.7% vs. 92.1%, ($p = 0.54$). The mean 2D-SWE values (kPa) were similar when no reability criteria were used in patients with esophageal varices (grade II and III) vs. those without or grade I esophageal varices: 31 ± 10.6 vs. 27.8 ± 13.8, ($p = 0.24$). After applying the reliability criteria ((SD)/median ratio ≤ 0.10), the mean 2D-SWE values (kPa) were significantly higher in patients with esophageal varices (grade II and III) vs. those without or grade I esophageal varices: 34 ± 12 vs. 23 ± 12.7, ($p = 0.03$). The best

cut-off value for the prediction of significant esophageal varices was 25.7 kPa (AUROC = 0.636, p = 0.03, Se 92.1%, Sp = 44.2%).
Conclusion: 2D-SWE is a feasible method in patients with cirrhosis and esophageal varices and seems to be able to predict the presence of esophageal varices when reliability criteria are used.

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Disclosure of Interest: None declared

OP141 MORTALITY AND DISEASE PROGRESSION AMONG CYSTIC FIBROSIS PATIENTS WITH NON-SPECIFIC LIVER ABNORMALITIES

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Introduction: CF liver disease (CFLD) is associated with a worse CF phenotype and reduces life expectancy. While less than 10% of patients develop CFLD, up to 30% have non-specific abnormalities on liver biochemistry and imaging (non-specific liver disease - NSCFLD) and little is known of the natural history of disease in this group.
Aims & Methods: The aim of this study was to prospectively determine the outcome of NSCFLD in a national cohort.
All children under 18 years old with CF in the Republic of Ireland were invited to participate and underwent in-depth clinical and nutritional assessments in 2007 and 2012. Liver disease status was classified using North American Cystic Fibrosis Foundation (NACFF) criteria as: No evidence of liver disease (NoLD), Non-specific liver disease (NSCFLD) and clinically significant liver disease (CFLD).
Results: 521 children were enrolled in 2007; mean age 9.04 SD4.9, 52% Male, mean follow-up 4.01 years SD1.05. In 2007 119 (22.8%) children were classified having NSCFLD, 35 (6.7%) as CFLD, and 367 (70.4) as NoLD. In 2012 all children underwent in-depth clinical re-evaluation. In 2012 10 (8.4%) children with NSCFLD had died (compared with 7 (1.9%) of those with NoLD and 11 (31.4%) of those with CFLD, P = 0.00). Of the children alive with NSCFLD in 2012, 3 (2.52%) were lost to follow-up, 13 (10.9%) progressed to CFLD, 41 (34.4%) remained unchanged and 50 (42%) had no evidence of liver disease (normal clinical biochemical and radiological parameters). Of the 13 who progressed to clinically significant liver disease, 8 (61.5%) were less than 10 years of age while 38.5% were over 10 years of age (P = NS). Of the 50 participants reclassified as NoLD in 2012, 44 had had liver ultrasound abnormalities and 6 liver biochemistry abnormalities in 2007. No child with both liver imaging and biochemical abnormalities at enrolment reverted to NoLD in follow up. However of the 5 participants with ultrasound and biochemical abnormalities, 4 have progressed to CFLD and the 5th still has NSCFLD.
Conclusion: While most children with CF and evidence of biochemical or ultrasonographic liver abnormalities alone will not develop more severe liver abnormalities in the medium term, a substantial minority progress to CFLD/cirrhosis – especially if they have both ultrasound abnormalities and laboratory derangements. Furthermore, mortality among children with NSCFLD is substantially higher than in CF children with normal livers.
Disclosure of Interest: None declared

OP142 LONG TERM CHANGE IN AETIOLOGY OF CIRRHOSIS AND HEPATOCELLULAR CARCINOMA IN CRETE,GREECE: A 25 YEAR STUDY

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Introduction: Over the last years Non Alcoholic Fatty Liver Disease (NAFLD) has emerged as a major aetiological factor in Cirrhosis and HCC. No sequential long term data exist for Greece.
Aims & Methods: We studied therefore the aetiological evolution of cirrhosis and HCC over a period of 25 years in the genetically homogeneous population of the island of Crete .We used the Data Base of our Unit which is the Reference Center for Liver Disease of the Island. A total of 820 cases of cirrhosis (561 male, median age 69 years) and 321 cases of HCC (234 male median age 70 years) were recorded and classified in 5 year periods according to aetiology (HBV, HCV, Alcohol, Alcohol plus viral and NAFLD). Primary Biliary Cirrhosis was not included
Results: Cirrhosis: There was a relative uniformity in absolute numbers over the years. However there was a significant change in aetiologies. Thus, while the association with HBV remained constant , there was a reduction of association with HCV (1990-1994:45%, 2010-2014: 12%) with a parallel increase of Alcoholic (1990-1994: 36%, 2010-2014:59%) and NAFLD associated cirrhosis (!990-1994: 2%, 2010-2014:16%). In HCC there was also a decrease in the association with HCV (90-94: 50%, 10-14: 21%) and a very significant increase in the association with NAFLD (90-94: 1%, 10-14:23%). HBV and alcohol were unchanged
Conclusion: 1) Aetiology of cirrhosis and HCC have considerably changed over the past 25 years in Crete. 2) The initial high HCV association has significantly decreased 3) Alcohol is now the main aetiological factor in cirrhosis 4) NAFLD has emerged as a continually increasing association with both cirrhosis and HCC.
Disclosure of Interest: None declared

OP143 THE IMPACT OF CLINICAL PORTAL HYPERTENSION ON THE PROGNOSIS OF PATIENTS WITH HEPATOCELLULAR CARCINOMA AFTER RADIOFREQUENCY ABLATION

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Introduction: Portal hypertension is an important prognostic factor for patients with advanced liver disease, but whether it could also determine the outcomes of patients with hepatocellular carcinoma (HCC) after radiofrequency ablation (RFA) is still obscure.
Aims & Methods: To assess the impact of clinical portal hypertension on the prognosis of patients with HCC undergoing percutaneous RFA. We enrolled 280 treatment-naïve HCC patients who also received upper gastrointestinal endoscopy examination at the time of HCC diagnosis. Clinical portal hypertension was defined as (1) platelet count < 100,000/mm^3 associated with splenomegaly, or (2) presence of esophageal/gastric varices by endoscopy.
Results: A total of 192 (68.6%) patients had clinical portal hypertension at the time of receiving RFA. Among them, 154 patients had splenomegly and blood platelet count < 100,000/mm^3 at the same time, 140 patients had esophageal varices and 25 patients had gastric varices. Patients with portal hypertension were younger in age, with low serum albumin and cholesterol levels, higher bilirubin, alanine aminotransferase levels, lower platelet count, lower hepatitis B virus carriers and higher rate of positive antibody against hepatitis C virus than their counterpart. After a median follow-up of 23.5 months (25-75 percentiles 13.1-43.6 months), 76 patients died. The cumulative five-year survival rates were 50.6% and 76.7% in patients with and in those without portal hypertension, respectively ($p = 0.016$). By multivariate analysis, age > 65 years hazard ratio (HR) 1.661, 95% confidence interval CI 1.028-2.684, $p = 0.038$), serum albumin levels ≤ 4.0 g/dL (HR 3.472, 95% CI 1.715-6.993, p = 0.001), multiple tumor (HR 1.753, 95% CI 1.059-2.903, p = 0.029) and serum alpha-fetoprotein level > 20 ng/mL (HR 1.831, 95% CI 1.134-2.957, p = 0.013) were independent risk factors associated with poor overall survival after RFA.
Conclusion: HCC patients with clinical portal hypertension had relatively poorer liver functional reserve than those without portal hypertension. However, portal hypertension was not an independent risk factor predicting overall survival for patients with small HCC undergoing RFA by multivariate analysis. Therefore, portal hypertension or EV is not the contraindication for RFA.
Disclosure of Interest: None declared

OP144 CLINICAL SIGNIFICANCE AND RISK FACTORS OF RECURRENCE BEYOND MILAN CRITERIA WITHIN 2 YEARS AFTER RADIOFREQUENCY ABLATION IN PATIENTS WITH SINGLE SMALL HCC

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Introduction: Radiofrequency ablation (RFA) is one of most commonly applied curative treatment modalities in patients with small hepatocellular carcinoma (HCC). However, clinical significance and risk factors of recurrence beyond Milan criteria within 2 years after RFA, a dreadful event excluding the possibility of further curative treatment, has not been fully evaluated.
Aims & Methods: Among 477 patients with single HCC < 3 cm undergoing percutaneous RFA as initial treatment modality at our institution from 2006 to 2009, 438 patients showing complete ablation were included in this study. Baseline patient characteristics including age, sex, etiology of the liver disease, Child-Pugh class, Eastern Cooperative Oncology Group performance status, and tumor characteristics including alpha-fetoprotein levels, tumor size, number, conspicuity, and proximity to the surface of the liver, colon, diaphragm and vascular structures were reviewed. Clinical outcomes of the whole patients and incidence, impact on overall survival, and risk factors of recurrence beyond Milan criteria within 2 years after RFA were also investigated.
Results: During the median follow-up period of 68.4 months (range: 1.0-117.1), recurrent HCC was noted in 302 patients (68.9%). Median time to recurrence was 19.7 months (range: 1.0-110.2). Recurrence beyond Milan criteria within 2 years after RFA was noted in 27 patients (8.0%) with the following reasons: detection of tumor(s) with size and/or numbers beyond Milan criteria (n = 11, 2.5%), vascular invasion (n = 3, 0.7%), and extrahepatic metastasis (n = 13, 2.9%). While 1-, 3-, and 5-year overall survival rates were 98.1%, 86.3%, and

72.8%, respectively in the whole patients, those were 92.6%, 46.5%, and 0.05% in patients with recurrence beyond Milan criteria within 2 years. Multivariable analysis identified older age (OR = 1.04; 95% CI 1.02-1.05; p < 0.001), albumin (OR = 0.53; 95% CI 0.39-0.71; p < 0.001), recurrence beyond Milan criteria within 2 years (OR = 7.72; 95% CI 4.91-12.13; p < 0.001) as the independent risk factors predictive of poor overall survival. Initial tumor size ≥ 20 mm (OR = 2.30; 95% CI 1.02-5.16; p = 0.044) and tumor adjacent to the colon (OR = 4.64; 95% CI 1.75-12.31; p = 0.002) were identified as independent risk factors predictive of recurrence beyond Milan criteria within 2 years.
Conclusion: Recurrence beyond Milan criteria within 2 years after RFA is independently predictive of poor overall survival and associated with size ≥ 2 cm in size and proximity to colon of tumor in patients with single small HCC.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 08:30–10:30
THERAPY UPDATE: EOSINOPHILIC OESOPHAGITIS – ROOM F2

OP145 FAMILIAL EOSINOPHILIC ESOPHAGITIS (EOE) UNCOVERS A NEW EOE-LIKE SYNDROME WITHOUT TISSUE EOSINOPHILIA

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Introduction: Eosinophilic esophagitis (EoE) is a chronic-inflammatory disease of the esophagus defined clinically by symptoms of esophageal dysfunction and pathologically by an eosinophil-predominant infiltration. EoE has a strong genetic component. We identified in four EoE-families totally five members with an EoE-like syndrome, presenting with typical symptoms of EoE responding promptly to treatment with topical corticosteroids, but without tissue eosinophilia. The purpose of this study was to investigate this intriguing syndrome of "EoE without eosinophilia", in order to improve the understanding of this inflammatory condition.
Aims & Methods: The five patients suffering from EoE-like syndrome were evaluated by laboratory analyses, endoscopy, histologic and quantitative immuno-histologic examinations and genome-wide association analyses. In addition, we searched in all 46 members of these EoE-families for EoE-associated molecular abnormalities.
Results: Using immunohistochemistry we detected in the esophagus of patients with EoE-like syndrome a chronic, Th2 type inflammation, but definitely a lack of eosinophils. In addition, we found the EoE-risk allele *TSLP rs3806932* in their genome. First generation offspring of EoE-like syndrome patients had on average a 40% risk of being affected by conventional EoE.
Conclusion: These five members of EoE families suffering from "EoE without eosinophilia" do formally not fulfill the diagnostic criteria of EoE. However, clinical manifestation, the finding of a Th2 type inflammation, the bequeath of conventional EoE to their offspring and the detection of the EoE-risk allele *TSLP rs3806932* in their genome strongly suggests a uniform underlying pathogenesis. Conventional EoE with the predominant eosinophilia might therefore be only one phenotype of this dysphagia syndrome. The role of the eosinophils and the disease-definition must therefore be reconsidered. Moreover, as these patients have endoscopically and histologically only discreet abnormalities, this syndrome might so far often be misdiagnosed as functional dysphagia.
Disclosure of Interest: None declared

OP146 LONG-TERM LOSS OF RESPONSE IN PROTON PUMP INHIBITOR-RESPONSIVE ESOPHAGEAL EOSINOPHILIA IS UNCOMMON AND INFLUENCED BY CYP2C19*2 GENOTYPE AND RHINOCONJUNCTIVITIS

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Introduction: Proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE) is diagnosed in at least a third of patients with suspected eosinophilic esophagitis (EoE). However, the durability and factors influencing the long-term efficacy of PPI therapy remain unknown.
Aims & Methods: We aimed to evaluate the durability and factors influencing long-term efficacy of PPI therapy. Retrospective multicenter cohort study of patients with PPI-REE who had at least 12 months of follow-up. PPI therapy was tapered to the lowest dose which maintained clinical remission. Primary outcomes were the proportion of patients with loss of histological response (< 15 eos/HPF) and predictors of loss of response. *CYP2C19* polymorphisms were determined from blood samples in a subset of patients.
Results: Seventy five PPI-REE patients were included [mean follow 26 months (12-85)], of whom fifty five (73%) had sustained histological remission on low-dose PPI therapy. Loss of response was significantly higher in those patients with a *CYP2C19*2* rapid metabolizer genotype (36% *vs.* 6%, p 0.01) and with rhinoconjuctivitis (40% *vs.* 13%, p 0.007). On multivariate analysis, a *CYP2C19*2* rapid metabolizer genotype (odds ratio (OR) 12.5; 95%CI:1.3-115.9) and rhinoconjunctivitis (OR 8.6; 95%CI:1.5-48.7) were independent predictors of loss of response. Among relapsing patients, eosinophilia was limited to the distal esophagus in 14/20 (70%). Nine of ten relapsers, with distal eosinophilia, all showing a *CYP2C19*2* rapid metabolizer genotype, regained histological remission after PPI dose intensification.
Conclusion: Most PPI-REE patients remain in long-term remission on low-dose PPI therapy. A CYP2C19*2 rapid metabolizer genotype and rhinoconjunctivitis were independent predictors of loss of response to PPI, but patients frequently responded to PPI therapy intensification.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 08:30–10:30
RATIONAL DIAGNOSTIC APPROACH TO BARRETT'S OESOPHAGUS – ROOM A2

OP147 IDENTIFICATION OF CLINICAL AND ENDOSCOPIC PREDICTORS FOR NEOPLASTIC PROGRESSION IN BARRETT'S ESOPHAGUS USING A PROSPECTIVE MULTI-CENTER COMMUNITY-BASED COHORT OF 1003 PATIENTS

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Introduction: The absolute risk to develop esophageal adenocarcinoma (EAC) from Barrett's esophagus (BE) is low, however, once diagnosed it is an aggressive and often fatal disease. Aim of this study was to assess the risk of neoplastic progression in BE and identify endoscopic and clinical predictors for neoplastic progression, to enable risk-stratification in BE patients and improve current surveillance strategies.
Aims & Methods: In 2003 a prospective surveillance study was initiated in 6 community-based hospitals in the Netherlands, coordinated by a tertiary BE referral center. Patients with known BE identified using the Dutch pathology registry (PALGA) and patients newly diagnosed with BE were asked consent to enter a prospective surveillance program. Exclusion criteria were no intestinal metaplasia, history of esophageal carcinoma and prevalent high-grade dysplasia (HGD) or EAC (defined as diagnosed at index endoscopy or within 6 months thereafter). All surveillance endoscopies were scheduled and performed according to international guidelines, using Seattle protocol biopsies. In each center, all endoscopies were performed by a single endoscopist. Two research nurses coordinated the surveillance program and attended all procedures for optimal data registration. Questionnaires to collect demographic and clinical information were completed at each endoscopy. Endoscopic and histological data from gastroscopies prior to inclusion were collected retrospectively. Endpoint of the study was progression to HGD/EAC during endoscopic follow-up. Univariate logistic regression was used to identify predictors of progression.
Results: 1003 patients were included: 726 (72%) men, mean age at diagnosis 55 ± 12 years, median BE length 3 cm (IQR 1-5), median surveillance time 7.1 years (IQR 3.4-11.1). A total of 52/1003 patients (5%) developed HGD (24/52) or EAC (28/52); median time to progression was 7.9 years (IQR 3.9-11.6). Annual risk of neoplastic progression was 0.64% per patient year. Presence of low-grade dysplasia (LGD) (OR 2.47, 95% CI 1.01-5.85)), age at baseline endoscopy (OR 1.03, 95% CI 1.00-1.05) and length of BE (OR 1.22 per cm, 95% CI 1.13-1.31) were predictive for neoplastic progression (table 1).

Table 1: Odds ratios

	OR	95% CI	p-value
Age at baseline endoscopy (years)	1.03	1.00-1.05	0.029
Male	1.29	0.67-2.49	0.453
BMI	1.05	0.99-1.10	0.096
PPI use	0.67	0.38-1.17	0.157
Total surveillance time (years)	1.04	0.97-1.06	0.559
BE length (per cm)	1.22	1.13-1.31	<0.001
LGD at baseline	2.47	1.05-5.81	0.038

Conclusion: This large prospective BE surveillance cohort is unique for its community based setting (avoiding referral bias) and long-term optimal surveillance circumstances. We found an annual risk of progression to HGD or EAC of 0.64% per patient year. BE segment length, presence of LGD and age at diagnosis were predictive for neoplastic progression and may therefore be used to tailor surveillance in BE patients.
Disclosure of Interest: A. Bureo Gonzalez: None declared, L. Duits: None declared, R. Mallant-Hent: None declared, J. Bergman Financial support for research: Boston Scientific, Olympus Endoscopy, Cook Medical, Boston Scientific, Covidien/Medtronics, Erbe, Ninepoint Medical, Consultancy: Cook Medical, Boston Scientific, Covidien/Medtronics, R. Pouw: None declared

OP148 PROSPECTIVE COMPARISON OF EMR VS ESD IN BARRETT'S NEOPLASIA: ARE WE TOO AFRAID OF KNIVES IN THE OESOPHAGUS?

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Introduction: Use of ESD in the Western setting is limited to a few centres with limited numbers of cases, due to concerns regarding complication rates and no established training pathway. The risks of ESD in the oesophagus are perceived to be high and the consequences disastrous. For this reason, endoscopic mucosal resection (EMR) is the most common technique used to resect early Barrett's cancer. The drawback of EMR is piecemeal resection and poor interpretation of histology.
Aims & Methods: We report our experience of oesophageal ESD in 51 cases and compare our data for EMR over the same period.
Results: 51 ESD resections for Barrett's neoplasia were performed between 2006 and 2014. 140 EMR's were performed in the same period. Mean age 71 years for ESD group and 75 for EMR group. All procedures were undertaken by a single expert endoscopist (PB).

Table 1: Lesion Characteristics & Post-resection Histology

	Mean Follow Up(Yrs)	Paris IIa (nodular)	Intra-mucosal (IMC)	Submucosal (SM1+)	Indeterminate Histology
ESD groupn = 51	4.2	92%	62%	32%	0%
EMR groupn = 140	5.7	10%	43%	15%	5%

The endoscopic cure rate in the ESD group was 83% and the EMR group was 82%. In the ESD group there was a recurrence rate of 3%, in the EMR group 16%. Additional radiofrequency ablation was required in 17% of patients in the ESD group and 34% of patients in the EMR group. There were no significant complications in the ESD group, there were 4 cases of bleeding and 4 cases of stricturing in the EMR group.
Conclusion: ESD for Barrett's neoplasia is feasible, safe and effective in Western hands. Our lesion selection data shows that ESD is being used mainly for nodular lesions and cancerous lesions as compared to EMR for flat and non-cancerous lesions. Neoplasia recurrence is higher in EMR vs ESD. The complication rates are similar. This calls for a randomised controlled trial comparing EMR vs ESD for the resection of nodular lesions in Barrett's neoplasia.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 08:30–10:30
THE DIFFICULT CIRRHOTIC PATIENT – ROOM A1

OP149 VALIDATION OF THE CLIF-ACLF SCORE IN PREDICTING MORTALITY IN ACUTE-ON-CHRONIC LIVER FAILURE PATIENTS IN A WARD

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Introduction: Admission of cirrhotic patients to intensive care unites is limited by high mortality, high costs and scarcity of intensive care beds.
Aims & Methods: We sought to validate the Chronic Liver Failure - Acute-on-Chronic Liver Failure (CLIF-ACLF) score[1] in patients with acute-on-chronic liver failure (ACLF) admitted in a Gastroenterology ward and compare it with the existing scoring systems Model for End-Stage Liver Disease (MELD), MELD-Sodium and Child-Turcotte-Pugh (CTP). Retrospective analysis of demographic, clinical and laboratorial data of patients admitted for acute cirrhosis decompensation between January 2013 and September 2014. Twenty eight (M28) and 90-day (M90) mortality were evaluated. Patients with and without ACLF were compared. CLIF-ACLF performance was compared with MELD, MELD-Sodium and CTP.
Results: 179 patients were included (male sex:73.7%, mean age:61 ± 11 years). 82.6% had alcoholic cirrhosis (with or without viral infection) and previous episodes of acute decompensation were absent in 24.6%. At admission 20.7% fulfilled criteria for ACLF and 7.8% developed ACLF during hospitalization (overall prevalence 28.5% - Grade 1:15.6%, Grade 2:12.3%, Grade 3:0.6%) . M28 e M90 were, respectively, 7.8% and 21.9% in patients without ACLF and 51.0% and 66.7% in patients with ACLF ($p < 0.001$). The AUROC of CLIF-SOFA in predicting M28 and M90 was respectively 0.809 ± 0.071 and 0.852 ± 0.054, and was superior to MELD (0.694 ± 0.076 and 0.689 ± 0.081), MELD-Sodium (0.715 ± 0.077 and 0.697 ± 0.081) and CTP (0.647 ± 0.08 e 0.684 ± 0.085); $p < 0.01$.
Conclusion: The application of ACLF criteria in the ward identifies patients with high mortality. The new CLIF-ACLF score accurately predicts short-term mortality of patients with ACLF hospitalized in a ward and is superior to MELD, MELD-Sodium and CTP.

Reference

1. Jalan R, Saliba F and Pavesi M, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. *J Hepatol* 2014; Nov; 61(5): 1038–47.

Disclosure of Interest: None declared

OP150 ULTRA-THIN DISPOSABLE GASTROSCOPE IS SAFE, FEASIBLE AND HIGHLY ACCURATE FOR SCREENING AND SURVEILLANCE OF GASTRO-OESOPHAGEAL VARICES IN PATIENTS WITH LIVER CIRRHOSIS: A PROSPECTIVE STUDY

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Introduction: Variceal haemorrhage is a serious consequence of portal hypertension. It is recommended that all patients with liver cirrhosis undergo endoscopic screening and surveillance for gastro-oesophageal varices. Upper gastrointestinal endoscopy is the gold standard technique, but can be costly and requires sedation.
Aims & Methods: The aim of this study is to evaluate and compare the role of an unsedated, disposable ultra-thin gastroscope against conventional upper gastrointestinal endoscopy in screening and surveillance of gastro-oesophageal varices in patients with liver cirrhosis. Forty six patients (56.4 ± 1.4 years; 35M:11F) with liver cirrhosis who were referred to the Gastrointestinal Investigation Unit at the Royal Adelaide Hospital for screening or surveillance of gastro-oesophageal varices were prospectively enrolled. In all subjects, unsedated gastroscopy was initially performed with a thin disposable endoscopy (E.G. Scan, South Korea) with lignocaine gargle, followed by the conventional upper endoscopy (Olympus QF 180, Japan) with conscious sedation. The 2 gastroscopies were performed by different gastroenterologists who were blinded to the results of the previous examination. Videos of all procedures were recorded for subsequent validation by an independent investigator in a random, blinded fashion, and determination of the presence of varices, variceal size and high risk stigmata. Patient tolerability was assessed by pain visual analogue scale (VAS: 0-10).
Results: Upper endoscopy was performed for variceal screening in 11 patients, primary surveillance in 30 patients, and secondary surveillance in 5 patients. All unsedated disposable endoscope were well tolerated, with a mean pain VAS score of 1.87 ± 0.33 (equivalent to "annoying") and no adverse events. Of the 25 patients who had oesophageal varices on the gold-standard conventional gastroscopy, varices were confirmed in 24 (96%) patients on disposable gastroscopy. Similarly, 18/21 (86%) patients who had no varices on conventional gastroscopy was confirmed on disposable scope, giving the overall accuracy of 91%. For the detection of varices, disposable endoscope had 96% sensitivity, 86% specificity, 89% positive predictive value, and 95% negative predictive value. The diagnostic accuracy increased to 96% (kappa score of 0.87) for high-risk varices characterised by large varices or high-risk stigmata. Compared to conventional sedated upper gastroscopy, the use of clinic-based unsedated disposable gastroscopy resulted in an estimated cost saving of $AUD 250 per case.
Conclusion: Unsedated disposable endoscopy with local anaesthetic gargle is well tolerated, safe and has excellent diagnostic accuracy for the detection of gastro-oesophageal varices. Together with the cost saving, the use of clinic-based disposable gastroscopy is a very attractive approach for variceal screening and surveillance program in large liver clinics as the gastroscopy results allow immediate determination of follow-up plan.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 08:30–10:30
SCREENING FOR COLORECTAL CANCER – ROOM A3

OP151 COST-EFFECTIVENESS ANALYSIS ON SURVEILLANCE FOLLOWING NEGATIVE COLONOSCOPY IN POPULATION-BASED COLORECTAL CANCER SCREENING

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Introduction: Population-based colorectal cancer (CRC) screening using the fecal immunochemical test (FIT) as a primary screening tool, with total colonoscopy (TCS) being performed for positive-FIT individuals, has been conducted in Japan as in several European countries. The cost-effectiveness of FIT-based screening has been reported in several studies including our recent study (Sekiguchi M, et al. *DDW* 2015). However, in screening program, no consensus has been reached on which should be used as a surveillance tool after negative TCS in terms of cost-effectiveness, FIT or TCS.
Aims & Methods: The aim of this study was to clarify which was a more cost-effective tool for surveillance following negative TCS in FIT-based screening, FIT or TCS. A Markov model was developed simulating the clinical course of CRC as a transition from normal epithelium, low-risk adenomatous polyps sized 1–4 mm and 5–9 mm, high-risk adenomatous polyps, and CRC to death from CRC. The initial population comprised 100,000 average-risk individuals aged 40 years. Transition probabilities, costs, and test characteristics were mostly based

on Japanese data, including data from the Japan polyp study (Matsuda T, et al. *UEGW* 2014); FIT and TCS cost $13.30 and $128.87, respectively. Two types of FIT-based screening strategies, one using FIT (strategy 1) and the other using TCS (strategy 2) as a surveillance tool after negative TCS, were evaluated for costs (US$), gained quality-adjusted life-years (QALYs), and the number of TCS procedures. In both strategies, those with positive FIT were invited to undergo TCS; polyps found were removed and surveillance TCS was repeated every 3 years until no more polyps were found. In the case of normal results on TCS, FIT was resumed 5 years after TCS in strategy 1, whereas TCS was repeated 10 years after in strategy 2. Screening compliance rates were set at 60% in the base-case analysis, and scenario analyses were performed on the compliance rates (10%–100%) and starting age of screening (50 years).

Results: QALYs and costs per person in strategy 1, 2, and no screening were as follows: strategy1, 23.000 QALYS and $787.65; strategy 2, 23.007 QALYs and $823.41; no screening, 22.799 QALYs and $1298.09. Both strategy 1 and 2 yielded higher QALYs with lower costs than no screening. Compared with strategy 1, strategy 2 increased QALYs with more costs. The incremental cost per QALYs gained for strategy 2 against strategy 1 was $5,108.57, which was much lower than the known upper limit of willingness-to-pay values ($50,000). However, the number of required TCS procedures (/100,000 persons) in strategy 2 was 202,988, which was twice as many as with strategy 1 requiring 100,740 TCS procedures. In the scenario analyses, the incremental cost per QALYs gained for strategy 2 against strategy 1 remained less than $50,000.

Conclusion: Whether FIT or TCS is used for surveillance following negative TCS, FIT-based CRC screening is more cost-effective than no screening. In the screening system, TCS can be used as a more cost-effective tool than FIT for surveillance following negative TCS; however, considering the increased number of TCS procedures, the choice should be determined according to the nationwide availability of TCS resources.

Disclosure of Interest: None declared

OP152 CORRELATION BETWEEN ADENOMA DETECTION RATE (ADR) IN DIRECT COLONOSCOPY BASED COLORECTAL CANCER (CRC) SCREENING AND ADR IN COLONOSCOPY IN THE FIRST ROUND OF FECAL IMMUNOCHEMICAL TEST (FIT) BASED CRC SCREENING

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Introduction: Adenoma detection rate (ADR) is the main quality indicator in CRC screening colonoscopy. An ADR <20% is associated with an increased risk of interval CRC after screening colonoscopy. However, there is no information on the recommended ADR in the work-up colonoscopy of FIT-based CRC screening programs

Aims & Methods: Our analysis evaluated if there was a correlation between the ADR in primary colonoscopy of a colonoscopy-based program and the corresponding figure in the work-up colonoscopy of a FIT-based program. We designed a post-hoc analysis within the first round of the COLONPREV study, a randomized controlled trial comparing the efficacy of biennial FIT and one-time colonoscopy for reducing CRC-related mortality. The study included asymptomatic people between 50-69 years from 15 hospitals in 8 Spanish regions. Colonoscopies were performed by the same endoscopists in each hospital. We evaluated the ADR by age group (50-59, 60-69), sex and region, and calculated the Pearson's correlation coefficient. Moreover, we developed a predictive model based on a multivariable lineal regression analysis including the confounding variables (i.e. age, sex, and region). Finally, we determined the ADR in work-up colonoscopy of a FIT-based program equivalent to the well-defined and accepted ADR of 20% in a colonoscopy-based program.

Results: Colonoscopy was performed in 5722 subjects (5059 primary colonoscopy, 663 after a positive FIT). The median ADR was 31% (range, 14-51%) in colonoscopy group and 55% (range, 21-83%) in FIT group. In the colonoscopy group, median ADR distribution was as follows: male, 37% (22-51%); female, 23% (14-51%); 50-59 years, 28% (14-47%); and 60-69 years, 36% (16-51%). In the FIT group, median ADR distribution was as follows: male, 67% (26-78%); female, 45% (21-83%); 50-59 years, 53% (21-78%); and 60-69 years, 56% (38-83%). There was a positive correlation in the ADR between primary colonoscopy and work-up colonoscopy (Pearson's coefficient 0.716; $p < 0.001$). The coefficient of multiple correlation of the predictive multivariable lineal regression model was 0.68. In this model, ADR in the FIT group was independently related to ADR in the colonoscopy group: regression coefficient for colonoscopy ADR, 0.71 ($p = 0.009$); sex, 0.09 ($p = 0.09$); age, 0.3 ($p = 0.5$); and region 0.00 ($p = 0.9$). Estimated ADR in work-up colonoscopy equivalent to the 20% ADR in primary colonoscopy was 45% (95% confidence interval, 34-57%)

Conclusion: ADR in primary and work-up colonoscopy of a FIT-positive result are positively and significantly correlated. According to this correlation, ADR should be set at 45% as quality indicator in FIT-based CRC screening programs.

Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 08:30–10:30

EPIDEMIOLOGY OF IBD – ROOM 7.1

OP153 HIGHLIGHTING OF EPIDEMIC AREAS OF CROHN'S DISEASE IN A POPULATION-BASED REGISTRY OVER 22 YEARS: GENETIC OR ENVIRONMENTAL CAUSE?

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Introduction: Our previous studies detected a spatial heterogeneity in standardized incidence ratios of Crohn's disease (CD), through a population-based IBD registry over a 17-year period, pointing the existence of clusters with low and high incidence

Aims & Methods: The first aim of the present study was to determine the origin of these clusters according with CD family history (CD-FH) or not over a 22-year period (1990-2011). The second aim of this study was to compare the clinical phenotype at CD diagnosis between clusters with high and low CD incidence. From 1990 to 2011, the Epimad population-based registry recorded 8,970 incident CD cases distributed in 273 administrative areas of Northern France. Isotonic scan statistics allowed the detection of clusters and their epicenter. Several data were collected at time of diagnosis including: gender, age, CD-FH, smoking status, phenotype (location, behavior and anoperineal lesion) according to Montreal classification and diagnosis management.

Results: Seven clusters including all patients ($n = 8,970$) have been identified in both analyses; 4 with high incidence (2,163 CD cases; RR from 1.27 to 1.46; $p < 10^{-3}$) and 3 with low incidence (861 CD cases; RR from 0.69 to 0.71; $p < 10^{-2}$). After exclusion of patients with CD-FH ($n = 1,086$) prone to have a genetic burden, the size of cluster with high incidence in the southeastern part of the area was greatly reduced.

Concerning clinical parameters; gender, median age at diagnosis, smoking status and CD phenotype were not different between clusters with high and low incidences.

Conclusion: Four clusters of epidemic CD areas have been identified in our population-based study over a 22-year period. Only one cluster was reduced in size when excluding CD-FH patients. These results assumed for a high impact of environmental risk factors in the origin of these clusters. It is now our challenge to highlight them.

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OP154 SHORT-TERM AND LONG-TERM DURABILITY IN THE RISE OF PAEDIATRIC INFLAMMATORY BOWEL DISEASE INCIDENCE IN SCOTLAND BETWEEN 1969-2013: A NATIONAL COHORT STUDY

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Introduction: Scotland has one of the highest rates of paediatric inflammatory bowel disease (PIBD) worldwide, with previously demonstrated medium-term increases in PIBD incidence between 1990-2008(1). However, it is not yet clear if this rise has been sustained over a more prolonged time-frame and if this increasing incidence has been preserved in recent years.

Aims & Methods: We aimed to evaluate the long-term temporal trends in PIBD incidence in Scotland over a 45 year period. National data from previously published incident cases of PIBD in Scotland during the periods 1969-1995 and 2003-2008 were examined; prospectively collected incident cases from 2009-2013 were also included. Incidence rates were calculated using publicly available population data from the Scottish government and trends across

cohorts calculated using Poisson regression analysis. Rates were standardised to the 2001 census population for comparison.
Results: There was a moderate, but significant, increase in PIBD incidence from 2.3/100,000/yr (95%CI 2.0-2.6) to 4.5/100,000/yr (95%CI 3.9-5.0) between the 1969-1974 and 1990-1995 epochs respectively ($p < 0.001$). A more dramatic rise was evident in the most recent cohort (2009-2013) with a rate of 10.4/100,000/yr (95%CI 9.6-11.5), showing a sustained increased from the 2003-2008 cohort (7.8/100,000/yr [95%CI 7.1-8.6]; $p < 0.001$). For Crohn's disease (CD) a more linear trend was observed with rates increasing steadily from 0.9/100,000/yr (95%CI 0.7-1.1) during 1969-1974, to 2.2/100,000/yr (95%CI 1.8-2.7) during 1986-1989 and 6.3/100,000/yr (95%CI 5.6-7.0) in the 2009-2013 cohort ($p < 0.001$). Between the 1969-1974 and 2009-2013 cohorts the incidence rate ratio (IRR) for PIBD and CD were 4.6 (95%CI 3.7-5.7) and 7.4 (95%CI 5.5-10.0) respectively; a 33% rise was also apparent between the two most recent cohorts (IRR 1.3 [95%CI 1.2-1.5]). The ratio of non-Crohn's colitis (ulcerative colitis and IBD unclassified combined) to CD has reversed from 2:1 to 4:6 over the 45-year period.
Conclusion: Using historical and contemporaneous data over a 45-year period in a well-defined and stable population we have demonstrated a sustained incidence rise which is durable in both the short- and long-term, with a 4.6-fold increase in PIBD and a 7.4-fold increase in CD across the study period. Despite no discernible changes in population structure, genetic susceptibility or diagnostic evaluation over the past 12 years we also show a sustained short-term increase in incidence suggesting that aetiological factors continue to exert their effects on at-risk individuals.

Reference

1. Henderson 1, et al *Inflamm Bowel Dis* 2012; 18(6): 999–1005.

Disclosure of Interest: None declared

OP155 FREQUENT RAPID CLINICAL PROGRESSION OF NEWLY DIAGNOSED CROHN'S DISEASE: RESULTS OF A PROSPECTIVE INCEPTION COHORT

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Introduction: Population-based studies have shown that structural and functional bowel damage of Crohn's disease (CD) is a dynamic, progressive process. However, timing and degree of progression are unpredictable.
Aims & Methods: We aimed to investigate the time course to progression in newly diagnosed CD, and to identify risk factors. This is a longitudinal, prospective, observational follow up study, of an inception cohort, in a tertiary referral center. Adults (≥18 y-o), suspected of CD or diagnosed with CD during the preceding six months prior to enrollment, were recruited. Enrollees were prospectively followed at 6 months intervals. Progression to complicated disease, CD-related hospitalizations or surgeries, was documented.
Results: A total of 161 patients were enrolled between 05/2013-04/2015. Of these, 119 fulfilled inclusion criteria and 79 attained a definite diagnosis of CD. Male/female ratio was 32/47, mean age at diagnosis was 34.1 ± 16 years, average BMI was 21.8 ± 5 kg/m^2, positive family history of IBD was detected in 20.3%. Mean CDAI at enrollment was 173 ± 91 (19-359), mean CRP 19.1 ± 32 gr%, and mean fecal calprotectin 1162 ± 1808 mg/gr stool. Mean time between commencement of symptoms and diagnosis was 9.3 ± 16.1 months. L1, L2, and L3 phenotypes were detected in 45.65%, 24.1%, and 24.1%of patients, respectively. Stricturing and penetrating disease were detected in 5.1% and 15.2% respectively, and perianal disease in 16.5%. Six and 12 months after diagnosis 19 and 20 patients (24% and 25.3%, respectively) experienced disease complications. Stricturing (B1) phenotype significantly differentiated complicators and non-complicators: 18.8% vs. 1.8%, respectively ($p = 0.034$). Drug exposure rates within 6 months from diagnosis in complicators and non-complicators were: corticosteroids 44.4% vs. 6.9% ($p = 0.001$), immunmodulators 27.8% vs.6.9% ($p = 0.03$), and biologics 16.7% vs. 8.8% ($p = NS$). Multivariate analysis demonstrated that demographics, Montreal criteria, and inflammatory markers at diagnosis were not associated with rapid complication. The model revealed that stricturing phenotype (OR 21.8, 95% CI 1.766-269.7), exposure to steroids (OR 9.8, 95% CI 2.04-47.6) or immunmodulators (OR 6.79, 95% CI 1.26-36.5) during the first 6 months since diagnosis were associated with rapid disease progression. Interestingly, exposure to biologics during the first 6 months of diagnosis was not associated with complication risk.
Conclusion: Early complications occurring within the first six months from diagnosis manifest in a quarter of newly diagnosed CD patients. These rapidly complicated CD patients are treated with significantly more steroids and immumodulators compared to non-rapidly complicated patients, but not with biologics. As complications emerge early and clinical and laboratory predictors for progression are unreliable, intensive follow-up for newly diagnosed patients and consideration of very early introduction of biologics to suspected complicators are warranted. More accurate molecular and serological characteristics are required to better phenotype these patients.
Disclosure of Interest: None declared

OP156 PHARMACOLOGICAL TREATMENT OF CROHN'S DISEASE CAN CHANGE THE COURSE DURING THE FIRST FIVE YEARS AFTER DIAGNOSIS. RESULTS FROM A SWEDISH PROSPECTIVE POPULATION-BASED COHORT

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Introduction: Although the pharmacological treatment of Crohn's disease has been intensified during later years with an increased use of immunomodulating drugs as well as the introduction of biologics, controversy still exists regarding the fundamental question whether the disease course can be changed with pharmacological treatment. We have previously reported that long symptom duration before diagnosis of Crohn's disease was associated with the prevalence of intestinal damage (1). Even if the patients received modern pharmacological treatment to a high extent, the bowel resection rate after one year was comparable with the IBSEN study (2) from the pre-biological era (12.5% vs 13.6%). We now report the five years result of the ICURE study (IBD Cohort Uppsala Region).
Aims & Methods: The aim of the study was to evaluate the frequency of intestinal resections in patients with Crohn's disease during the first 5 years after diagnosis. Within the Uppsala health care region of Sweden (population 642,000) all patients in all age groups with newly diagnosed Crohn's disease were included prospectively during the years 2005-2009 (n = 268). The average incidence was 9.9/100 000/year. After 5 years follow-up all journal records were analysed for surgery, medication and mortality.
Results: During follow-up 17 patients died (6.3%), whereof three cases related to the Crohn's disease (dehydration due to high ileostomy output, small bowel carcinoma and small bowel obstruction with sepsis). 226 of the surviving patients had a complete 5-year follow-up (90%). After 1 year the bowel resection rate was 12.4% and after 5 years it was 14.9% using Kaplan-Meier survival function. Patients < 17 years had a 5 years resection rate of 6.1%. 57% of the patients were treated with antimetabolites and 21% were treated with anti-TNF-alpha antibodies. Stricturing and penetrating behaviour were independent risk factors for bowel resection in a multivariate analysis.
Conclusion: The number of patients with Crohn's disease in need for intestinal resection within 5 years after diagnosis was only 15%, to be compared with a recent meta-analysis estimating the surgery rate to 24% for patients diagnosed 2000-2011 (3). Only 2.5% of the patients were subjected to surgery after the first year. 61% had been treated with either antimetabolites or anti-TNF-alpha antibodies, or a combination of these two. The disease-specific mortality after 5 years was 1.1%.

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Disclosure of Interest: None declared

OP157 CHOLANGIOGRAPHIC EVIDENCE OF SCLEROSING CHOLANGITIS AFTER TWO DECADES OF INFLAMMATORY BOWEL DISEASE: MRI SCREENING IN A POPULATION-BASED COHORT

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Introduction: The prevalence of primary sclerosing cholangitis (PSC) has been reported in the range of 2.4-7.5% in ulcerative colitis (UC) and 1.2-6.4% in Crohn's disease (CD). However, PSC may have a mild disease course and preliminary data have suggested that the true prevalence in inflammatory bowel disease (IBD) could be significantly higher (>10%). In the present study we aimed to determine the prevalence of PSC in longstanding IBD by performing magnetic resonance cholangiography (MRC) screening in a population-based cohort.
Aims & Methods: A standardized MRC protocol was included as part of the 20 years follow-up of the IBSEN (*IBD South-East Norway*) inception cohort. Out of 756 patients included at baseline with a definite diagnosis of IBD, 587 were alive at the time of 20 year follow-up. N = 470 (80.0%) attended and were offered MRC. Two experienced abdominal MRI readers blinded for clinical history and

previous imaging scored independently for radiological presence of PSC-like changes by using a previously validated classification system. Final diagnosis was made by reader consensus.
Results: MRC was successfully performed in 322 patients (68.5% of the attending), comprising 153 (47.5%) women with a median age 51.4 years (range 28.8-84.4) and median IBD duration of 20.1 years (17.9-23.8). N = 222 (68.9%) of the patients were classified as UC and 100 (31.1%) as CD. The MRC-examined subgroup of the cohort was comparable to the total alive population at the time of follow-up regarding age, gender, IBD type, extension and behaviour of the disease. MRC screening identified 24 (7.4%) with definite or probable large duct PSC, out of which 9 (2.7%) were previously known. The prevalence of PSC-like changes varied by gender (5.9% in men and 9.2% in women), and IBD type (9.0% in CD and 6.8% in UC patients), but these differences were not statistically significant. Extensive colitis was observed in 12 (80.0%) of the UC patients with PSC-like changes compared to 88 (45.1%) without PSC (p = 0.014). Disease distribution for CD patients with PSC-like changes was colonic (4), ileocolonic (4) and ileal (1). In patients with PSC-like changes, a chronic persistent IBD activity was more common, than in patients without PSC (p = 0.025).
Conclusion: Two decades after the diagnosis of IBD, cholangiographic evidence of large duct PSC was observed in 7.4% of the patients, more than twice the number of clinically recognized cases. Surprisingly, the prevalence did not vary significantly with gender or IBD type. Consistent with previous reports, colitis and persistent low-grade disease activity seems to be characteristic of PSC-IBD.
Disclosure of Interest: None declared

OP158 DO PATIENTS WITH LONGSTANDING INFLAMMATORY BOWEL DISEASE (IBD) HAVE A HIGHER CANCER RISK THAN CONTROLS? RESULTS FROM THE IBSEN (INFLAMMATORY BOWEL SOUTH-EASTERN NORWAY) STUDY

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Introduction: Inflammatory bowel disease (IBD) has been associated with a broad specter of both intestinal and extraintestinal malignancies.
Aims & Methods: Our aims were twofold - to determine cancer prevalence in an unselected population-based cohort of IBD patients 20 years after diagnosis and to assess if IBD patients had an increased cancer-specific risk compared with the normal age- and gender- matched population. The IBSEN (Inflammatory Bowel South-Eastern Norway) study prospectively followed all patients (n = 756) diagnosed with IBD from January 1, 1990, to December 31, 1993, in four geographically well-defined areas in southeastern Norway. This well characterized population-based cohort was prospectively followed for 20 years. Each IBD patient was matched with up to 25 controls (matching variables: age, sex, and county). Data on all cancer cases were collected from the Cancer Registry of Norway. Cox regression model was fitted to calculate cancer-specific (all cancers and gastrointestinal cancers only) risks for patients compared with their matched controls.
Results: In total, we analyzed 519 UC (51.4% males) and 237 CD (50.2% males) patients and 18825 controls. The median age at diagnosis was 37 years in the UC group and 28 in the CD group. There were 105 cancers (13.9%) in the IBD group and 1830 (9.7%) in the controls. Overall, IBD patients had 1.5 times higher risk of cancer development than their matched controls (HR = 1.52, 95% CI 1.26-1.83, p < 0.001). Males with IBD had a significantly increased risk of CRC (colo-rectal cancer) compared to controls (HR = 2.54, 95% CI 1.40-4.63, p = 0.002).The cancer-specific risk was slightly higher in UC than in CD patients compared to the normal population (HR = 1.79, 95%CI 1.42-2.23, p < 0.001) and (HR = 1.51, 95%CI 0.98-2.31, p = 0.056); for UC and CD respectively.
Conclusion: During 20 years' disease course IBD patients had about 50% increased cancer risk compared to matched controls. Most of the excess risk is comprised by increased risk for CRC in male IBD patients.
Disclosure of Interest: None declared

OP159 CANCER AND INFLAMMATORY BOWEL DISEASE PHENOTYPE: A PROSPECTIVE MULTICENTER NESTED CASE-CONTROL IG-IBD STUDY

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Introduction: Concern exists about the cancer risk using thiopurines (IS) and/or anti-TNFs in Inflammatory Bowel Disease (IBD), while the role of IBD phenotype in determining this risk is undefined.
Aims & Methods: In prospective, multicenter, nested case-control study at 3 years, we aimed to characterize incident cases of cancer in IBD. The role of IBD phenotype *vs* IS and/or anti-TNFs use in determining the incidence of cancer was investigated. From January 2012 to December 2014, all incident cases of cancer in IBD patients referring to 16 Units (≥2 visits/year) were recorded. Each IBD patient with cancer (IBD-K) was matched with 2 IBD patients with no cancer (IBD-C) for: IBD type (Crohn's Disase, CD vs Ulcerative Colitis, UC), gender, age (±5 years). Statistical analysis: data expressed as median (range), Wilcoxon test, Chi-squared test, multivariate logistic regression analysis.
Results: During the 3 years' follow up, 44,619 IBD patients (21,953 CD, 22,666 UC) were considered. Incident cancer occurred in 174. IBD patients (IBD-K): 99 CD (CD-K) and 75 UC (UC-K). Cancer incidence was 3.9/1000 IBD patients (174/44,619), being higher in CD (4.5/1000 [99/21,953]) than in UC (3.3/1000 [75/22,666]; p = 0.042). Cancers included or involved: digestive system (39.1%; n = 68), skin (13.2%; n = 23: 9 NMSC, 11 melanoma, 3 others), urinary tract (11.5%; n = 20), lung (9.2%; n = 16), breast (7.5%; n = 13), genital tract (6.3%; n = 11), thyroid (n = 8; 4.6%), lymphoma (3.5%, n = 6 CD: 3 NHL[IS 1;IS + anti-TNFs 1]), others (5.1%; n = 9). Cancers of the digestive system included (n = 68): 48 (71%) colorectal (CRC), 8 ileal (12% all CD), 12 (17%) others. Cancer sites and CRC incidence were comparable in CD vs UC (n = 24/99; 35.2% vs n = 24/75; 32%). The percentage of patients with perforating CD was higher in CD-K vs CD-C (26% (26/99 vs 15%; 30/198; p = 0.02). The percentage of patients with extensive UC was higher in UC-K vs UC-C (55%; 41/75 vs 34%; 51/159; p = 0.03). Risk factors for any cancer included perforating CD (OR 2.33; 95% CI 1.01-5.47) and IS + anti-TNFs use in CD (OR 1.94, 95% CI 1.1-3.5), pancolitis (OR 2.95; 95% CI 1.35-6.71) and surgery in UC (OR ; 5.09: 95%CI: 1.73-17.15). When excluding CRC from the analysis, perforating CD, pancolitis and surgery in UC, but not IS + anti-TNFs in CD, were risk factor for cancer in IBD.
Conclusion: In a prospective, multicenter, nested-case control study, CD phenotype, penetrating CD and extensive UC represented risk factors for any cancer in IBD.
Disclosure of Interest: L. Biancone Lecture fee(s): MSD, Takeda, Abbvie, Zambon, A. Armuzzi Lecture fee(s): Abbvie, Astra Zeneca, Chiesi, Ferring, MSD, Otsuka, Takeda, Zambon, Consultancy: Abbvie, Hospira, Lilly, MSD, Sofar, M. L. Scribano Lecture fee(s): Zambon, Consultancy: Biogen Idec, Takeda, Mundipharma, R. D'Inca' Lecture fee(s): Hospira, Abbvie, MSD, Cadigroup, C. Papi Consultancy: Takeda, Abbvie,MSD, sofar, Chiesi, L. Spina: None declared, E. Angelucci: None declared, C. Petruzziello: None declared, L. Guidi: None declared, A. Kohn: None declared, F. Mocciaro: None declared, P. Alvisi: None declared, A. Ruffa: None declared, R. Monterubbianesi: None declared, W. Fries Lecture fee(s): Abbvie, MSD, Hospira, Ferring, G. Riegler Lecture fee(s): Takeda, MSD, M. Daperno Financial support for research: MSD, Lecture fee(s): Abbvie, MSD, Hospira, Mundipharma, Takeda, Sofar, Chiesi, Ferring, F. Castiglione Lecture fee(s): Takeda, Chiesi, MSD, Abbvie, Sofar, G. Condino: None declared, S. Renna: None declared, E. Calabrese Lecture fee(s): Abbvie. MSD, R. Di Mitri: None declared, G. Meucci: None declared, F. Rogai: None declared, S. Ardizzone Lecture fee(s): MSD, abbvie, A. Rossi: None declared, A. Orlando: None declared, F. Pallone Lecture fee(s): Zambon, Takeda

OP160 EXTRACOLONIC NEOPLASIAS IN INFLAMMATORY BOWEL DISEASE PATIENTS: DATA FROM THE GETECCU ENEIDA REGISTRY

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Aims & Methods: a) To know the prevalence and distribution of ECNs in IBD patients; b) To estimate the incidence rate of ECNs; c) To evaluate the association between ECNs and the treatment with IMMs and anti-TNF agents
Inclusion criteria: IBD patients included in ENEIDA Project from GETECCU. To estimate the incidence rate of ECNs, only patients diagnosed with IBD after the implementation of ENEIDA in each center (2007 in most of them) were considered (inception cohort).
Results: 11,047 patients met the inclusion criteria with a median follow-up of 98 months. 48% of patients had been exposed to IMMs or anti-TNFs. The prevalence of ECNs was 3.6%. In the multivariate analysis, age (OR = 1.03, 95%CI = 1.03-1.04) and to have been ever smoker (OR = 1.2, 95%CI = 1.04-1.6) were the only variables associated with a higher risk of ECN. 3,485 patients

comprised the inception cohort, with a median follow-up of 27 months. 45% of patients had been exposed to IMMs or anti-TNFs at any time during follow-up (42% thiopurines, 3.5% methotrexate, 20% anti-TNFs). 38 patients developed ECNs (1.1%). In the multivariate analysis, age was the only variable associated with a higher risk of ECN (HR = 1.04, 95%CI = 1.02-1.07). The treatment with IMMs or anti-TNFs was not associated with a higher risk of ECN. The relative risks (RR) of melanoma and bladder, lip and oral cavity, and lung cancer were increased compared with the background population. The RR of lip and oral cavity, melanoma, thyroid and breast cancer in ulcerative colitis, and the RR of bladder cancer and non-Hodgkin lymphoma were increased in Crohn's disease patients.
Conclusion: Older age and smoking habit were associated with a higher prevalence ECNs. Older age was associated with a higher incidence of cancer. Neither thiopurines/methotrexate nor anti-TNF drugs seem to increase the risk of ECNs. The RR of melanoma and tobacco-related cancers were increased in IBD patients.
Disclosure of Interest: None declared

OP161 UNCHANGED SURGERY AND HOSPITALIZATION RATES IN AN EAST-WEST EUROPEAN INCEPTION COHORT DESPITE DIFFERENCES IN USE OF BIOLOGICALS – 3-YEAR FOLLOW-UP OF THE ECCO-EPICOM COHORT

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Introduction: The EpiCom-cohort is a European prospective population-based cohort of unselected, uniformly diagnosed patients with inflammatory bowel disease (IBD) in 2010 from Western and Eastern European countries. The cohort aims at describing differences in occurrence, treatment strategies, and disease course within Europe.
Aims & Methods: Patients were followed prospectively from the time of diagnosis. Clinical data on surgery, hospitalization and medical treatment were captured throughout the follow-up period. The aim of the study was to investigate differences in treatment strategy and disease outcome between Eastern and Western Europe during the first 3 years of follow-up.
Results: A total of 934 patients aged ≥15 years from 21 centres (13 Western, 8 Eastern European) were eligible for follow-up of whom 501 (54%) had ulcerative colitis (UC), 335 (36%) had Crohn's disease (CD), and 98 (10%) had IBD unclassified (IBDU). At 3-years follow up 80 patients had undergone 1st surgery (resections or colectomy) (17 from Eastern Europe, 63 from Western Europe), 120 had received biological therapy (12 from Eastern Europe, 108 from Western Europe) and 180 were hospitalized (35 from Eastern Europe, 145 from Western Europe). Crude annual rates for surgery, biological treatment and hospitalization are shown in Table 1. The cumulative probability of CD patients receiving treatment with 5-ASA within the three first years of disease was 90% in Eastern Europe and 55% in Western Europe ($p < 0.05$), 69% and 64% for prednisolone, 49% and 61% for immunomodulators, respectively. For UC patients the cumulative probability of receiving 5-ASA was 100% in Eastern Europe and 86% in Western Europe ($p < 0.05$), 40% and 47% for prednisolone, 20% and 26% for immunomodulators, respectively. Cox regression analysis revealed that hospitalization, surgery, and need for higher treatment steps was associated with stricturing or penetrating disease in CD and extensive disease in UC.
Conclusion: In an era of early and aggressive immunological therapy, surgery and hospitalization rates were similar in Eastern and Western Europe and comparable to population-based cohorts from the pre-biological era. This similar disease course was in spite of more early and aggressive treatment with biologics, with significantly more patients in Western Europe receiving biologics. The use of 5-ASA for CD is frequent and differs between Eastern and Western Europe.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 08:30–10:30
NEW PHARMACOLOGICAL AND NON-PHARMACOLOGICAL TREATMENT ALTERNATIVES FOR IBS – ROOM E1

OP162 BIFIDOBACTERIUM LONGUM NCC3001 IMPROVES DEPRESSION AND REDUCES BRAIN EMOTIONAL REACTIVITY IN PATIENTS WITH IRRITABLE BOWEL SYNDROME (IBS): A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED TRIAL

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Introduction: Specific probiotic bacteria can improve gut symptoms of IBS[1], however, their efficacy in treating co-morbid anxiety or depression in this population is unknown. We have previously shown that the probiotic *B. longum NCC3001* normalizes anxiety-like behaviour and hippocampal neurotrophin levels in murine models of low-grade gut inflammation[2].
Aims & Methods: To evaluate the effects of *B. longum NCC3001* on anxiety and depression in patients with IBS and to study the underlying mechanisms. We conducted a randomized, double-blind, placebo-controlled, single center study in adult patients with IBS with diarrhea or mixed stool pattern (Rome III criteria) and mild to moderate anxiety and/or depression. *B. longum* or placebo (maltodextrin) was administered daily for 6 weeks. Validated questionnaires were used to assess anxiety and depression (HAD score, STAI), IBS symptoms (adequate relief question, IBS Birmingham and Bristol scale), quality of life (SF-36) and somatization (PHQ-15) before, at the end and 1 month after the treatment (follow-up). We assessed brain activation patterns using the backward masked fear paradigm (fMRI), cognitive function (memory and concentration), serum BDNF and inflammatory markers, and gut microbiota profiles (16S rRNA Illumina).
Results: We randomized 44 patients, 38 of them (*B. longum* = 18, placebo = 20) completed the study. At six weeks, depression scores improved in patients treated with *B. longum* compared with placebo (RR 2.94, 95% CI 1.05-8.23, $p = 0.01$) and this was maintained at follow-up. More patients treated with *B. longum* than placebo reported adequate relief of overall IBS symptoms (RR 2.1, 95% CI 1.15-3.83, $p = 0.02$) but no statistically significant changes were found in the IBS Birmingham scores. The physical subdomain of quality of life improved in *B. longum* treated group compared with placebo ($p = 0.03$, Mann–Whitney $U = 228.5$), with trends for improvement in the mental subdomains of vitality and emotional role functioning. Functional MRI revealed significant reductions from baseline in response to negative emotional stimuli in multiple brain areas involved in emotion processing, including amygdala, frontal and temporal brain regions ($p < 0.001$), in *B. longum* treated patients compared with placebo. No statistically significant differences were observed in anxiety, cognitive function, inflammatory markers, serum BDNF levels or gut microbiota profiles in *B. longum*-treated patients compared to placebo.
Conclusion: Our results demonstrate that six-week treatment with *B. longum NCC3001* improves comorbid depression, overall gastrointestinal symptoms and quality of life in patients with IBS. This is associated with changes in the brain activation patterns in the amygdala and fronto–limbic regions, suggesting that reduction in limbic reactivity may underlie the beneficial effect of this probiotic.

References

1. Ford et al. *Am J Gastroenterol* 2014.
2. Bercik et al. *Gastroenterology* 2010.

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Disclosure of Interest: M. Pinto-Sanchez: None declared, G. Hall: None declared, K. Ghajar: None declared, A. Nardelli: None declared, C. Bolino: None declared, C. Welsh: None declared, A. Rieder: None declared, J. Traynor: None declared, C. Gregory: None declared, J. Lau: None declared, A. Ford: None declared, G. Bergonzelli Shareholder: Nestle Research Center, M. Surette: None declared, S. Collins: None declared, P. Moayyedi: None declared, P. Bercik Financial support for research: Study supported by a grant from Nestle Switzerland

Abstract number: OP161 Table 1: Crude rates for surgery, biological therapy and hospitalization (*$p < 0.05$)

		Biological treatment		Surgery		Hospitalization	
		1 year	3 years	1 year	3 years	1 year	3 years
Crohnsdisease	Eastern Europe	4 (5%)	7 (8%)	10 (12%)	14 (17%)	16 (19%)	20 (24%)
Western Europe	50 (20%)*	67 (27%)*	26 (10%)	40 (16%)	46 (18%)	63 (25%)	
Ulcerative colitis	Eastern Europe	1 (1%)	5 (4%)	2 (2%)	3 (2%)	8 (6%)	15 (12%)
Western Europe	18 (5%)*	32 (9%)*	9 (2%)	18 (5%)	47(13%)	68 (18%)	

OP163 THE IMPACT OF LOW FODMAP DIETARY ADVICE AND PROBIOTICS ON SYMPTOMS IN IRRITABLE BOWEL SYNDROME: A RANDOMISED, PLACEBO-CONTROLLED, 2X2 FACTORIAL TRIAL

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Introduction: Controlled trials using complete feeding diets have demonstrated that dietary restriction of fermentable carbohydrates (low FODMAP diet, LFD) reduces symptoms in patients with irritable bowel syndrome (IBS). However, a randomised, placebo controlled dietary advice trial has not been performed. Also, LFD has a negative impact on the gastrointestinal microbiota and the benefit of combining LFD with probiotics is unknown.

Aims & Methods: This randomised controlled trial aimed to investigate the effect of LFD dietary advice with a probiotic on symptom response compared with a sham diet in patients with IBS. Adults with IBS referred to a secondary care dietetic service were screened for inclusion (n = 162). Eligible patients were randomised to LFD or sham (placebo) dietary advice and to the multi-strain probiotic VSL#3 or placebo for 4 weeks in a 2x2 factorial design. The sham (placebo) diet was designed to be equivalent in nutrients and FODMAP content to habitual diet. Outcome measures included the global symptom question ('did you have adequate relief of your IBS symptoms over the last 7 days?') and the validated IBS symptom severity scale (IBS-SSS, maximum score 500) at baseline and follow up. Statistical analysis was performed using logistic and linear regression.

Results: A total of 104 patients were recruited and 95 completed the study (63 females, 66%). There were 8 withdrawals (4 LFD, 4 sham) and 1 loss to follow up (sham). There was no significant interaction between diet (LFD/sham) and probiotic (VSL#3/placebo) for adequate relief or IBS-SSS. In the intention-to-treat analysis, a higher proportion of patients reported adequate relief at follow up in LFD (57%) versus sham (38%, $p = 0.05$; RR 1.51, 95% CI 0.99, 2.29) and for probiotic (57%) versus placebo (37%, $p = 0.05$, RR 1.52, 95% CI 0.99, 2.33). Mean IBS-SSS scores were significantly lower following the LFD versus sham (165.5 vs 231.8, $p < 0.001$) but not different for probiotic versus placebo (196.9 vs 201.7, $p = 0.75$), after adjusting for baseline values. Subscores for IBS-SSS were significantly lower after LFD versus sham for days of pain (28.6 vs 44.7, $p < 0.001$), distension (27.3 vs 41.6, $p = 0.001$) and satisfaction with bowel habit (40.7 vs 54.5, $p < 0.001$).

Conclusion: This is the first randomised placebo-controlled trial evaluating the effect of LFD advice which demonstrates greater effectiveness compared with sham advice for IBS symptoms. The effectiveness of this probiotic is equivocal. Whether concomitant probiotic treatment is able to prevent the impact of LFD on the microbiota will be investigated.

Disclosure of Interest: None declared

OP164 THE EFFECT OF DIETARY GUIDANCE ON THE DUODENAL ENDOCRINE CELLS IN PATIENTS WITH IRRITABLE BOWEL SYNDROME

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Introduction: Altered neuroendocrine system is one of the pathophysiological factors in irritable bowel syndrome (IBS). The densities of the gut endocrine cells are found abnormal in IBS patients. Dietary guidance with low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet has improved the symptoms and quality of life of IBS patients (1) and normalized the densities of several endocrine cell types in the stomach (2) and the colon (3).

Aims & Methods: The aim of the current study is to investigate the effect of dietary guidance on the duodenal endocrine cells in the same cohort of patients with IBS. The study included 14 IBS patients (9 females and 5 males, age range 20-45 years) and 14 control subjects (9 females and 5 males, age range 26-70 years). The patients received three 45-min sessions of individualized dietary guidance. The patients and controls underwent gastroscopies at baseline and again for the patients at 3–9 (median 4) months after receiving the last session of dietary guidance. Biopsy samples were taken from pars descendens of the duodenum and were immunostained by Avidin-biotin-Complex method for all types of endocrine cells. The endocrine cells were quantified using computerized image analysis.

Results: The daily total consumption (mean ± SEM values) of fruits and vegetables high in FODMAPs decreased significantly from 16.2 ± 5.3 g before receiving dietary guidance to 9.2 ± 3.2 g after receiving dietary guidance ($P = 0.02$). The densities of the duodenal endocrine cells before and 3–9 (median 4) months after receiving dietary guidance are presented in Table 1.

Table 1: Densities of immunoreactive endocrine cells in the duodenum of control subjects and of IBS patients before and after receiving dietary guidance

	Endocrine cell densities (cells/mm2)			
Hormone	Control	Before guidance	After guidance	*P*-value
Chromogranin A	235.9 ± 31.9	36.9 ± 9.8	103.7 ± 16.9	0.007[b]
Serotonin	76.1 ± 11.9	6.8 ± 1.8	20.6 ± 6.0	0.03[a]
Somatostatin	43.1 ± 5.2	10.7 ± 1.5	24.4 ± 2.4	< 0.0001[c]
Cholecystokinin	80.7 ± 4.0	64.1 ± 4.2	77.8 ± 8.2	0.21
Secretin	76.9 ± 3.8	54.4 ± 2.1	61.1 ± 3.4	0.05
Gastric inhibitory peptide	54.3 ± 4.9	39.3 ± 2.9	45.9 ± 4.3	0.096

Data are presented as the mean ± SEM. a: $P < 0.05$, b: $P < 0.01$, c: $P < 0.0001$

Conclusion: The main triggers of the gut endocrine cells are the luminal contents of the gut, especially nutrients. This study is the first to show that the interaction between the ingested food and the endocrine cells is reflected by a change in the densities of the duodenal endocrine cells in IBS patients towards the values of healthy controls after receiving dietary guidance. The positive effects of dietary guidance may be attributed to changes in the gut endocrine cells densities, thus improving the symptoms of IBS.

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Disclosure of Interest: None declared

OP165 A REASON WHY LACTOSE-FREE DIET CAN BE CLINICALLY INEFFECTIVE IN LACTOSE INTOLERANCE PATIENTS

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Introduction: Lactose intolerance is highly prevalent in Mediterranean area. A substantial proportion of patients remain symptomatic notwithstanding lactose-free diet.

Aims & Methods: Assess in a series of IBS consecutive patients: 1) the prevalence of lactose intolerance (LI); 2) the frequency of association of lactose intolerance with small intestinal bacterial overgrowth (SIBO); 3) the possibility of SIBO as a cause of symptom persistence in patients with lactose intolerance on lactose-free diet. Patients were recruited from November 2011 to July 2012 at the Gastroenterology Unit of Mauriziano Hospital U. I^{st,} Turin, Italy. Lactose malabsorption was assessed by means of Lactose Hydrogen Breath Test (LHBT) and SIBO by means of Glucose Hydrogen Breath Test (GHBT), using Breath Tracker digital microlyzer, on 500 IBS patients (360 F; mean age 45 ± 23 SD years) and 50 controls (30 F mean age 43 ± 24 SD age). Lactose intolerance patients with SIBO were treated either with rifaximin 1200 mg a day for 2 weeks plus exclusion diet, or only with exclusion diet, randomly, on 1 to 1 basis, for 6 months. Symptoms frequency and intensity (abdominal pain, bloating, diarrhea) were recorded by means of a visual analogue scale. Statistical analysis were carried out by SPSS software.

Results: Prevalence of lactose intolerance resulted to be 59% in IBS patients and 6% in controls, with a statistically significant difference ($p < .001$). SIBO was present in 72% of patients with lactose intolerance in IBS group, ad in none of the subjects with lactose malabsorption (3) from the control group. No significant difference was registered in gender and age between the 2 groups. After 6 months, 105 out of 106 patients affected by LI + SIBO treated with rifaximin + lactose free diet (99%), and 34 out of 107 patients affected by LI + SIBO treated only with lactose free diet (32%) resulted completely asymptomatic, with statistically significant difference ($p < 0.001$).

Conclusion: Lactose intolerance is a common condition in patients with IBS in Northwest Italy (59%), very frequently associated with SIBO (72%). This association turned out to be a major cause of symptom persistence in patients on lactose-free diet until successful eradication of SIBO was achieved.

Disclosure of Interest: None declared

OP166 ELUXADOLINE DEMONSTRATES SUSTAINED EFFICACY FOR THE TREATMENT OF IRRITABLE BOWEL SYNDROME WITH DIARRHOEA IN PHASE 3 CLINICAL TRIALS

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Introduction: Eluxadoline (ELX), is a locally active, mixed mu-opioid receptor agonist and delta-opioid receptor antagonist being developed to treat irritable bowel syndrome with diarrhoea (IBS-D).

Aims & Methods: To assess the efficacy of ELX in two double-blind, placebo (PBO)-controlled Phase 3 trials (IBS-3001, IBS-3002). Patients (pts) meeting Rome III criteria for IBSD were randomised to twice-daily ELX (75 or 100 mg) or PBO. Efficacy was evaluated through 26 weeks (wks). Efficacy was assessed via a composite response endpoint, requiring simultaneous improvement in abdominal pain and stool consistency. Pts who met both daily pain responder (≥30% improvement in abdominal pain) AND daily stool consistency responder (Bristol Stool Scale score of <5) criteria for ≥50% of days were considered responders. To assess both onset and sustainability of response, responder analyses included monthly, 3-month and 6month assessments of the composite endpoint. For the monthly or 3-month intervals pts had to record ≥72% daily diary entries of symptoms to be assessed for response on the composite endpoint, whereas for the 6-month interval ≥60% daily diary entries were required.

Results: A total of 2428 IBS-D pts were enrolled across both trials. Significantly more pts ($p \leq 0.017$) receiving ELX 100 mg were composite responders than pts receiving PBO over every time interval examined using the Cochran–Mantel–Haenszel (CMH) analysis (Table 1). Longitudinal analyses (LA) at specific time points supported the CMH results. No age or gender differences were detected in the composite response rates. The proportions of pts with adverse events (AEs) were similar across the ELX 75 mg (60.2%), ELX 100 mg (58.2%) and PBO (55.7%) groups; this was also true for serious AEs (4.2%, 4.8% and 3.0%, respectively). The most common AEs were in the gastrointestinal system: 30.0%, 27.7% and 19.4% for ELX 75 mg, ELX 100 mg and PBO, respectively.

Conclusion: Phase 3 trial results demonstrated that ELX was an effective treatment for IBS-D, exhibiting rapid onset of action and sustained efficacy over 6 months.

Disclosure of Interest: W. Chey Financial support for research: Ironwood, Perrigo, Prometheus, Nestle, Consultancy: Actavis, AstraZeneca, Astellas, Asubio, Ferring, Furiex, Ironwood, Nestle, Proctor & Gamble, Prometheus, Salix, SK, Sucampo and Takeda, L. Dove Financial support for research: Actavis, Furiex Pharmaceuticals (subsidiary), Shareholder: Actavis, Furiex Pharmaceuticals (subsidiary), D. Andrae Financial support for research: Actavis, Furiex Pharmaceuticals (subsidiary), Shareholder: Actavis, Furiex Pharmaceuticals (subsidiary), J. M. Davenport Financial support for research: Actavis, Furiex Pharmaceuticals (subsidiary), Shareholder: Actavis, Furiex Pharmaceuticals (subsidiary), L. Turner Financial support for research: Actavis, Furiex Pharmaceuticals (subsidiary), Shareholder: Actavis, Furiex Pharmaceuticals (subsidiary), R. Lopez Financial support for research: Actavis, Furiex Pharmaceuticals (subsidiary), Shareholder: Actavis, Furiex Pharmaceuticals (subsidiary), P. Covington Consultancy: Actavis, Shareholder: Furiex Pharmaceuticals (subsidiary)

OP167 EFFECT OF ELUXADOLINE ON HEALTH-RELATED QUALITY OF LIFE IN ADULTS WITH IRRITABLE BOWEL SYNDROME WITH DIARRHOEA: RESULTS FROM TWO RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 TRIALS

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Introduction: Eluxadoline, a locally active, mixed mu-opioid receptor agonist and delta-opioid receptor antagonist, significantly improved both abdominal pain and diarrhoea in two Phase 3 trials (IBS-3001 and IBS-3002) in patients with irritable bowel syndrome with diarrhoea (IBSD). The objective of this analysis was to evaluate the impact of eluxadoline treatment on health-related quality of life (HRQoL) in patients with IBS-D based on data from IBS-3001 and IBS-3002.

Aims & Methods: Adults meeting Rome III criteria for IBS-D were randomised to twicedaily oral eluxadoline (75 or 100 mg) or placebo for 26 weeks in IBS-3002 and 52 weeks in IBS-3001. The Irritable Bowel Syndrome Quality of Life questionnaire (IBS-QOL), consisting of 34 items, each with a 5-point response scale (1 = "not at all", 5 = "extremely"/"a great deal"), was completed at baseline and Weeks 4, 8, 12, 18 and 26 in both trials and at Week 30 in IBS-3002 and Weeks 36, 44 and 52 in IBS-3001. Mean IBS-QOL total scores were evaluated for trends by treatment groups by employing a longitudinal mixed-effects polynomial model fitted to pooled data to estimate treatment effects of eluxadoline. Cumulative distribution functions for changes from baseline to Weeks 12, 26 and 52 in IBS-QOL total scores were plotted.

Results: Of the 2428 patients in the two Phase 3 trials, 2404 (99%) had baseline IBS-QOL scores (n = 1270, IBS-3001; n = 1134, IBS-3002). The mean age was 45.4 years; 66.1% of patients were female. Patients treated with eluxadoline 75 and 100 mg had consistently higher IBSQOL total scores over 52 weeks of treatment compared with patients who received placebo (Table). The longitudinal mixed-effects model showed a significant treatment effect for both the eluxadoline 75 mg ($t = 4.34$; $p < 0.0001$) and 100 mg groups ($t = 4.45$; $p < 0.0001$). Cumulative distribution function plots of change from baseline scores confirmed that patients treated with eluxadoline 75 and 100 mg showed consistently higher increases in IBS-QOL total scores compared with patients who received placebo over a range of improvement levels for Weeks 12, 26 and 52.

Table: Post-baseline model estimates for IBS-QOL total scores for the pooled analysis cohort: Weeks 4, 12, 26 and 52

	Placebo (n = 807)	Eluxadoline 75 mg (n = 797)	Eluxadoline 100 mg (n = 800)
Week 4, mean (SE)	55.6 (0.71)	61.0 (0.67)	60.5 (0.67)
Week 12, mean (SE)	64.8 (0.76)	71.4 (0.71)	70.8 (0.71)
Week 26, mean (SE)	66.1 (0.87)	73.0 (0.80)	72.2 (0.82)
Week 52, mean (SE)	66.2 (1.04)	73.6 (0.94)	78.7 (1.03)

SE, standard error

Conclusion: Compared with placebo, twice-daily eluxadoline treatment significantly improved overall HRQoL among patients with IBS-D over the course of the treatment periods in two Phase 3 trials as measured by the IBS-QOL, with patients treated with eluxadoline 100 mg showing particularly strong effects.

Disclosure of Interest: J. Buono Financial support for research: Actavis, Shareholder: Actavis, D. Andrae Financial support for research: Actavis, Furiex Pharmaceuticals (subsidiary), Shareholder: Actavis, Furiex Pharmaceuticals (subsidiary), P. Covington Consultancy: Actavis, Shareholder: Furiex Pharmaceuticals (subsidiary)

OP168 CONSISTENCY IN EFFICACY OUTCOMES OF ELUXADOLINE-TREATED PATIENTS WITH IRRITABLE BOWEL SYNDROME WITH DIARRHOEA USING RECENT AND TRADITIONAL ENDPOINTS

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Introduction: Eluxadoline (ELX), a locally active, mixed mu-opioid receptor agonist and delta-opioid receptor antagonist, demonstrated improvements in the symptoms of irritable bowel syndrome with diarrhoea (IBS-D) based on a composite endpoint of improved stool consistency and reduced abdominal pain.

Aims & Methods: To further examine the consistency of ELX efficacy outcomes in two double-blind, placebo (PBO)-controlled Phase 3 trials (IBS-3001, IBS-3002), results of the daily composite response endpoint were compared with Global Symptom Score (GSS) and the patient (pt)-friendly, traditional adequate

Abstract number: OP166 Table 1: Composite response rate at varying intervals

CMH composite response rate (%) [p values of ELX vs PBO]

		Wks 1–4	p	Wks 5–8	p	Wks 9–12	p	Wks 13–16	p	Wks 17–20	p	Wks 21–24	p	Wks 1–12	p	Wks 1–26	p
IBS-3001	PBO	12.9		19.9		21.8		21.1		21.8		20.4		17.1		19.0	
	ELX 75 mg	20.6	0.003	26.5	0.023	23.7	0.514	22.7	0.563	27.6	0.047	27.4	0.016	23.9	0.014	23.4	0.112
	ELX 100 mg	22.5	<0.001	28.9	0.002	30.3	0.005	29.1	0.007	28.9	0.017	28.2	0.008	25.1	0.004	29.3	<0.001
IBS-3002	PBO	12.0		19.9		22.0		20.9		22.5		19.9		16.2		20.2	
	ELX 75 mg	25.2	<0.001	31.5	<0.001	32.3	0.001	30.7	0.002	31.2	0.007	28.9	0.004	28.9	<0.001	30.4	0.001
	ELX 100 mg	26.7	<0.001	33.5	<0.001	31.9	0.002	33.8	<0.001	31.2	0.007	32.5	<0.001	29.6	<0.001	32.7	<0.001

LA composite response rates (odds ratios and p values of ELX vs PBO)

		Wk 4	p	Wk 8	p	Wk 12	p	Wk 16	p	Wk 20	p	Wk 24	p	Wk 26	p
IBS-3001	ELX 75 mg	1.51	0.025	1.50	0.026	1.50	0.027	1.49	0.029	1.49	0.031	1.48	0.034	1.48	0.036
	ELX 100 mg	1.76	0.002	1.75	0.002	1.73	0.003	1.72	0.003	1.71	0.004	1.69	0.005	1.69	0.005
IBS-3002	ELX 75 mg	2.64	<0.001	2.60	<0.001	2.55	<0.001	2.50	<0.001	2.46	<0.001	2.41	<0.001	2.39	<0.001
	ELX 100 mg	2.71	<0.001	2.74	<0.001	2.77	<0.001	2.80	<0.001	2.83	<0.001	2.86	<0.001	2.88	<0.001

Abstract number: OP168 Table 1: Efficacy outcomes

		IBS-3001			IBS-3002		
Responders (%)*p value vs PBO*		**PBO**	**ELX 75 mg**	**ELX 100 mg**	**PBO**	**ELX 75 mg**	**ELX 100 mg**
Daily composite endpoint	Wks 1–12	17.1	23.9*0.014*	25.1*0.004*	16.2	28.9 < *0.001*	29.6 < *0.001*
	Wks 1–26	19.0	23.4*0.112*	29.3 < *0.001*	20.2	30.4*0.001*	32.7 < *0.001*
GSS	Wks 1–12	28.8	35.1*0.048*	34.7*0.063*	29.6	43.6 < *0.001*	42.4 < *0.001*
	Wks 1–26	32.3	36.3*0.221*	37.1*0.144*	34.3	45.1*0.002*	43.2*0.012*
AR	Wks 1–12	43.8	52.9*0.008*	54.2*0.002*	49.2	60.1*0.003*	58.4*0.011*
	Wks 1–26	40.0	45.7*0.097*	49.5*0.005*	43.7	52.8*0.013*	53.7*0.006*

relief (AR) endpoint. Pts meeting Rome III criteria for IBS-D were randomised to twice-daily ELX (75 or 100 mg) or PBO. Efficacy was evaluated through 26 weeks (wks). The primary endpoint was composite response (based on simultaneous improvement in daily worst abdominal pain [0–10 scale] and stool consistency [Bristol Stool Scale 1–7] with ≥50% of days demonstrating a response) evaluated over Wks 1–12 and 1–26 (with ≥60/84 or ≥110/182 days of diary compliance, respectively). Pts indicated whether they had AR from IBS symptoms over the past wk and rated their daily IBS symptoms over the past 24 h (0 = none, 4 = very severe). Efficacy assessments included Cochran–Mantel–Haenszel (CMH) analysis requiring AR response of ≥6/12 or ≥13/26 wks and, for assessment of GSS, CMH analysis of ≥50% of days with either daily GSS < 2 or GSS improved by ≥2 compared with the baseline average. Pooled data using analysis of covariance (ANCOVA) assessed change from baseline (CFB) in GSS.

Results: A total of 2428 pts with IBS-D were enrolled across both trials. Average GSS scores decreased in all groups and in both studies from baseline through Wk 26. Table 1 shows responder outcomes for the composite, GSS and AR endpoints. A significantly greater proportion of pts receiving ELX were composite responders compared with pts receiving PBO ($p \leq 0.014$), with the exception of pts receiving ELX 75 mg in IBS-3001 over Wks 1–26. Comparable results were seen for GSS and AR endpoints with ELX 75 and 100 mg. Efficacy in the ELX 100 mg group was more robust than in the 75 mg group in both trials, and results from IBS-3002 were generally more robust than those from IBS-3001. Pooled data for ANCOVA CFB for GSS also demonstrated superiority over PBO at Wks 12 and 26 ($p \leq 0.008$).

Conclusion: Individual studies and pooled data demonstrated that ELX was superior to PBO in relieving IBS-D symptoms. Efficacy outcomes for the GSS endpoint and the more pt-friendly, traditional AR endpoint were consistent with the primary efficacy composite endpoint over 12 and 26 wks.

Disclosure of Interest: M. Zuckerman Consultancy: Actavis, Inc. and has taken part in Actavis, Inc. advisory boards, L. Dove Financial support for research: Actavis, Furiex Pharmaceuticals (subsidiary), Shareholder: Actavis, Furiex Pharmaceuticals (subsidiary), D. Andrae Financial support for research: Actavis, Furiex Pharmaceuticals (subsidiary), Shareholder: Actavis, Furiex Pharmaceuticals (subsidiary), J. M. Davenport Financial support for research: Actavis, Furiex Pharmaceuticals (subsidiary), Shareholder: Actavis, Furiex Pharmaceuticals (subsidiary), L. Turner Financial support for research: Actavis, Furiex Pharmaceuticals (subsidiary), Shareholder: Actavis, Furiex Pharmaceuticals (subsidiary), R. Lopez Financial support for research: Actavis, Furiex Pharmaceuticals (subsidiary), Shareholder: Actavis, Furiex Pharmaceuticals (subsidiary), P. Covington Consultancy: Actavis, Shareholder: Furiex Pharmaceuticals (subsidiary)

OP169 THE RESTORE-4 STUDY: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL-GROUP PHASE II STUDY ASSESSING THE EFFICACY AND SAFETY OF ONO-2952, A NOVEL AND SELECTIVE ANTAGONIST OF TRANSLOCATOR PROTEIN

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Introduction: Translocator protein (TSPO) is mainly located in the outer mitochondrial membrane of steroid-producing cells, including brain glial cells, and transports cholesterol from intracellular sources into the mitochondria, a rate limiting step of neurosteroidogenesis. TSPO ligands have been suggested to regulate levels of neurosteroids which are known to act as allosteric modulators of both excitatory and inhibitory neurotransmission. We have demonstrated that ONO-2952, a novel and selective TSPO antagonist, inhibits stressinduced defecation and visceral hyperalgesia in rat stress models, suggesting a therapeutic potential in the treatment of stress-related disorders such as irritable bowel syndrome (IBS). We evaluated the efficacy and safety of ONO-2952 in a Phase 2 study in patients with diarrhea-predominant IBS (IBS-D).

Aims & Methods: A randomised, double-blind, placebo-controlled study was conducted at 49 centres in the United States and recruited 200 female patients (aged 18-65 years) with IBS-D according to Rome III criteria. Patients were randomly assigned to receive either 20 or 60 mg ONO-2952 or placebo (1:1:1 ratio) orally once-daily for 4 weeks. Patients recorded their IBS symptoms on a daily basis in an e-diary during a 2-week baseline, the 4-week treatment period and for 4 weeks post-treatment. Safety monitoring was performed throughout the study. The co-primary endpoints were change from baseline to week 4 in stool consistency, stool frequency and abdominal pain. Secondary endpoints included FDA responder analyses. Patients were considered responders if they met the FDA daily responder criteria for at least 50% of time over the interval from weeks 1-4.

Results: Demographics and baseline characteristics were comparable for the 3 treatment arms. Per protocol set analyses demostrated improvements over placebo in the number of days per week with at least one stool having a BSS classification of 6 or 7 and mean weekly score of the worst abdominal pain experienced during the past 24 hours were observed with 60 mg ONO-2952 over the 4-week treatment period but did not achieve significance at a 5% level ($P < 0.10$).

A statistically significant difference in the odds ratio for the percentage of responders was observed following ONO-2952 60mg compared with placebo for the change from baseline of 40% (odds ratio: 2.44; 95% CI: 0.95, 6.23; $p < 0.10$) and 50% in abdominal pain (odds ratio: 2.89; 95% CI: 1.04, 8.00; $p < 0.05$).

ONO-2952 was well-tolerated and had a favourable safety profile. The majority of AEs were mild in intensity and unrelated to study drug. A similar pattern of central nervous system (CNS) AEs was observed across all treatment groups and there were no clinically significant AEs related to the CNS.

Conclusion: ONO-2952 demonstrated a greater potential to impact clinical symptoms compared to placebo in female patients with IBS-D. Those given ONO-2952 60mg were more likely to be clinical responders on both abdominal pain and stool consistency, in addition to a composite of these endpoints. Further examination of ONO-2952 is warranted to assess its potential as a treatment for IBS.

Disclosure of Interest: W. Whitehead Consultancy: Received consultancy fees from Ono Pharmaceuticals, T. Nabata Conflict with: Employee of Ono Pharma UK Ltd., K. Duffy Conflict with: Employee of Ono Pharma UK Ltd., J. Sharpe Conflict with: Employee of Ono Pharma UK Ltd., M. Bruce Conflict with: Employee of Ono Pharma UK Ltd.

OP170 EFFICACY OF ORAL IBODUTANT IN IBS-D FEMALE PATIENTS MEASURED BY URGENCY SCORE: AN IRIS-2 EXPLORATORY ANALYSIS

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Introduction: Irritable bowel syndrome with diarrhoea (IBS-D) is particularly debilitating due to urgency and episodic incontinence. Ibodutant, a selective potent antagonist of neurokinin-2 receptor is in Phase III development for IBS-D. A phase II (IRIS-2) study tested the efficacy of 3 oral doses of ibodutant (1 mg, 3 mg, 10 mg) vs placebo in 559 IBS-D patients (333 females) defined by Rome III criteria, over a daily 8-week oral treatment, followed by 2-weeks treatment withdrawal resulting in a total of 10 weeks of daily and weekly measurements of symptoms. Based on the combined response of satisfactory relief of IBS symptoms and abdominal pain/discomfort according to the 75% rule, a statistically and clinically relevant efficacy was demonstrated in the female subgroup (n = 333) at the 10 mg dose with 46.84% of responders vs 24.36% in placebo ($p = 0.0034$).

Aims & Methods: To evaluate the benefit of ibodutant in a female IBS-D population exposed to oral daily ibodutant doses of 1, 3 and 10 mg over 8 weeks of treatment and 2 weeks of treatment withdrawal in terms of the mean stool urgency score changes versus baseline.

Among data collected through the IVRS/IWRS diary to characterize the efficacy profile of ibodutant, stool urgency was assessed as measure of IBS-D severity. Mean change after 4 weeks, 8 weeks of treatment and after 2 weeks of treatment withdrawal vs baseline (Visit 2-randomisation) (daily IVRS/IWRS diary records) were recorded according to a 5-point scale ranging from 0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe to 4 = very severe. Urgency (5-point scales) response was defined as intensity reduction of ≥ 1 score point compared to baseline. This was a pre-specified analysis of variance (ANOVA) by gender.

Results: At baseline, female patients (59.57% of total patients) reported a moderate urgency intensity with a mean score value of 2.4 (±0.7), without relevant differences between the treatment groups. In this population, ibodutant confirmed the high clinically and statistically significant superiority over placebo in terms of improving stool urgency scores measured after the treatment (Least Square Means: -33.71 in placebo, -34.86 in 1 mg, -38.34 in 3 mg, -38.17 in 10 mg treatment arm), with a mean estimated score reduction of -4.47 ($P = 0.007$) in the 10 mg treatment arm vs baseline and 2 weeks after treatment withdrawal. A mean score reduction of -4.63 ($P = 0.004$) was also shown in females at 3 mg dose, whereas in males there was no statistically significant change.

Table: Stool Urgency Score Mean change during the Treatment and Withdrawal Period in IBS-D female population (n = 333)

Treatment	Estimated mean change vs placebo (SE)	P-value	CI 95%
Ibodutant 1 mg	-1,15 (1,617)	0.475	-4,32; 2,01
Ibodutant 3 mg	-4,63 (1,623)	0.004	-7,81; -1,45
Ibodutant 10 mg	-4,47 (1,655)	0.007	-7,71; -1,22

SE= Standard Error CI=Confidence Interval

Conclusion: Ibodutant doses of 10 mg and 3 mg given once daily over 8 weeks of treatment significantly improved mean stool urgency scores in female IBS-D patients. This decrease of stool urgency scores was maintained also over the ensuing 2-week treatment-free withdrawal phase.

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Disclosure of Interest: J. Tack Consultancy: Menarini Ricerche Spa, K. Schumacher Financial support for research: Menarini Ricerche Spa, S. Scartoni Financial support for research: Menarini Ricerche Spa, G. Tonini Financial support for research: Menarini Ricerche Spa, K. Ott Financial support for research: Menarini Ricerche Spa, I. Koch Financial support for research: Menarini Ricerche Spa, I. Otranto Financial support for research: Menarini Ricerche Spa, F. Masciopinto Financial support for research: Menarini Ricerche Spa, M. Bertolotti Financial support for research: Menarini Ricerche Spa, A. Capriati Financial support for research: Menarini Ricerche Spa, C. Maggi Financial support for research: Menarini Ricerche Spa

TUESDAY, OCTOBER 27, 2015 08:30–10:30

OBESITY AND CANCER: IS THERE A LINK? – ROOM E4

OP171 A CCRK INFLAMMATORY CIRCUITRY DRIVES OBESITY-ASSOCIATED HEPATOCARCINOGENESIS THROUGH CONCORDANT ACTIVATION OF MULTIPLE ONCOGENIC CASCADES

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Introduction: Recent large-scale prospective and population-based studies have underscored obesity as an important cause of certain cancers including hepatocellular carcinoma (HCC). In two cohorts of more than 900,000 United States and 5 million United Kingdom adults, overweight and obese men were shown to have much higher risks of HCC mortality and incidence when compared to women. Given the prevalence of obesity in developed countries and its rapid increase in developing countries, there is a compelling need to understand the molecular pathways that promote hepatocarcinogenesis in obese individuals. Accumulating evidence has unmasked the molecular linkage between androgen receptor (AR) signaling and gender disparity in HCC. Our previous genome-wide location and functional analysis has pinpointed cell cycle-related kinase (CCRK) as a critical mediator of AR oncogenic activity in hepatitis B virus-related HCC through glycogen synthase kinase-3β (GSK-3β)/β-catenin/enhancer zeste of homolog 2 (EZH2) signaling (1-3).
Aims & Methods: Here we investigated whether CCRK plays an oncogenic role in obesity-related hepatocarcinogenesis.
Results: Using a murine dietary obesity-promoted HCC model, we showed that lentiviral-mediated knockdown of *Ccrk* dramatically reduced hepatic lipid accumulation, inflammation and tumorigenicity. An obesity-induced pro-inflammatory cytokine, interleukin-6 (IL-6), was found to trigger signal transducer and activator of transcription 3 (STAT3) signaling to up-regulate *CCRK* expression in human hepatic cells, which in turn stimulated a positive feedback circuit involving EZH2 and nuclear factor-κB (NF-κB). In addition, both *in vitro* and *in vivo* data suggested that CCRK simultaneously activated the mechanistic target of rapamycin complex 1 (mTORC1) and β-catenin pathways crucial for many cellular processes including lipogenesis, survival and proliferation. Importantly, CCRK and its signaling components were significantly and concordantly over-expressed in human HCCs associated with nonalcoholic fatty liver disease.
Conclusion: Our findings delineate a tumor-initiating circuitry in which obesity-mediated chronic inflammation induces an IL-6-STAT3-CCRK-EZH2-NF-κB loop to drive lipogenesis and hepatocarcinogenesis through concordant mTORC1 and β-catenin activation. This study unveils the central role of CCRK in regulating multiple oncogenic cascades, thus providing a therapeutic target to combat this unrelentingly-increasing dreadful disease.

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Disclosure of Interest: None declared

OP172 ESOPHAGEAL ADENOCARCINOMA FOLLOWING OBESITY SURGERY IN A POPULATION-BASED COHORT STUDY

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Introduction: Obesity is strongly associated with EAC. Yet, whether weight loss reduces the risk of EAC is unclear.
Aims & Methods: To test the hypothesis that the risk of esophageal adenocarcinoma (EAC) decreases following weight reduction achieved by obesity surgery. This population-based cohort study included a majority of individuals who underwent obesity surgery in Sweden in 1980-2012. The incidence of EAC following obesity surgery was compared to the incidence in the corresponding background population by means of calculation of standardized incidence ratios (SIRs) with 95% confidence intervals (CIs). The risk of EAC after obesity surgery was also compared with the risk in non-operated obese individuals by means of multivariable Cox regression, providing hazard ratios (HRs) with 95% CIs, adjusted for potential confounders.
Results: Among 34,437 study participants undergoing obesity surgery and 239,775 person-years of follow-up, 8 cases of EAC occurred (SIR of 1.6, 95% CI 0.7-3.2). No clear trend of decreased SIRs was seen in relation to increased follow-up time after surgery. The SIR of EACs (n = 53) among 123,695 non-operated obese individuals (673,238 person-years) was increased to a similar extent as in the obesity surgery cohort (SIR = 1.9, 95% CI 1.4-2.5). Cox regression showed no difference in risk of EAC between operated and non-operated participants (adjusted HR = 0.9, 95% CI 0.4-1.9).
Conclusion: The risk of EAC might not decrease following obesity surgery, but even larger studies with longer follow-up are needed to establish this association.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 08:30–10:30

FROM OMICS TO BETTER UNDERSTANDING OF PATHOGENESIS – ROOM E2

OP173 COMPARATIVE GENOMIC ANALYSIS OF HPV POSITIVE VERSUS HPV NEGATIVE OESOPHAGEAL ADENOCARCINOMA IDENTIFIES A DIFFERENTIAL MUTATIONAL LANDSCAPE

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Introduction: High-risk human papillomavirus (hr-HPV) has been implicated in a subset of patients with oesophageal adenocarcinoma (OAC) [1-3]. We therefore hypothesized that HPV associated OAC may have a distinct distribution of molecular aberrations and genomic abnormalities compared with HPV negative oesophageal cancer.
Aims & Methods: As such, whole exome sequencing (WES) was performed to explore the genomic landscape and potential molecular signature of HPV positive versus viral negative OAC.
Four hr-HPV-positive and 8 HPV-negative treatment naive fresh-frozen OAC tissue specimens were analysed to identify somatic genomic mutations. Seventy-eight recurrent and pathway related mutations were validated by Sanger sequencing and mutation specific PCR. Data was subjected to cancer driver gene identification and pathway analysis. The off-target reads were utilized for viral integration studies.
Results: The HPV-positive OAC group was younger ($p = 0.015$) and harboured approximately 50% less non-silent somatic mutations than the HPV-negative esophageal cancer patients (1.31 mutations/Mb versus 2.56 mutations/Mb, $p = 0.026$). TP53 aberrations were absent in the HPV-positive EAC group whereas 50% of the HPV-negative OAC patients exhibited TP53 mutations. Apart from TP53, genes previously described as mutated significantly in EAC i.e. SYNE1, LRP1B, CSMD3 were repeatedly detected in our cohort. HPV negative cancers were enriched with cancer driver gene mutations, but not HPV-positive tumours. Viral integration analysis identified sub-fragments of hr-HPV sequences at low frequency. Enriched A > C transversions at AA dinucleotide was observed in 5/7 Siewert class I OAC samples but none (0/5) in Siewert class II tumours ($p = 0.027$).
Conclusion: These findings demonstrate distinct genomic differences between HPV-positive and HPV-negative OAC suggesting different biological mechanisms of tumour formation.

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Disclosure of Interest: None declared

OP174 MOLECULAR BASIS OF COLORECTAL TUMORS DEVELOPED THROUGH SERRATED PATHWAY

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Introduction: Recent genomic research has revealed that CRC can develop through various pathways, resulting in tumors with distinct molecular characteristics. Serrated pathway has been considered as an alternative pathway of colorectal cancer (CRC) distinct from the adenoma-carcinoma sequence. To clarify involvement of molecular alterations in serrated pathway, we performed epigenetic and genetic analyses.

Aims & Methods: A total of 45 sessile serrated adenoma/polyp (SSA/P) and 14 traditional serrated adenoma (TSA) samples were obtained from patients who underwent endoscopic submucosal dissection. Samples of 17 high-methylation CRCs, which seemed to be developed through serrated pathway, were also included. To epigenotype serrated lesions and high-methylation CRCs, the methylation levels of six Group-1 and 14 Group-2 markers, established in our previous study, were analyzed quantitatively by pyrosequencing. Subsequently, we performed target exon sequencing analysis of 126 candidate CRC driver genes, using HaloPlex target enrichment system, and evaluate how carcinogenic pathways, e.g. RTK/RAS, PI3K, WNT, TGF-ß, BMP and TP53 signaling, are associated with CRC development through serrated pathway.

Results: SSA/P showed high methylation of both Group-1 and Group-2 markers, thus high-methylation epigenotype, and frequent *BRAF* mutation (36/45 cases, 80%), which were characteristics of high-methylation CRC. Traditional serrated adenoma (TSA) showed high methylation of Group-2 markers but low methylation of Group-1 markers, thus intermediate-methylation epigenotype, and less frequent BRAF mutation (43%, $P=0.02$) but significantly frequent *KRAS* mutation (50%, $P=0.003$). High-methylation CRC showed even higher methylation of genes e.g. *MLH1* than SSA/P, suggesting that methylation of genes could increase during development from adenoma to cancer in the serrated pathway. Significantly frequent somatic mutations in non-synonymous mutations ($P<0.0001$) and indels ($P=0.002$) were identified in high-methylation CRC. Mutation frequencies, however, were not different between *MLH1*-methylayed and *MLH1*-unmethylated SSA/P samples. Significantly mutated genes in cancer included mismatch repair genes e.g. *MSH3* and *MSH6*, and those involved in PI3K, WNT, TGF-β, and BMP signaling, but not in TP53 signaling.

Conclusion: For serrated pathway, SSA/P, but not TSA, is considered to be precursor lesions of high-methylation CRC with *BRAF* mutation. Further DNA methylation accumulation occurs, including *MLH1*, during development from adenoma to cancer in serrated pathway. While abrogation of mismatch repair genes was suggested to be important, *MLH1* methylation might be insufficient, and additional abrogation by mutation of genes e.g. *MSH3* and *MSH6* might be necessary to develop cancer with hypermutation phenotype, involving abrogation of PI3K, WNT, TGF-β, and BMP signaling.

Disclosure of Interest: None declared

OP175 WHOLE METHYLOME ANALYSIS OF COLORECTAL TISSUE SAMPLES USING METHYL CAPTURE SEQUENCING REVEALED EPIGENETIC ALTERATIONS OF FREQUENTLY MUTATED GENES DURING NORMAL-ADENOMA-CARCINOMA SEQUENCE PROGRESSION

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Introduction: During colorectal carcinogenesis, accumulation of genetic and epigenetic alterations leads to adenoma-carcinoma transition in colon. The colorectal carcinoma (CRC), which is a rather heterogeneous malignant disease, can develop through various different molecular ways, therefore the mutations of key tumor suppressor and/or oncogenes cannot provide complete explanation in several cases.

Aims & Methods: In this study, parallel analysis of genetic and epigenetic alterations was performed during the colorectal normal-adenoma-carcinoma sequence progression focusing on the role and possible epigenetic regulation of genes frequently mutated in CRC.

Mutations of 12 CRC oncodiagnostic panel genes (APC, BRAF, CTNNB1, EGFR, FBXW7, KRAS, MSH6, NRAS, PIK3CA, SMAD2, SMAD4, TP53) were analyzed by 454 sequencing on GS Junior platform on 54 colorectal tissue samples (9 normal, 25 AD, 20 CRC). Whole methylome analysis was performed from 30 colorectal tissue samples (9 colorectal carcinoma (CRC), 15 adenoma (AD) and 6 normal adjacent tissue (NAT) samples) by next generation sequencing (Illumina) after enrichment of methylated DNA using MethylCap kit (Diagenode). Methylation alterations were determined on the whole sequence of the selected oncodiagnostic panel genes including promoter regions, gene body regions and mutation hot spots. Promoter regions were determined according to the 'Integrative annotation of chromatin elements from ENCODE data'. For validation, Illumina BeadChip450K methylation data of Luo et al. (GSE48684) were also involved.

Results: In CRC samples the most frequently mutated genes were TP53, KRAS and APC with 40%, 30% and 25% frequencies. APC mutation could be detected in 32% of adenoma samples, KRAS was found to be mutated in 24% of adenomas, while none of the adenoma samples carried TP53 mutation. Parallel mutation-methylation data were available from 26 samples (4 NAT, 15 AD, 7 CRC). In adenoma compared to NAT samples, aberrant methylation was detected in gene body regions of APC, CTNNB1, TP53 and SMAD4 genes and in promoter regions of APC (hypermethylation), FBXW7 and SMAD4 genes (hypomethylation). In CRC compared to NAT samples, gene body hypermethylation was found in APC, and promoter hypomethylation was determined in CTNNB1, SMAD2, SMAD4 and NRAS genes. The results of the GSE48684 methylation analysis also confirmed the APC hypermethylation and CTNNB1, SMAD2 promoter hypomethylation in CRC. Between adenoma and CRC samples the most significant methylation differences were observed in APC, CTNNB1, TP53 and MSH6 genes ($p < 0.01$).

Conclusion: DNA methylation alterations, partly in the promoter regions of the frequently mutated genes, can also contribute to functional disturbance of the CRC-related genes during the colorectal cancer development and progression. Beside the frequent APC, KRAS and TP53 mutations, aberrant promoter methylation of key genes such as APC and beta-catenin suggests the essential role of epigenetic regulation from early stage of colorectal carcinogenesis.

Disclosure of Interest: None declared

OP176 PROFILING AND MODULATION OF SKELETAL MUSCLE MICRORNAS IN NON-ALCOHOLIC FATTY LIVER DISEASE PATIENTS AND IN INSULIN-RESISTANT C2C12 MUSCLE CELLS

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Introduction: Intramyocellular lipid deposition associates with mitochondrial dysfunction and insulin resistance (IR), constituting a key pathophysiological event in human non-alcoholic fatty liver disease. Further, recent evidences support a functional role for microRNAs (miRNA/miRs) in regulating muscle IR. Finally, tauroursodeoxycholic acid (TUDCA) is a cytoprotective bile acid in both liver and muscle cells, in part, by acting as a molecular chaperone and stabilizing mitochondria.

Aims & Methods: Our aims were to profile global muscle miRNA expression in human patients at different NAFLD stages and evaluate their potential functional role, as well as modulation by TUDCA, in insulin-resistant C2C12 cells. Skeletal muscle biopsies were obtained from morbid obese NAFLD patients undergoing bariatric surgery. Muscle RNA was run in TaqMan MicroRNA arrays. qPCR array data was analyzed using the HTqPCR package in Bioconductor. Differential expression analysis was performed with interquantile range values > 1.5 using the lmfit function of the Limma package and the Benjamini-Hochberg conditional hypergeometric test algorithm. C2C12 cells were incubated with or without palmitic acid (PA), in the presence or absence of 100 μM of TUDCA, for evaluation of the insulin-signaling pathway, mitochondrial function and overall cellular toxicity.

Results: Six muscle miRNAs were found to progressively and significantly increase from steatosis to more severe NASH (at least $p < 0.05$). These included miR-339-3p, a regulator of glucose synthesis, and miR-361, previously found to be increased in the serum of type II diabetes (T2D) patients. Inversely, eight miRNAs were decreased, including miR-20b, down-regulated in T2D patients plasma.

Incubation of C2C12 cells with PA increased mitochondrial dysfunction and apoptosis (at least $p < 0.05$) while decreasing mitochondrial ATP production ($p < 0.05$), all of which were prevented by co-incubation of cells with TUDCA ($p < 0.05$).

Of note, miR-339-3p was also increased by PA and inhibited by TUDCA ($p < 0.05$). Inversely, MAPK phosphatase-7 (MKP-7), a negative regulator of JNK and a target of miR-339-3p was decreased in cells incubated with PA and rescued by TUDCA co-incubation (at least $p < 0.05$). In fact, C2C12 cells exposed to PA displayed JNK phosphorylation and activation, with concomitant downstream deregulation of the insulin-signaling pathway (at least $p < 0.05$). Remarkably, these events were prevented by co-incubation of cells with TUDCA ($p < 0.05$).

Conclusion: Collectively, T2D-associated miRNAs are differently modulated with NAFLD severity in the skeletal muscle, with miR-339-3p arising as a likely mechanistic target contributing for IR. In addition, TUDCA attenuates

muscle cell IR and lipoapoptosis and may ameliorate NAFLD-associated muscle dysfunction. (PTDC/BIM-MEC/0873/2012, SFRH/BD/104160/2014, FCT, Portugal).
Disclosure of Interest: None declared

OP177 IMMUNE AND METABOLIC DISORDERS IN OBESE PATIENTS WITH HEPATIC STEATOSIS AND HYPERTENSION ASSOCIATE WITH PPAR-GAMMA2 PRO12ALA AND ACE I/D GENES' POLYMORPHISMS

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Introduction: Hepatic steatosis (HS) and arterial hypertension (AH) have multiple common mechanisms of development involving metabolic and immune changes. Among them, impairment or inhibition of receptor molecules controlling enzymes responsible for oxidation and fatty acids synthesis, appear to contribute to fat accumulation. However, HS is to some extend still accepted as a non-systemic pathology, rather than systemic disease, not limited to liver but involving interaction between genetically determined mechanisms of metabolism regulation and vascular inflammation.
Aims & Methods: The aim of study was to investigate the influence of Pro12Ala polymorphism of Peroxisome proliferator Activated Receptor Gamma (PPAR-γ2) gene and Insertion/Deletion (I/D) polymorphism of Angiotensin Converting Enzyme (ACE) gene on metabolic profile and cytokines in obese patients with common combination of HS and AH.
Study included 154 HS patients with AH (87 male, 67 female, age 50.06 ± 7.34). Duration of HS: 1-5 years, AH 3-21 years. NAFLD/NASH diagnosis based on EASL (2009) and AGA/AASLD/ACG (2012) recommendations. Metabolic disorders were defined with body mass index (BMI), glycemia, immunoreactive insulin (IRI), total cholesterol (TC), low and high density cholesterol (LDL-C, HDL-C), triglycerides (TG), C-peptide (CP) levels and HOMA-IR index. TNF-α and leptin plasma levels were assessed by ELISA. Genes' polymorphism of PPAR-γ2 (Pro12Ala), and ACE (I/D) alone or in combination was studied with PCR.
Results: Differences of BMI, plasma glucose, IRI, HOMA-IR, CP and leptin are independent from ACE gene genotypes ($p > 0.05$). Pro-allele carriers of PPAR-γ2 gene have higher BMI than AlaAla carriers (32.7 ± 2.1 and 27.9 ± 1.1 kg/m^2 vs 25.6 ± 0.8 kg/m^2, accordingly ($p < 0.05$); leptin level – 14.3 ± 0.41 and 8.6 ± 0.25 ng/ml vs 3.7 ± 0.22 ng/ml, ($p < 0.001$), glucose level – to 10.2% and 10.9% accordingly ($p < 0.05$); CP level was higher in ProPro-genotype than in Ala-allele carriers to 15.7% ($p < 0.05$). Risk group for dyslipidaemia are ProPro-genotype carriers of PPAR-γ2 gene with higher level of TC, TG and LDL-C by 16.4%, 17.3% and 27.9% ($p < 0.05$) and lower level of HDL-C in women by 25.6% ($p = 0.038$). Lipids levels are independent on ACE I/D polymorphism. Baseline TNF-α plasma levels did not significantly deviate between genotypes of PPAR-γ2 gene, but D-allele carriers (I/D + DD) of ACE gene had higher baseline TNF-a plasma levels (91.61 pg/ml and 109.11 pg/ml, accordingly, $p < 0.01$).
Conclusion: Metabolic disorders in HS hypertensive patients are associated with PPAR-γ2 Pro-allele (carbohydrates) and ProPro-genotype (lipids). Presence of D-allele of ACE gene is associated with reliably higher TNF-α plasma levels.
Disclosure of Interest: None declared

OP178 RECONSTRUCTING THE EVOLUTIONARY HISTORY OF METASTATIC OESOPHAGEAL ADENOCARCINOMA USING WHOLE GENOME SEQUENCING

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Introduction: Metastases are responsible for greater than 90% of all cancer deaths, yes little is known about the governing principles that guide disease progression. This holds particularly true for metastatic oesophageal adenocarcinoma (OAC). It remains unclear whether metastases have the ability to continually evolve, and acquire subclones that breed a competitive survival advantage or whether heterogeneity in metastases is a reflection of the architecture of the primary tumour, hence supporting the bulk of tumour evolution to be an early event.
Aims & Methods: Whole-genome sequencing (WGS) was performed across multiple primary and metastatic samples obtained from a rapid autopsy programme with the aim of delineating the clonal ordering of metastatic events in OAC. 10 rapid autopsies have been completed to date, within 6 hours of death and 5 cases have been analysed. WGS was performed on 41 fresh frozen samples from the primary and multiple nodal and distant organ metastases (liver, pancreas, adrenal). Subclonal copy number analysis was performed using the ASCAT/Battenberg algorithm and single nucleotide variants (SNVs) were clustered based on their allele frequency using a Bayesian Dirichlet process. Phylogenetic trees were annotated with copy number and point mutation events in order to identify potential drivers of progression.
Results: The ancestral clone contained a median of 24% and up to 90% of the total number of SNVs (range 8238-29883 SNVs). TP53 coding mutations and amplifications in MYC, GATA4, CCND1, KRAS and CDK6 were early events in the evolutionary tree. Both patterns of branching and linear evolution were observed. Metastases in solid organs (pancreas, liver) and lymph nodes could be traced back to spatially distinct areas of the primary tumour. Interestingly, solid organ metastases occurred at similar instances and in some cases preceded local nodal metastases.
Conclusion: Through the development of the first rapid autopsy programme in this cancer, we have begun to reconstruct the evolution of metastatic OAC. We demonstrate that distant organ seeding may occur prior to local nodal involvement hence challenging our traditional clinical staging algorithms. Further cases and samples are being analysed to support our findings.
Disclosure of Interest: None declared

OP179 EFFECT OF CO-MORBIDITIES ON URINARY METABOLIC PROFILING IN THE CHARACTERISATION OF PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Introduction: Several studies have successfully used metabolic profiling (metabonomics) of urine to distinguish patients with IBD from healthy controls (1); many discriminatory metabolites identified relate to microbial or host-microbial cometabolism, supporting the concept of gut dysbiosis in IBD pathogenesis. An individual's metabolic phenotype may be influenced by factors including comorbidities such as diabetes mellitus, and previous studies have been restricted to IBD patients with no significant comorbidities which does not accurately reflect clinical practice. In order to assess the potential of metabonomics in a clinically relevant population, this study analysed urinary metabolic profiles of IBD patients with and without comorbidities.
Aims & Methods: Nuclear magnetic resonance spectroscopy was used to acquire urinary metabolic data from 51 IBD patients with at least one significant comorbidity (including diabetes mellitus, asthma and ischaemic heart disease), 46 patients with IBD alone, and 54 healthy controls. Groups were matched for age, sex, race, BMI and IBD diagnosis. As a preliminary analysis, resonances specific for metabolites influenced by gut microbes based on prior observations were integrated and analysed using appropriate univariate statistics.
Results: Univariate analysis showed that hippurate excretion was significantly lower in patients with IBD and comorbidities compared to healthy controls ($p = 0.01$), as well as patients with IBD alone ($p = 0.04$) confirming results of other published studies. In addition, trimethylamine (TMA) levels were relatively increased in patients with IBD and comorbidities ($p = 0.03$) and IBD alone ($p = 0.07$) compared to healthy controls, although trimethylamine-N-oxide (TMAO) levels showed no significant difference due to IBD or comorbid status.
Conclusion: In this study urinary hippurate was significantly lower in IBD patients, regardless of other comorbid diagnoses or treatments, which is consistent with previous studies. Hippurate is not a specific marker for IBD but rather related to gut microbiome metabolic dysfunction as it has also been observed when comparing the urine metabolic profile of lean and obese people and in intestinal parasitic infections. The relative increase in TMA has not been previously reported in humans, but correlates with a study that shows increasing TMA with progression of IBD in the IL10 knock-out mouse model (2). Future work will include multivariate analysis of this dataset to elucidate metabolic phenotypes associated with complex comorbidities in IBD.

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Disclosure of Interest: None declared

OP180 HISTONE H3K27 TRIMETHYLATION IN NORMAL COLON IS ASSOCIATED WITH THE DEVELOPMENT OF COLORECTAL TUMORS WITH CPG ISLAND METHYLATOR PHENOTYPE

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Introduction: Epigenetic alterations, including DNA methylation and histone modifications, play critical roles in the development of colorectal cancer (CRC). These epigenetic alterations are thought to be the main driving force in CRCs derived from sessile serrated adenomas (SSAs) exhibiting concurrent hypermethylation of multiple loci, which is termed as CpG island methylator phenotype (CIMP). Recent studies have shown that SSAs are associated with an increased risk of synchronous CRC. These findings are indicative of the epigenetic field effect in the normal-appearing colonic mucosa of SSA patients. In addition, recent studies suggest a tight association between bivalent chromatin domain in embryonic stem cells (ESCs) and aberrant DNA methylation in cancer cells. However, the chromatin signature in adult normal colon is not well characterized.
Aims & Methods: We aimed to clarify the chromatin signature in background normal colonic mucosa of CRCs with or without CIMP, and its association with aberrant DNA methylation in matched CRCs. Histone modifications (H3K4me3 and H3K27me3) in crypts isolated from surgically resected colonic tissues were

analyzed by performing chromatin immunoprecipitation (ChIP)-sequencing. Genome-wide DNA methylation was assessed by using the Infinium HumanMethylation450 BeadChip. Histone modifications of selected genes were analyzed by ChIP-PCR.
Results: We found that genes marked by bivalent chromatin domain in ESCs are significantly associated with H3K27me3 in noncancerous colonic mucosa of patients with CIMP-positive tumors. Moreover, a large number of genes marked by H3K27me3 in noncancerous colonic mucosa were specifically methylated in CIMP-positive CRCs. In contrast, such enrichment of H3K27me3 was not observed in colonic mucosa of patients with CIMP-negative tumors. We identified a series of genes which were marked by H3K27me3 in the background colonic mucosa of CIMP-positive CRCs and were aberrantly methylated in CIMP-positive CRCs. To evaluate the clinical implication of the histone marks in colonic mucosa, we next assessed histone marks of selected genes in a large number of fresh frozen noncancerous colonic mucosa specimens.
Conclusion: Our results are indicative of a tight association between H3K27me3 mark in adult normal colon, bivalent chromatin domain in ESCs and aberrant DNA methylation in cancer cells. Our results suggest that H3K27me3 may act as a pre-mark in the noncancerous colon mucosa of patients at a high risk of CIMP-positive cancer and that histone marks in colonic mucosa may be a predictive biomarker of the CRC risk.
Disclosure of Interest: None declared

OP181 LABEL FREE PROTEOMICS IDENTIFIES OLFACTOMEDIN-4 AS A MARKER OF EPITHELIAL TRANSITION OF EARLY CRC STAGES

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Introduction: Colorectal cancer (CRC) is the third leading cause of cancer death worldwide. CRC prognosis being closely linked to staging at diagnosis, new early diagnostic tools are awaited. Formalin-Fixed Paraffin-Embedded (FFPE) tissues stored in hospital biobanks represent a valuable resource for retrospective analysis, as larger populations can be studied, increasing the possibility to identify significant and specific potential new diagnosis/ prognosis biomarkers.
Aims & Methods: To identify biomarker from early CRC stages patients, we performed a retrospective study on 36 CRC tissue samples ($pT_1N_0M_0$, $n=16$ and $pT_2N_0M_0$, $n=20$) compared together and with 40 control tissue samples (20 patients with diverticulitis, using paired inflamed (DI) and healthy tissue (DH)). Each tissue slice was macrodissected to enrich in epithelial cells. We used FFPE-FASP kit (Expedeon) for sample preparation and protein digests were analyzed using label free proteomics (using 2D-*nano*Aquity UPLC separation online with *Q*-Tof Synapt HDMS^{TM} G2, Waters). We performed protein identification and differential analysis using Progenesis QI for proteomics (Nonlinear Dynamics). The validation of Olfactomedin-4 (OLFM4) and 2 other potential markers was obtained by immunohistochemistry on a new and independent set of 40 patients with early CRC stages.
Results: We selected 149 proteins differentially distributed between T1 and T2 CRC stages which are not significantly distributed between CRC and DH or DI. Only 30 proteins were significantly more abundant in T1 *versus* T2 and 119 were distributed inversely (minimum fold ratio > 2). Among those, ATP synthase subunit beta, Aspartate-tRNA ligase, Haptoglobin and Kininogen were previously identified. We selected several potential markers for validation by immunohistochemistry. OLFM4 validated the difference observed by proteomics (pT1N0M0 < pT2N0M0). Validation was also performed on other protein like Kininogen as this protein was previously found in serum of early CRC.
Conclusion: This FFPE retrospective proteomic study done on very early CRC stage highlighted proteins previously identified as potential CRC, other cancers and new potential biomarkers. These might be involved in early CRC stages epithelium progression and might represent early CRC biomarkers. OLFM4 was validated by IHC on new patients and could be implicated in early tumour progression.
Disclosure of Interest: None declared

OP182 GUT MICROBIOTA MOLECULAR SPECTRUM IN HEALTHY CONTROLS, DIVERTICULAR DISEASE, IBS AND IBD PATIENTS: TIME FOR MICROBIAL MARKER OF GASTROINTESTINAL DISORDERS?

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Introduction: Increasing evidence has emerged on the analysis of bacterial species making up the gastrointestinal microbiota. However few data exist on differences in gut microbiota composition in GI diseases, such as IBD, IBS and diverticular disease compared to healthy controls.
Aims & Methods: Aim of our study was to evaluate the differences in gut microbiota composition between IBD, IBS and diverticular disease (DD) patients. 10 Crohn's Disease (CD), 5 Ulcerative Colitis (UC), 4 DD, 3 IBS patients, and 8 controls (CD) were enrolled and fecal samples collected from each. Microbiota composition was assessed by a metagenomic gene-targeted approach (16S rRNA) using the Roche 454 GS Junior, following DNA isolation from stool samples stored at –80°C. Data were analyzed in Qiime. Individual species richness was estimated using Chao1 alpha-diversity index. We also explored the differential relative abundance of several taxa of interest, selected according to literature.
Results: Bacteria amplicons were detected in all samples. Prevalent classes of bacteria were: Bacteroidia (min 13.06% - max 91.55%), Firmicutes (min 7.48% - max 86.10%) and Proteobacteria (min 0.48% - max 46.48%). Fusobacteria were found only in CD and DD patients (min 0.67% > max 50.71%). IBD microbiota composition differed significantly compared to all other. In particular, UC patients showed a reduced concentration in Bacteroidetes and an increased presence of Firmicutes vs. CT, DD and IBS. On the other side, Bacteroidetes and Firmicutes composition varied among CD patients, being increased or reduced when compared to the other groups. Proteobacteria were increased in all diseased group compared to CT, being more represented in CD and IBS-D. Moreover, Actinobacteria were increased in IBD and DD vs. IBS and CT. The most represented species in IBD and DD vs. other groups was Collinsella Aerofaciens. Rikenellaceae were suppressed in IBD patients, as well as Fecalibacterium Prausnitzii. Akkermansia Muciniphila was present only in IBS patients. Enterobacteriaceae were increased only in CD patients vs. other groups. Finally, while chao1 score was similar between CT, IBS and DD, it was deeply reduced in IBD patients.
Conclusion: These preliminary data show that starting from microbiota, GI disease can be a continuous pathological spectrum where IBD display one extreme in gut microbiota composition while controls display the other. Furthermore, GI diseases share some microbial patterns, sharing perhaps common pathophysiological pathways. New analyses are needed to confirm this hypothesis and evaluate therapeutical implications.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 08:30–10:30
IMPROVING COLONOSCOPIC PATHOLOGY RECOGNITION – ROOM E3

OP183 NARROW BAND IMAGING OPTICAL DIAGNOSIS OF SMALL COLORECTAL POLYPS IN ROUTINE CLINICAL PRACTICE: THE DETECT INSPECT CHARACTERISE RESECT AND DISCARD (DISCARD 2) STUDY

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Introduction: Accurate optical characterisation and removal of small adenomas (<10mm) at colonoscopy would allow hyperplastic polyps to be left in situ and surveillance intervals to be determined without delay for histopathology. Although accurate in specialist practice, the performance of narrow band imaging (NBI) colonoscopy in routine clinical practice is poorly understood.
Aims & Methods: NBI assisted optical diagnosis was compared with reference standard histological diagnosis in a prospective, blinded calibration study. Adults undergoing routine colonoscopy in 6 general (community) hospitals in northeast England. Participating colonoscopists (N = 28) were trained using the NBI International Colorectal Endoscopic (NICE) classification. By comparing optical and histological findings in patients with only small polyps, test sensitivity was determined at two thresholds: presence of adenoma and need for surveillance. Accuracy of characterising adenomatous polyps <10mm was compared using hierarchical models, allowing determinants of accuracy to be explored.
Results: Of 1688 patients recruited, 723 (42.8%) had polyps <10mm with 567 (78.4%) having only polyps <10mm. Overall, the median patient age was 64.3 years (interquartile range 55.0 to 70.2) and 53.1% were male. Test sensitivity (presence of adenoma, N = 499 patients) by optical diagnosis was 83.4% (95%CI: 79.6% to 86.9%), significantly less than the required 95% sensitivity ($p < 0.001$). Test sensitivity (need for surveillance) was 73.0% (95%CI: 66.5% to 79.9%). Analysed at the polyp level, test sensitivity (chracterisation of an adenoma, N = 1620 polyps) was 76.1% (95%CI: 72.8% to 79.1%). In fully adjusted analyses, test sensitivity was 99.4% (95%CI: 98.2% to 99.8%) if two or more NICE adenoma characteristics were identified (relating to colour, vessel structure and surface pattern). Colonoscopist expertise and confidence in diagnosis did not independently improve test accuracy.
Test sensitivity at the four thresholds:
1.The presence of a histological confirmed adenoma: 83.4% (HR'+IR'+LRS'+LRNS'/HR + IR + LRS + LRNS = 297/356)
2.Identifying the need for surveillance (vs. no surveillance): 73.0% (HR'+IR'+LRS'/HR + IR + LRS = 119/163)
Conclusion: NBI assisted optical diagnosis cannot yet be recommended for application in routine clinical practice. Further work is required to evaluate

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		Histological Surveillance Interval					
		Adenoma				No adenoma	
		Surveillance			No Surveillance		
	NBI Surveillance Interval	HR	IR	LRS	LRNS	NANS	Total
Surveillance	High Risk' (HR')	***9***	4	0	3	2	18
	Intermediate Risk (IR')	3	***30***	12	10	2	57
	Low Risk Surveillance' (LRS')	2	13	***46***	52	13	126
No surveillance	Low Risk No Surveillance' (LRNS')	0	4	*9*	***100***	***19***	132
	No adenoma No surveillance' (NANS')	0	4	27	***28***	***107***	166
	Total	14	55	94	193	143	499

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	# of polyps	# of frames	# of frames with correct localization	# of frames per polyp	# of frames with correct localization per polyp	# of polyps with at least one frame with correct localization
<10mm	22	430	308 (71.6%)	19.5 ± 6.3 (2-25)	14 ± 6.8 (1-24)	22 (100%)
IIa + IIb	11	218	169 (77.5%)	19.8 ± 5.3 (6-25)	15.4 ± 7 (2-24)	11 (100%)
Is	9	162	105 (65%)	18 ± 7.6 (2-25)	11.7 ± 7.3 (1-22)	9 (100%)
Ip	2	50	34 (68%)	25 ± 0 (25-25)	17 ± 1.4 (16-18)	2 (100%)
≥10 mm	9	182	122 (67%)	20 ± 7.1 (5-25)	13.8 ± 8.3 (3-25)	9 (100%)
IIb	1	12	6 (50%)			1 (100%)
Is	2	46	31 (67.4%)	23 ± 2.8 (21-25)	15.5 ± 12 (7-24)	2 (100%)
Ip	6	124	85 (68.5%)	20.7 ± 7.8 (5-25)	14.5 ± 8.3 (3-25)	6 (100%)

whether variation in test accuracy is related to polyp characteristics or colonoscopist training.
Disclosure of Interest: None declared

OP184 COLONIC POLYPS ARE CORRECTLY IDENTIFIED BY A COMPUTER VISION METHOD USING WM-DOVA ENERGY MAPS

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Introduction: Polyp miss-rate is a drawback of colonoscopy that results in a lack of total effectiveness in preventing colorectal cancer. The miss-rate increases significantly in small polyps.
Aims & Methods: To evaluate the usefulness of a computer vision method for the identification of colonic polyps.
612 polyp images were used from a data base (CVC-ClinicDB) containing an average number of 20 frames (range 2-25) of 31 different polyps. Our method is based on a model of appearance for polyps which defines a polyp as a protrusion enclosed by valleys of different intensity image. Valley information allows the creation of energy maps (WM-DOVA) related with the likelihood of polyp presence in the image.
Results: 22 polyps were small (< 10 mm), representing a total of 430 frames of the database: 11 non-polypoid (IIa and IIb), 9 sessile (Is) and 2 pedunculated (Ip) with a total of 218, 162 and 50 frames, respectively. All polyps were correctly localized in at least one frame. The number of frames with correct localization was 308 (71.6%) in small polyps compared with 122/182 (67%) in polyps ≥10 mm ($p = 0.2$) (table). Small non-polypoid polyps were correctly localized in more frames than all the other types: 169/218 (77.5%) vs 261/394 (66.2%); $p = 0.003$. In the 182 frames without a correct polyp location, the possible causes of failure were: folds in 81 (43.8%), polyps in a lateral position in 57 (30.8%), blood vessels in 21 (11.3%), absence of valleys in 12 (6.5%), fecal content in 7 (3.8%) and others in 4 (2.1%).
Conclusion: Computer vision method WM-DOVA shows good performance for the identification of colonic polyps, particularly those small non-polypoid which are the most difficult to detect during colonoscopy. These results indicate a potential applicability in clinical practice and warrant further clinical studies.
Disclosure of Interest: None declared

OP185 COMPUTER AIDED DIAGNOSIS OF THE MICROVASCULATURE OBSERVED BY ENDOCYTOSCOPY PROVIDE FULLY AUTOMATED DIAGNOSIS OF COLORECTAL LESIONS

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Introduction: Endocytoscopy (EC) is the next generation of ultra-magnification endoscopy that allows visualization of the glandular structure and cellular atypia. EC in conjunction with NBI (EC-NBI) enable the ultra-magnified microvessels of the lesion to be observed without dye. We called these findings as endocytoscopic vascular pattern (EC-V). We reported that the EC-V diagnosis highly correlated with the histopathologic diagnosis. Furthermore EC-V simplifies the complicatedness of conventional EC observation. Because conventional EC classification (EC-C) which evaluate the cellular and glandular structure atypia requires dye staining, whereas EC-V requires no dye staining. [1] However, for accurate diagnosing by EC-V, it requires training and experiences. We have also reported that the efficacy of computer aided diagnosis for EC-C. [2]
Aims & Methods: The aim of this study is to construct automatic diagnostic system for EC-V (EC-NBICAD). The algorithm of this system was programmed based on 288 features of each image by texture analysis which can quantify the pattern of picture. Support vector machine was used for classifier and a total of 979 EC-NBI images (non-neoplastic; 381, neoplastic; 598) were used for machine learning. To validate the diagnostic ability of EC-NBICAD, the randomly selected 100 images (neoplastic; 50, non-neoplastic; 50) which were not used for machine learning, were evaluated by EC-NBICAD. The sensitivity, specificity and accuracy for distinguishing neoplastic lesions from non-neoplastic lesions were calculated.
Results: The EC-NBICAD calculated the probability of the output pathological prediction. We defined over 90% probability as "high confidence". High confidence pathological prediction was made in 67% (67/100) images of the subject images. The sensitivity, specificity and accuracy of EC-NBICAD output with high confidence were 97.8%, 92.9% and 95.9%, respectively. By contrast, the overall sensitivity, specificity and accuracy for the all the subject images were 98.0%, 82.0% and 90.0%, respectively.
Conclusion: The diagnostic ability of EC-NBICAD was substantially good, although it was tentative system. However, further training images should be collected, because they will increase the rate of high confidence histopathological prediction.
Acknowledgement: We express great gratitude to Prof. Kensaku Mori and Yukitaka Nimura (Nagoya University, Information and Communications Headquaters) for their invaluable support as co-researchers.

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Disclosure of Interest: None declared

OP186 IN VIVO REAL-TIME PREDICTION OF COLORECTAL POLYP HISTOLOGY USING AN OPTICAL BIOPSY FORCEPS SYSTEM BASED ON LASER-INDUCED FLUORESCENCE SPECTROSCOPY

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Introduction: In order to reduce procedural time, costs and potential risks associated with the resection of diminutive colorectal polyps, the ASGE recently proposed performance thresholds that a new technology should meet for the accurate real-time assessment of the histology. Within this study, we prospectively assessed whether the newly introduced WavSTAT 4 optical biopsy forceps system can accurately predict polyp histology according to the ASGE PIVI statement.

Aims & Methods: Consecutive patients undergoing screening or surveillance colonoscopy were included. Real-time histology of 142 diminutive colorectal polyps was evaluated using the WavSTAT 4 system and compared to the results of conventional histology. The accuracy of predicting histology with the optical biopsy system for colorectal polyps according to the ASGE PIVI statement was assessed.

Results: The overall accuracy of the WavSTAT 4 system for prediction of adenomatous polyp histology was 84.1% with a sensitivity, specificity, and negative predictive value of 81.5%, 85.2%, and 95.4%. When only distal colorectal diminutive polyps were considered, the negative prediction for excluding adenomatous histology was increased to 98% (accuracy: 81.7%, sensitivity: 88.9%, specificity: 80.6%). On site-surveillance intervals were correctly predicted with an accuracy of 89.6% with WavSTAT 4 when compared to recent histology based US guideline recommendations. In all patients in which histology and WavSTAT 4 based surveillance intervals differed, WavSTAT 4 predicted narrower surveillance intervals.

Conclusion: The WavSTAT 4 optical biopsy system is accurate enough to leave distal colorectal polyps in place without resection or to resect and discard them without pathologic assessment. The WavSTAT system therefore has the potential to reduce costs and risks associated with the redundant removal of diminutive colorectal polyps.

Disclosure of Interest: None declared

OP187 CLASSIFICATION OF CELL NUCLEI MORPHOLOGY OF EC3A FINDINGS IN COLORECTAL ENDOCYTOSCOPY

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Introduction: Endocytoscopy (EC) is a next-generation endoscopy that enables diagnostic imaging at 450× magnification. To date, excellent results have been achieved using EC classifications for qualitative diagnosis and assessment of depth of invasion of colorectal lesions (neoplasia/non-neoplasia accuracy: 96.5%; accuracy for carcinomas with massive submucosal invasion (SM-m): 96.3%).(1, 2)

Aims & Methods: In the EC classifications, lesions diagnosed as EC3a vary extensively from adenoma to SM-m, including some lesions that are unsuitable for endoscopic treatment. Therefore, to improve the accuracy of asssessing the depth of invasion based on the EC classification, we investigated the presence or absence of certain endoscopic factors in EC3a findings that could be indicators of SM-m. Among lesions that were observed by EC between May 2005 and January 2015, we retrospectively examined 277 lesions diagnosed as EC3a or EC3b, according to the EC classification. Patients with unclear glandular lumen were excluded. The presence or absence of four findings that are indicators of SM-m were examined by EC. The four factors were: 1) extremely enlarged nuclei (EEN), 2) stratified nuclei (SN), 3) marked vascular dilatation (MVD), and 4) fine granular structure (FGS). Based on the results, we thoroughly examined the diagnostic accuracy of EC3a findings in the diagnosis of depth of invasion.

Results: Based on the results of multiple logistic regression analysis, the factors useful for the diagnosis of SM-m were EEN ($p < 0.01$), SN ($p < 0.01$), and FGS ($p < 0.05$). Of these, EEN and SN had odds ratios > 10 and were considered important predictors of SM-m invasion. So we diagnosed the lesions which were positive for EEN and SN as EC3a-high grade, whereas lesions negative for such findings were diagnosed as EC3a-low grade. As a result, 32 of 119 lesions were diagnosed as EC3a-high grade. Of these, the final pathological diagnosis was SM-m in 19 lesions, and muscularis propria cancer (MP) in five lesions. The diagnostic efficiency was as follows: sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and positive likelihood ratio of 88.9%, 91.3%, 75.0%, 96.6%, 90.8%, and 10.2, respectively. In the EC diagnosis above, interobserver validation (κ) of the three endoscopists were 0.63, 0.64, and 0.69, whereas good values were obtained for intraobserver validation (κ) at 0.73, 0.79, and 0.67.

Conclusion: In the diagnosis of colorectal lesions by EC, EC3a findings of EEN and SN are important indicators of SM-m. Results also suggested that taking into consideration the findings as for EC3a may improve the diagnostic accuracy for SM-m.

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Disclosure of Interest: None declared

OP188 A RANDOMIZED THREE-ARM COMPARISON OF HIGH DEFINITION ALONE WITH HIGH DEFINITION DYE SPRAYING AND ELECTRONIC VIRTUAL CHROMOENDOSCOPY USING ISCAN FOR DETECTION OF COLONIC DYSPLASTIC LESIONS DURING IBD SURVEILLANCE COLONOSCOPY

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Introduction: Dye spraying chromoendoscopy is considered to be the standard of practise for IBD surveillance colonoscopy. However, the resolution of high definition colonoscopy has increased significantly and electronic filter techniques allow detailed assessment of mucosal and vascular patterns.

Aims & Methods: The aim of this study was to compare different techniques including high definition colonoscopy (HD), dye spraying (0.2% indigo carmine) chromoendoscopy (DSC) and electronic virtual chromoendoscopy using i-SCAN (EVC) to detect colonic dysplastic lesions in IBD patients. A randomized study (NCT02098798) was conducted to determine the detection rates of dysplasia with HD alone, DSC or EVC in patients with long standing IBD (at least 8 years from diagnosis). Consecutive patients with inactive disease (Mayo endoscopic subscore 0-1 or Harvey- Bradshaw Index <4) were enrolled in 1:1:1 ratio into three arms of the study, using Pentax EPKi processor and high-resolution video colonoscope (EC-3490Fi; Pentax Tokyo). The endoscopic activity in UC was assessed with Mayo endoscopic subscore and in CD with the Simple Endoscopic Score (SES-CD). The colonic lesions were classified by the Paris classification and Kudo pit pattern. Neoplastic changes were classified according to the new Vienna classification. The lesions of dysplasia (polypoid/non-polypoid), SSAs, adenoma-like polyps (ALPs), hyperplastic polyps (HPs) and non-neoplastic inflammatory polyps (IPs) were identified.

Results: 155 patients (73 female, median age 48 years, range 20-77 years) were assessed by HD (n = 54, 34.8%), VEC (n = 52, 33.5%) and DSC (n = 49, 31.6%). Twenty-three SSAs were found in fourteen patients (9%); thirty-four ALPs were found in twenty-three patients (14.8%); six dysplastic lesions were found in 5 patients (3.2%); fifty HPs were found in forty patients (25.8%) and fourteen IPs were found in twelve patients (7.7%). The number and percentage of each lesion found in each group is detailed in table 1.Tubular adenoma was detected more often in the HD group than other groups ($p < 0.05$). HD had a sensitivity of 91.67%, specificity of 85%, PPV 91.67% and NPV 85% in detecting dysplastic lesions. On the other hand, DSC had a sensitivity of 81.82%, specificity of 95.65%, PPV 90%, NPV 91.6% and EVC had a sensitivity of 90.48%, specificity of 82.3%, PPV 86.36% and NPV 87.5%.

Table 1: Colonic lesions found in each surveillance group

Lesions	HD (n = 54)	DSC (n = 49)	EVC (n = 52)	p
Serrated adenoma	11(19.6%)	2 (5.9%)	10(26.3%)	0.07
Tubular adenoma	21 (37.5)	7(20.6%)	6(15.8%)	0.04
Polypoid/nonpolypoid	2 (3.6%)	1(2.9%)	2(5.3%)	0.53
Adenocarcinoma	**0 (0%)**	**1(2.9%)**	**0 (0%)**	**0.24**

Conclusion: This randomized study found that HD alone had the best detection rate for adenoma. However, we could not demonstrate superiority of DSC in sensitivity of detecting dysplastic lesions compared to HD and EVC.

Disclosure of Interest: None declared

OP189 DYSPLASIA ASSOCIATED TO INFLAMMATORY BOWEL DISEASE IS HIGHLY DETECTED WITH CHROMOENDOSCOPY BUT POORLY CHARACTERIZED: PROSPECTIVE MULTICENTER NATION-WIDE STUDY (CROMO STUDY)

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Introduction: Pan-colonic chromoendoscopy (CE) with targeted biopsies for dysplasia (N-IBD) detection in long-standing inflammatory bowel disease (L-IBD) is strongly endorsed by main scientific societies. However, effectiveness of this strategy is controversial and poorly evaluated outside controlled trials.

Aims & Methods: To assess the effectiveness of CE with targeted biopsies for N-IBD detection and characterization in a clinical setting. Patients with L-IBD were prospectively included in a multicenter nation-wide cohort study during 2 years until June 2014. Each colonic segment was evaluated with white light (WL) followed by 0.4% indigo carmine CE. Specific lesion's features selected from literature were recorded for each lesion before being sampled or removed. Endoscopists' histology prediction based on optical diagnosis was compared with histopathology as gold standard

Results: 350 patients were included: 53% male; median time evolution 15 years, 79% ulcerative colitis and 21% Crohn's disease, 70% pancolitis, 7% primary sclerosing cholangitis and 8% first degree relative with colorectal cancer. 597 lesions were detected (median per patient: 1.7; range: 0-14): 1 (0.1%) invasive cancer, 100 (16.7%) N-IBD (5 high-grade dysplasia, 95 low-grade dysplasia) and 496 (83%) benign lesions. N-IBD detection miss rate with WL was 58/100, resulting in a 56.4% incremental yield for CE. Positive and negative predictive values (PPV, NPV) for N-IBD optical diagnosis were 42% (35-49%) and 93% (90-95%) respectively. Independent lesions' characteristics predictive of N-IBD and their PPV and NPV are shown in table.

Lesions' characteristics	OR (95% CI)	P	PPV (%)	NPV (%)
Proximal location	2.0 (1.1-2.6)	0.020	21	87
Loss of Innominated lines	2.0(1.0-3.7)	0.004	22	90
Polypoid morphology	2.7 (1.5-4.8)	0.001	28	88
Kudo III-IV	5.0 (2.7-8.4)	0.000	43	86

Conclusion: Outside clinical trials, CE is an effective strategy for L-IBD surveillance and detects 2-folds more N-IBD than WLE. In vivo lesion characterization is difficult: whereas benign lesions are highly predicted, N-IBD is not well recognized. Thus, CE targeted biopsies/removal of any mucosal abnormality not highly suspicious of benignity is still recommended.

Disclosure of Interest: None declared

OP190 ACCURACY OF THE FULL SPECTRUM ENDOSCOPY (FUSE) SYSTEM FOR ASSESSMENT OF DISEASE ACTIVITY IN INFLAMMATORY BOWEL DISEASES (IBD) COMPARED TO HIGH-DEFINITION ENDOSCOPY

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Introduction: In 2013, full-spectrum-endoscopy (FUSE) was introduced as a novel colonoscopy platform. In contrast to other endoscopy systems illumination with the FUSE system is achieved by LEDs and not by a xenon light source. In addition, the FUSE-system does not provide high-definition imaging yet. In patients with IBD, precise assessment of disease activity (i.e. mucosal healing) is of paramount importance to predict disease outcome and to guide therapy.

Aims & Methods: Aim of the study was to determine whether FUSE has the potential to assess disease activity in patients with IBD as compared to a matched cohort of patients undergoing high-definition white-light endoscopy (HD-WL). Therefore, consecutive patients with IBD undergoing FUSE colonoscopy were matched to patients with IBD undergoing high-definition white-light endoscopy at the same endoscopy unit. The mucosal vascular pattern and any mucosal abnormalities were recorded. Inflammation in ulcerative colitis was recorded according to Mayo ulcerative endoscopic score (MUES) and in Crohn's disease according to Crohn's Disease Endoscopic Index of Severity (CDEIS). Subsequent to endoscopic characterization targeted biopsies were obtained for histopathological analysis of disease activity.

Results: 85 cases were included. Mean age of patients was 37 years (Range 18 to 72 years). 59% of patients had diagnosis of Crohn's disease and 41% diagnosis of ulcerative colitis. Accuracy of FUSE and HD-WL endoscopy for diagnosis of disease activity in IBD were not statistically significant different (81% versus 76%). In the subgroup analysis FUSE and HD-WL endoscopy yielded in under-diagnosis and overdiagnosis of disease activity in 57% versus 46% and 43% versus 54% of not correctly predicted cases, respectively. Overall, FUSE was more accurate for diagnosis of disease activity in Crohn's disease patients while HD-WL endoscopy was more accurate for diagnosis of disease activity in ulcerative colitis.

Conclusion: Despite the use of LEDs resulting in a darker image and high-resolution imaging, the FUSE system seems to be equal effective to high-definition white-light imaging for diagnosis of disease activity in patients with IBD.

Disclosure of Interest: None declared

OP191 CONFOCAL LASER ENDOMICROSCOPY IN ULCERATIVE COLITIS: A LONGITUDINAL STUDY OF RESPONSE TO MEDICAL THERAPY

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Introduction: Confocal laser endomicroscopy (CLE) enables real-time *in vivo* microscopy during endoscopy and can predict relapse in inflammatory bowel disease patients in remission. However, little is known about how endomicroscopic features changes with time. The aim of this longitudinal study was to correlate colonic CLE features in ulcerative colitis with histopathology and macroscopic appearance before and after intensification of medical treatment.

Aims & Methods: The aim of this longitudinal study was to correlate colonic CLE features in ulcerative colitis with histopathology and macroscopic appearance before and after intensification of medical treatment. Twenty-two patients with ulcerative colitis in clinical relapse and seven controls referred for colonoscopy were enrolled. The colonic mucosa was examined with high-definition colonoscopy, histopathology, and CLE at four colonic sites. Subsequently, patients requiring medical treatment escalation were referred for re-endoscopy after 6-8 weeks enabling longitudinal data analysis.

Results: Generalized estimating equations showed that the frequency of fluorescein leakage ($p<0.001$), microerosions ($p<0.001$), tortuosity of the crypts ($p=0.001$), distortion of the crypts openings ($p=0.001$), presence of inflammatory infiltrates ($p<0.001$), and decreased crypt density ($p<0.001$) were significantly higher in endoscopically active ulcerative colitis (endoscopic Mayo Clinic subscore > 1) compared to inactive ulcerative colitis and controls. Furthermore, colonic fluorescein leakage $r_s=0.42$ ($p<0.001$), microerosions $r_s=0.54$ ($p<0.001$), crypt tortuosity $r_s=0.66$ ($p<0.001$), distortion of crypt opening $r_s=0.63$ ($p<0.001$), decreased crypt density $r_s=0.54$ ($p<0.001$), and inflammatory infiltrates $r_s=0.28$ ($p=0.004$) were all significantly correlated with the histopathological score [2]. A decrease in histopathological score after medical treatment escalation was correlated with improvement in crypt tortuosity $r_s=0.35$ ($p=0.016$), distortion of crypt openings $r_s=0.30$ ($p=0.045$), and decreased crypt density $r_s=0.33$ ($p=0.026$). No correlation was found between decrease in histopathological score and colonic fluorescein leakage, microerosions, and inflammatory infiltrates.

Conclusion: pCLE can identify subtle mucosal changes in active ulcerative colitis, which are related to the grade of severity of the disease. After medical treatment escalation, improvement of abnormal colonic crypt architecture can be detected by CLE. In contrast, we did not observe a resolution of intestinal barrier impairments, which may reflect that few patients reached complete endoscopic remission during the follow-up period. Future studies will have to assess whether CLE parameters can be incorporated into an endomicroscopic score for ulcerative colitis, which may refine the definition of mucosal healing.

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TUESDAY, OCTOBER 27, 2015 08:30–10:30
H. PYLORI: IT STILL BUGS US – ROOM E5

OP192 EUROPEAN REGISTRY ON H. PYLORI MANAGEMENT (HP-EUREG): FIRST-LINE TREATMENTS AND INTERIM ANALYSIS OF 11,272 PATIENTS

A. G. Mcnicholl[1], on behalf of Hp-EuReg Investigators, A. Gasbarrini[2], B. Tepes[3], D. S. Bordin[4], F. Lerang[5], M. Leja[6], T. Rokkas[7], D. Vaira[8], O. Shvets[9], L. Kupcinskas[10], A. Perez-Aisa[11], T. Axon[12], G. M. Buzas[13], M. Castro[14], I. Simsek[15], M. Katicic[16], J. C. Machado[17], V. Lamy[18], K. Przytulski[19], L. Rodrigo[20], L. Boyanova[21], P. Bytzer[22], C. Beglinger[23], L. G. Capelle[24], A. Goldis[25], L. Veijola[26], M. Vujasinovic[27], L. Bujanda[28], A. Huerta[29], L. Jonaitis[30], J. Molina-Infante[31], M. Caldas[32], M. Ramas[32], M. Garcia-Donday[32], F. Megraud[33], C. O'Morain[34], J. P. Gisbert[35], on behalf of Hp-EuReg Investigators
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Introduction: The most efficient management strategy of *H. pylori* infection is still to be found.
Aims & Methods: To evaluate the management of *H. pylori* infection by gastroenterologists in Europe. A systematic prospective registry of the clinical practice of European gastroenterologists regarding *H. pylori* infection and treatment (30 countries-250 recruiters). An electronic clinical research file (e-CRF) was created to systematically register all adult patients infected with *H. pylori*. Variables included: Patient's demographics, previous eradication attempts, prescribed eradication treatment, adverse events, and outcomes.
Results: Up to now, 11,272 patients have been included, and 9,181 have finished follow up (59% females, 87% caucasian). Mean age was 55 years. 4.2% had drug allergies (81% to penicillin). 20% had gastroduodenal ulcer. 77% were first-line treatments, 16% -2nd, 4.5% -3rd, 1.3% -4th. 61% were triple regimens (PPI + 2 antibiotics), 16% non-bismuth quadruple concomitant, 11% sequential, and 7% bismuth quadruple. 30% of patients had adverse events mostly mild (53%) and lasted average 6.4 days, causing treatment discontinuation in 0.3%. Overall eradication rate (considering all lines of treatment) was 80%, and only 67% of eradication failures were retreated. First-line ITT results: 10 day triple (PPI + clarithromycin + amoxicillin), sequential, concomitant and bismuth quadruple therapies achieved 78%, 87%, 88 and 92% eradication rates respectively. Expanding the regimen up to 14 days increased efficacy of triple (81%), and concomitant (90%) regimens.
Conclusion: *H. pylori* management by gastroenterologists in Europe is extremely diverse. It is important to notice that the overall eradication rate is clearly suboptimal, mainly due to the use of standard triple therapy as a first-line treatment in areas where it is not recommended. Continuation of this registry and deeper evaluation of its data may offer valuable information to improve *H. pylori* management.
Disclosure of Interest: None declared

OP193 EFFICACY OF SITAFLOXACIN-BASED HELICOBACTER PYLORI ERADICATION TREATMENT FOR PATIENTS WITH METRONIDAZOLE-RESISTANCE STRAIN

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Introduction: Bacterial resistance to antibiotics often leads to failure of *Helicobacter pylori* eradication therapy. A tailored *H. pylori* eradication regimen based on clarithromycin-susceptibility and maintaining acid secretion was developed to counter this situation. The fluoroquinolone sitafloxacin has a low minimum inhibitory concentration for *H. pylori* and has efficacy in 3rd-line eradication treatment and for patients with penicillin allergy. A sitafloxacin-based regimen with maintenance of acid inhibition might therefore have a higher success rate also in first-line treatment.
Aims & Methods: Our aim is to investigate the efficacy of sitafloxacin-based triple therapy and document its efficacy in relation to antimicrobial susceptibility.
In 180 *H. pylori*-positive Japanese patients (for first-line treatment: n = 45, second-line; n = 41, third-line: n = 94), we investigated the efficacy of a sitafloxicin-based regimen of rabeprazole 10mg four-times-daily dosing (q.i.d.), metronidazole 250mg twice-daily (b.i.d.), and sitafloxacin 100mg b.i.d. for 1 week. At eight weeks after the treatment period patients were given the [13C]-urea breath test to assess eradication status.
Results: The eradication rate was 92.2% (95% CI: 87.3% > 95.7%, 166/180) and one patient experienced appearance of nettle rashhives and dropped out from this study. Although the eradication rate was higher in patients treated as first-line therapy (100%, 95% CI: 83.4% > 100%) than in those treated as second-line (92.7%, 80.1% > 98.5%) or third-line therapy (88.3%, 80.0% > 94.0%), no significant differences were noted with respect to number of past therapy attempts (p = 0.054). Eradication rates in patients infected with sensitive- and resistant-strains to metronidazole were 96.6% (28/29) and 96.3% (77/80) (p = 0.941), respectively, while rates in sitafloxacin were 98.4% (60/61) and 50.0% (1/2) ($p < 0.001$).
Conclusion: A sitofloxacin-based triple therapy with metronidazole and rabeprazole q.i.d. achieved an eradication rate exceeding 88%, irrespective of eradication history, CYP2C19 genotypes and metronidazole resistance. Especially, higher than 95% of patients infected with metronidazole resistant *H. pylori* strain were eradicated by this sitafloxacin-based regimen, suggested that this treatment might overcome metronidazole resistance. Recently, because prevalence of metronidazole-resistant strains of *H. pylori* was increased in many geographic areas, this treatment may be rescue regimen in areas with high prevalence of metronidazole resistance.
Disclosure of Interest: None declared

OP194 HELICOBACTER PYLORI ERADICATION RATES UPON ANTIBIOTIC SUSCEPTIBILITY TESTING

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Introduction: *Helicobacter pylori* infection is a major cause of dyspepsia, peptic ulcer and recognized cause of gastric cancer.
Aims & Methods: The objectives of this study were to evaluate the antibiotics resistance, efficacy of the therapeutic guided by antibiotic susceptibility, and to identify factors associated with antibiotic resistance and treatment failure. Retrospective study of patients who underwent culture guided treatment for *Helicobacter pylori* infection (after two eradication ineffective attempts), in a tertiary center, between October 2012 and January 2015. Demographic data, history of peptic ulceration, family history of gastric cancer, the antibiotic susceptibility results and success of the antibiotic susceptibility based therapy (with Helicobacter pylori antigen in stool) were recorded. Statistical analysis was performed with SPSS version 21.0 for Windows.
Results: We performed antibiotic susceptibility test in 38 patients, 60.5% (n = 23) female and 39.5% male (n = 15), mean age 49.7 years (22-71). There was resistance to macrolides in 92.1% of patients, metronidazole in 76.3%, ciprofloxacin in 52.6%, tetracycline in 2.6%. There was no resistance to amoxicillin or rifampicin. Most patients showed resistance to two antibiotics (47.4%), 39.5% were resistant to three or more antibiotics and 10.5% were resistant to only one antibiotic. In patients over 50 years there was a significantly higher proportion of resistance to three or more antibiotics (p = 0.020). The search of *H. pylori* antigen in feces was carried out in 47.4% of patients (n = 18): negative in 61.1% and positive in 38.9%. In patients with a positive result (eradication failure) there was a significantly higher proportion with resistance to three or more antibiotics (p = 0.049).
Conclusion: The success rate of treatment guided by antibiotic susceptibility test is low. Prevalence of resistance to antibiotics is very high. Patients over 50 years are resistant to multiple antibiotics and, in turn, the failure of treatment guided by the antibiotic susceptibility is higher in patients with resistance to multiple antibiotics.
Disclosure of Interest: None declared

OP195 EFFICACY OF VONOPRAZAN-BASED THERAPY IN H.PYLORI ERADICATION

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Introduction: Proton pump inhibitor (PPI)-based triple therapy is one of the most popular eradication therapy for *H. pylori* (HP) in the world.
However, first-line eradication rate has been decreasing in Japan.
One of the major reasons of this phenomenon is that HP acquired resistance to the clarithromycin (CAM). It is known that most antibiotic agents, including CAM are not effective under strong acidic condition. Therefore, in order to improve the eradication rate, gastric acid secretion must be reduced more rapidly and strongly.
Vonoprazan is newly developed potassium competitive acid blocker (P-CAB) and more effective in reducing gastric acid secretion than PPI.
Therefore, it is expected that we are able to obtain high eradication rate by using Vonoprazan.
Aims & Methods: The aim of this study was to clarify the effect of the Vonoprazan-based eradication therapy.
The subjects were 252 patients who were positive in urine antibody test. The patients who had gastric ulcer, duodenal ulcer, or gastric cancer were excluded. HP positive patients were grouped into two: Vonoprazan group (VG) and conventional PPI group (PG). We evaluated the first-, the second-, and the third-line eradication rate.
Each regimen of VG (Feb.2015-Mar.2015) was **7 days, Vonoprazan 20mg bid + AMPC750mg bid + CAM200mg bid (first-line eradication), 7 days,**

Vonoprazan 20mg bid + AMPC750mg bid +MNZ 250mg bid (second-line eradication), 14 days, Vonoprazan 20mg bid + AMPC 1000mg bid (third-line eradication).
The each regimen of PG (Feb.2014-Jan.2015) was **7 days, PPI bid + AMPC750mg bid +CAM200mg bid (first-line eradication), 7 days, PPI bid +AMPC750mg bid +MNZ 250mg bid (second-line eradication), 14 days, PPI bid +AMPC 1000mg bid (third-line eradication).**
One of the following PPI was used: Lansoprazole 30mg, Rabeprazole 20mg, Esomeprazole 20mg. After one month, HP status was assessed by 13C urea breath test. We investigated each regimen of VG and PG.
Results: The total number of VG patients was 62 and that of PG was 190.
The number of each regimen of VG was 40 in the first-line eradication, 14 in the second –line eradication, and 11 in the third-line eradication. The number of each regimen of PG was 125 in the first-line eradication, 41 in the second-line eradication, and 24 in the third-line eradication, respectively.
The first-line eradication was achieved in 92.5% in VG vs. 76.8% in PG ($p = 0.03$).
The second eradication was achieved in 100% in VG vs. 92.7% in PG ($p = 0.3$).
The third eradication was achieved in 100% in VG vs. 33.3% in PG ($p = 0.03$).
There was no significant difference in the eradication rate among PPI.
Conclusion: Vonoprazan-based regimen was superior to conventional PPI regimen.
From our result of the third-line eradication regimen, CAM may no longer be needed for HP eradication.
Disclosure of Interest: None declared

OP196 NON-BISMUTH QUADRUPLE "CONCOMITANT" THERAPIES IN THE ERADICATION OF HELICOBACTER PYLORI: STANDARD VS. OPTIMIZED (14 DAYS, HIGH-DOSE PPI) REGIMENS IN CLINICAL PRACTICE

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Introduction: Non-bismuth quadruple "concomitant" regimen is increasingly used as first-line *H. pylori* eradication treatment.
Aims & Methods: To evaluate the efficacy and tolerability of the standard and optimized "concomitant" regimens.
Design: Prospective multicenter study. *Patients*: Consecutive *H. pylori*-infected patients. *Treatment*: In a first phase, patients received a standard concomitant therapy (CONC10): omeprazole 20 mg, amoxicillin 1 g, clarithromycin 500 mg and metronidazole 500 mg for 10 days b.i.d. In a second phase, patients received the same regimen but with esomeprazole 40 mg b.i.d. and lasting 14 days (CONC14+). *Outcome*: Eradication was confirmed with ^{13}C-urea breath test 4-8 weeks after therapy. *Compliance/tolerance*: Compliance and adverse events were determined through questioning and recovery of empty medication envelopes.
Results: 1,000 consecutive patients were included (mean age 48 years, 47% males, 21% peptic ulcer): 370 in CONC10 and 630 in CONC14+. Compliance with both regimens was 95%. Per-protocol eradication rates with CONC10 and CONC14+ were 88% (95% CI = 85-91%) and 93% (92-95%) ($p < 0.01$). Respective intention-to-treat cure rates were 87% (83-89%) and 91% (89-93%) ($p < 0.05$). Adverse effects (mostly mild) were reported in 34% of patients in CONC10, and in 46% in CONC14+ ($p < 0.05$), the most common being metallic taste, diarrhea, nausea and abdominal pain. In the multivariate analysis, only compliance (OR = 4.7) and optimization of treatment (OR = 1.7) were associated with higher efficacy.
Conclusion: An optimized (14-day and high-dose esomeprazole) non-bismuth quadruple "concomitant" regimen is more effective than the standard one for the eradication of *H. pylori*, and achieves over 90% cure rate. Although the incidence of adverse events is higher with the optimized treatment, these are mostly mild, and do not negatively impact the compliance.
Disclosure of Interest: None declared

OP197 EVOLUTION ERADICATION RATES WITH SECOND-LINE THERAPY FOR HELICOBACTER PYLORI INFECTION AND FACTORS ASSOCIATED WITH ERADICATION THERAPY

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Introduction: In Spain, the rate of eradication of *Helicobacter pylori* with the first-line treatment with an inhibitor of the proton pump, amoxicillin and clarithromycin has been decreasing due to the high prevalence of resistance to clarithromycin. Therefore the second line eradication therapy with triple therapy containing fluoroquinolones is one of the recommended treatment options.
Aims & Methods: Assess the trend of eradication rates of *H. pylori* with second-line therapy (inhibitor of the proton pump, amoxicillin and levofloxacin) in patients who failed to standard triple therapy in our health area during the last four years and identify risk factors related to eradication failure.
We reviewed test of urea in breath obtaining a total of 2652 studies in the period January 2011 to December 2014, 145 patients were included with *H. pylori* infection that failed to standard triple therapy and received second-line therapy fluoroquinolone based. We retrospectively investigated *H. pylori* eradication rates with respect to the year of therapy as well as demographic and clinical factors. *H. pylori* eradication was confirmed by a 13C-urea breath test or a rapid urease test at least 4 weeks after the completion of triple therapy.
Results: The mean age +/- SD was 50.3 +/- 16.2 years. 63.4% women. The overall H. pylori eradication rate was 83.4%. Annual eradication rates from 2011 to 2014 were 91.2%, 70.6%, 80% and 85.3% respectively, by per-protocol analysis. The eradication rate in second-line triple therapy initially decreased and started to increase in efficiency over the last year during the last four years studied ($p = 0.078$). By clinical entity *H.pylori*, the eradication was 83.3% of functional dyspepsia and 84.2% of ulcer dyspepsia. Gastric and duodenal ulcers had an eradication rate of 66.7% and 88.9% respectively. Higher eradication rate for males 88.7% has been observed. The eradication rate in smokers was 88%, while in non-smokers 81.1% (p = ns)
Conclusion: In our health area the efficacy of second-line triple therapy for *H. pylori* infection has decreased in recent years with no-significant increase in the past year, according to the last four years studies. It suggests an increase of *H. pylori* strains resistant to antibiotics. Therefore, other second-line therapies may be necessary for the eradication of *H. pylori*. This therapy has superior efficacy in ulcer dyspepsia regarding functional dyspepsia and eradication greater in males.
Disclosure of Interest: None declared

OP198 EFFECTS OF COMMUNITY SCREENING FOR HELICOBACTER PYLORI: 13-YEAR FOLLOW-UP OF A RANDOMIZED CONTROLLED TRIAL (HEP-FYN)

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Introduction: Dyspepsia is a common condition and dyspepsia-related healthcare costs are high. Dyspeptic symptoms may improve after *Helicobacter pylori* (Hp) eradication in 10% of patients
Nearly all peptic ulcers are caused by either Hp infection or non-steroidal anti-inflammatory drugs (NSAID) use, including aspirin. Eradication of Hp reduces the recurrence of peptic ulcer from 80% to a few per cent in patients with Hp related peptic ulcers.
Recurrence after Hp eradication is rare. Population Hp screening and eradication seems an attractive option; ^{13}C-Urea Breath Test (UBT) is accurate, inexpensive and non-invasive and Hp can be permanently eradicated.
Aims & Methods: The aim of this study was to evaluate the long-term effect of population screening and eradication of *Helicobacter pylori* on dyspepsia prevalence and the incidence of peptic ulcer disease (PUD) and as secondary outcomes: to assess the effect on dyspepsia related health-care consumption and quality of life.
HEP-FYN is a prospective intervention study initiated in 1998 – 1999. At baseline 20,011 individuals aged 40 – 65 years were randomized to Hp screening and treatment or to the control group. Both groups received a questionnaire on dyspepsia and quality of life, at inclusion and after 1, 5 and 13 years. Register data on contacts to hospitals and general practitioners, comorbidity, use of endoscopies and prescription medication as well as socioeconomic factors were obtained for all randomized individuals. Complete Case analysis was performed for the outcome dyspepsia, while both per protocol and intention to treat analyses were possible for the outcome PUD. Risks were examined using logistic regression, providing odds ratios (OR) and 95% confidence intervals (CI).
Results: The participation rate at baseline was 63%. During the follow-up period 12% died or moved outside the Region of Southern Denmark. Those remaining, who had participated at the 5-year follow-up were invited to the 13-year follow-up, 8,658 (78%) of these participated. Screening for Hp did not reduce the prevalence of dyspepsia or the incidence of PUD significantly. Presence of dyspepsia at baseline was a strong predictor of dyspepsia after 13 years with an adjusted OR of 5.27 (95%CI: 4.67 – 5.95). Use of high-dose acetylacetic acid (ASA) or non-steroidal anti-iflammatory drugs (NSAID) increased the risk of dyspepsia. Age above 45 and higher level of education was associated with lower dyspepsia prevalence at the 13 years follow-up.
The incidence rate of PUD in nonparticipants was higher than for those enrolled. The strongest predictor of PUD was previous PUD. Odds of PUD increased with age, use of low dose asperin, and ASA/NSAID. Higher level of education was associated with a lower OR of PUD.
Except for use of proton pump inhibitors, which was significantly higher in the screened group compared to the control group, there were no significant differences in use of health resources between groups.
Hp screening had no long-term effect on quality of life.
Conclusion: This randomized clinical trial of population Hp screening and eradication with 13-years follow-up showed no significant long-term effect when compared to current clinical practice in this low prevalence area.
Disclosure of Interest: None declared

OP199 HELICOBACTER PYLORI ERADICATION ASSOCIATED WITH DECREASING LEVEL OF AUTOANTIBODIES TO THYROID PEROXIDASE

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Introduction: Previously the close relationship between *Helicobacter pylori* (HP) infection and autoimmune thyroid disease had been described. It is not known whether it is possible to reduce the progression of autoimmune thyroiditis via *H. pylori* eradication.
Aims & Methods: The aim of the study was to investigate the influence of successful HP eradication on level of the autoantibodies against thyroid peroxidase (anti-TPO) in patients with autoimmune thyroiditis.
Ninety eight HP-positive patients with autoimmune thyroiditis aged 52 ± 3 years were prospectively included in this study. The control group consist on thirty HP-negative subjects aged 54 ± 2 years suffered from autoimmune thyroiditis. The 14 days first-line therapy - clarithromycin 500 mg, pantoprazole 40 mg, amoxicillin 1 g twice a day had been prescribed to all patients. The anti-TPO level had been measured using ELISA kits before and after (on 15th, 30th day) eradication treatment. All patients gave written informed consent.
Results: The successful HP-eradication rate was 86%. We revealed dramatic reduction in the level of anti-TPO up to 62% ($p < 0.001$) on 30th day in successfully treated patients. We also noticed significant reduction in the severity of tissue inflammation on ultrasound pictures. Meanwhile in control group as well as in patients resistant to first-line therapy the the serum changes of anti-TPO were irrelevant (-4.8%; $p > 0.05$ on 30th day after eradication).
Conclusion: Our results support the hypothesis of a strong association between infection of *H. pylori* and development of autoimmune thyroiditis. The optimistic data of HP-eradication influence on anti-TPO level suggests the need for larger clinical trials and possible optimization of autoimmune thyroiditis diagnostic and treatment protocol.
Disclosure of Interest: None declared

OP200 INTERLEUKIN-22 IS A CRITICAL MEDIATOR OF VACCINE-INDUCED REDUCTION OF HELICOBACTER INFECTION IN THE MOUSE MODEL

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Introduction: Despite the proven ability of immunization to reduce *Helicobacter* infection in mouse models, the precise mechanism of protection has remained elusive.
Aims & Methods: In this study, we evaluated the role of IL-22 in the vaccine-induced reduction of *Helicobacter* infection.
Results: We first observed that IL-22 production is increased in the stomach during the vaccine-induced reduction of *Helicobacter* infection. These high IL-22 levels were associated with an increase production of antimicrobial peptides (AMP) such as RegIIIb by stomach epithelial cells. FACS analysis revealed that the main source of IL-22 is $CD4^+$ T cells especially IL-17 producing cells. In immunized mice, intraperitoneal injection of anti-IL-22 antibodies significantly impaired the vaccine-induced reduction of *Helicobacter* infection. Importantly, IL22-Fc injections to mice chronically infected with *Helicobacter* dramatically reduced bacterial load. Finally cationic AMP (AMPc) were extracted from stomachs and incubated with *Helicobacter* to evaluate their bactericidal effects. AMPc extracted from stomachs of vaccinated mice or mice injected with IL-22Fc kill *Helicobacter in vitro*. On the contrary, AMPc extracted from stomachs of non-immunized or immunized mice injected with anti-IL-22 antibodies did not kill *Helicobacter*.
Conclusion: Collectively theses results demonstrated that IL-22 plays a critical role in vaccine-induced reduction of *Helicobacter* infection, by inducing the expression of AMPc capable to kill *Helicobacter*.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 08:30-10:30
A GLOBAL VIEW ON LIVER CIRRHOSIS - ROOM E6

OP201 PRESEPSIN AS A NEW BIOMARKER FOR OLD EXPECTATIONS IN THE DIAGNOSIS AND PROGNOSIS OF BACTERIAL INFECTION IN CIRRHOSIS

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Introduction: Bacterial infections are frequent complications in cirrhosis with significant mortality. Early diagnosis is essential but still a diagnostic challenge from both the clinical and the laboratory part. The aim of this study is to evaluate and compare the diagnostic and prognostic value of presepsin plasma levels with CRP and PCT in bacterial infections of patients with cirrhosis.
Aims & Methods: A total of 216 patients with cirrhosis (54.4% males, age: 57.6 ± 10.3 years and median MELD score: 13 [95% CI: 10-17]) were consecutively enrolled. At admission enrollment presence of bacterial infection were assessed on the basis of conventional criteria, liver-oriented scores were calculated and plasma presepsin, CRP and PCT levels were measured. A short-term follow-up study was conducted to assess the development of organ system failure(s) and 28-day mortality associated to bacterial infections.
Results: Bacterial infection was found in 75 (34.7%) patients. Plasma presepsin levels were significantly higher in patients with infection as compared to those without (1002 pg/mL [575-2149] vs. 477 [332-680] pg/mL, $p < 0.001$), increasing correspondingly with the severity of the infection. Presepsin levels were obviously higher in infectious episodes (32%) complicated by organ dysfunction(s), namely acute-on chronic liver failure (ACLF) (32%), than those without (2358 pg/mL [1398-3666] vs. 710 pg/mL [533-1277], $p < 0.001$). The diagnostic accuracy of presepsin for identifying patients with severe infection was similar to PCT and clearly superior to CRP established by ROC analysis (AUC: 0.846, 0.845 and 0.659, respectively, p = NS for presepsin vs. PCT, and $p < 0.01$ for both the presepsin vs. CRP and PCT vs. CRP). At the optimal cut-off value of presepsin (>1206 pg/ml) sensitivity, specificity, PPV and NPV were as follows: 87.5%, 74.5%, 61.8% and 92.7%, respectively. Rate of 28-day mortality was higher among patients with >1277 pg/ml compared to those with ≤1277 pg/ml (46.9% vs. 11.6%, $p < 0.001$). In a binary logistic regression model, comprising gender, age, MELD score and acute phase proteins (APPs) one-by-one, MELD score >21 point (OR: 5.24, p = 0.025), PCT >0.5 pg/ml (OR: 9.10, p = 0.006) or CRP >40 mg/l (OR: 4.03, p = 0.039) but not presepsin level were independet risk factor for 28-day mortality.
Conclusion: Presepsin is a valuable new biomarker for defining severity of infections in cirrhosis proving same efficacy as PCT. However, for the prediction of short-term mortality, liver-oriented scores and admission level of conventional APP proteins, particularly PCT are the appropriate tools.
Disclosure of Interest: None declared

OP202 SPONTANEOUS FUNGAL PERITONITIS: A RARE BUT SEVERE COMPLICATION OF LIVER CIRRHOSIS

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Introduction: Spontaneous peritonitis (SP) is the most common infectious complication in liver cirrhosis, mainly due to bacteria. Although Spontaneous Fungal Peritonitis (SFP) is a rare condition, it is associated to worse outcome. This entity remains unclear.
Objective: Characterization, risk factors and prognosis in SFP.
Aims & Methods: Retrospective case-control study of 253 consecutive admissions by peritonitis in cirrhotic patients, between 2006-2014. SP diagnosis was considered if polymorphonuclear leukocytes >250 in ascitic fluid in intrabdominal infectious focus absence. It was selected patients with SFP (cases:8), that were compared with SBP with microbiologic analysis of ascitic fluid (controls:119). The variables evaluated were socio-demographic, clinic, cirrhosis etiology, cirrhosis severity, analysis, invasive procedures and prognosis.
Results: During period study, 231 patients developed SP and 8 SFP (3.5%; male: 75.0% vs 84.9%; p = 0.458 and mean age: 63.1 ± 11.2 vs 63.4 ± 8.6years; p = 0.955). Of SFP cases, 62.5% were co-infected with bacterial agent. In all cases were isolated *Candida spp*., mainly *Candida albicans* (37.5%) and *Candida krusei* (25.0%). Patients with SFP had more ascitic fluid lactate dehydrogenase levels (288.4 ± 266.6 vs 161.0 ± 179.5; p = 0.011), serum leukocytes (15187.5 ± 5432.3 vs 10969.8 ± 6949.5; p = 0.028), serum urea (69.8 ± 3.1 vs 36.3 ± 25.5; 9 = 0.001) and higher number of invasive procedures (colonoscopy: 25.0% vs 0.8%, p = 0.001; urinary catheterization: 87.5% vs 49.6%, p = 0.038; nasogastric intubation: 87.5% vs 26.9%, p = 0.001). There was no statistically significant difference between two groups relatively to MELD, MELD-Na and Child-Pugh scores. SFP was associated with worse prognosis, particularly more length of stay (30.0 ± 32.9 vs 18.9 ± 17.0days; p = 0.031), more admission-diagnosis time (15.8 ± 24.2 vs 2.1 ± 5.7dias; p = 0.001) and more global mortality (62.5% vs 31.9%; p = 0.039). The mortality rate at 30 days was statically significant higher in SFP (50.0% vs 24.4%; p = 0.034), with mean diagnosis-death time of 17.6 ± 11.5 days.
Conclusion: Despite a rare condition, SFP is a severe complication of liver cirrhosis associated with high mortality. The lactate dehydrogenase in ascitic fluid, serum leukocytes and urea, invasive procedures and more length of stay seem to be risk factors for SFP. Given only the ascitic fluid culture be able to differentiate spontaneous bacterial peritonitis and SFP, the clinical suspicion id crucial to early diagnosis and treatment.
Disclosure of Interest: None declared

OP203 BRAIN METABOLISM IN PATIENTS WITH MINIMAL HEPATIC ENCEPHALOPATHY ON 3.0-TESLA MAGNETIC RESONANCE SPECTROSCOPY

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Introduction: Minimal hepatic encephalopathy (MHE) is a clinical problem in liver cirrhosis (LC) patients. MHE involves cognitive dysfunction and poor driving skills, which lead to a decline in the patient's quality of life. Brain metabolism changes have been reported in patients with overt hepatic encephalopathy. However, these pathological changes remain to be investigated in patients with MHE.

Aims & Methods: Aims The aim of this study was to evaluate changes in the brain metabolism of MHE patients using high-resolution 3-Tesla (3T) ^{1}H (proton)−magnetic resonance spectroscopy (MRS).

Methods: We examined 21patients with liver cirrhosis [males, 15; females, 6; mean age, 60 years old (mean ± SD; 60 ± 12)].

The patients were evaluated for neuropsychiatric symptoms using the neuropsychiatric tests Digit symbol test (DST), Block design test (BDT) and Number connection test A, B (NCT A, B). MHE was diagnosed in patients who exhibited two or more abnormalities on these tests.

All patients were examined with ^{1}H (proton)−magnetic resonance spectroscopy (MRS) using 3T MRI. The findings were compared between the MHE group (7 patients) and the non-MHE group (14 patients).

Results: MRS study indicated that the brain glutamine (Gln) levels were significantly increased ($p < 0.01$) in the MHE group (Gln/Cre + PCre:2.05 ± 0.17) compared with the non-MHE group (Gln/Cre + PCre:1.05 ± 0.09) . In contrast, the brain myoinositol (mIns) levels significantly decreased ($p < 0.01$) in the MHE group (mIns/Cre + PCre:0.32 ± 0.04) compared with the non-MHE group (mIns/Cre + PCre:0.57 ± 0.04).

We also observed a significant negative correlation ($r = 0.767$, $p < 0.01$) between the brain Gln and mIns levels.

Blood tests revealed no significant differences between the MHE and non-MHE groups in the blood ammonia levels. However, a positive correlation ($r = 0.455$, $p < 0.05$) was noted between the blood ammonia and brain Gln levels, whereas a negative correlation ($r = 0.674$, $p < 0.05$) was noted between the blood ammonia and brain mIns levels .

Conclusion: The present results indicated that there is a marked increase in the brain Gln and a marked decrease in the mIns within the brain in patients with MHE compared with those without MHE. These data demonstrated that disturbed brain metabolism, similar to that observed in patients with overt hepatic encephalopathy, is also already present in patients with MHE.

In addition, the results suggested that the quantification of these phenomena using MRS could be useful for an early and objective diagnosis of MHE.

Disclosure of Interest: None declared

OP204 ASSOCIATION BETWEEN 90-DAY MORTALITY AND THE ALCOHOLIC HEPATITIS HISTOLOGICAL SCORE

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Introduction: The diagnosis of acute alcoholic hepatitis (AAH) may be based on clinical and biochemical data, but a definite diagnosis requires histological confirmation. A histological classification system has been recently proposed to predict 90-day mortality in patients with AAH.

Aims & Methods: To analyse the spectrum of histological findings in patients with AAH and assess the ability of alcoholic hepatits histological score (AHHS) to predict 90-day mortality.

Retrospective analysis of patients admitted to our department due to AAH, between November 2009 and October 2014, who underwent transjugular liver biopsy (TJLB). We analysed the following histological findings: cholestasis, steatosis, megamitochondria, Mallory bodies, necroinflammatory lesions, polymorphonuclear (PMN) infiltrate and satellitosis. The AHHS was calculated and we analysed the association between AHHS and 90-day mortality.

Results: Of 59 patients admitted due to AAH, 34 (57.6%) underwent TJLB (70.6% men, mean age 48.5 ± 8.9 years). BHTJ was performed 4.5 ± 2.9 days after admission. All patients had a METAVIR score = F4. Mortality at 90 days was 29.4%. The presence of cholestasis ($p = 0.05$), the absence of megamitochondrias ($p < 0.001$) and a higher AHHS ($p < 0.001$) were significantly associated with mortality at 90 days. There was no significant difference in steatosis, necroinflammatory lesions, PMN infiltrate and satellitosis. All patients with an AHHS ≥ 7 died (AUROC 1, sensitivity and specificity of 100%, $p < 0.001$).

Conclusion: In this group of patients with AAH, the presence of cholestasis and absence of megamitochondrias on histology were significantly associated with 90-day mortality. The AHHS was predictive of mortality at 90 days and may be used as an additional data in clinical decisions.

Disclosure of Interest: None declared

OP205 HIGH NUMBER OF OPPORTUNITIES IN PRIMARY AND SECONDARY CARE TO PREVENT ALCOHOL INDUCED CIRRHOSIS

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Introduction: Mortality from liver disease is higher in the UK than in most other European countries. As a result, recent attention has been placed on strategies that can be used to improve prevention of this disease.

Aims & Methods: The aim of this study was to describe patterns of healthcare utilisation of patients with alcoholic cirrhosis in order to identify factors that may be useful in the earlier identification of people at risk of alcoholic cirrhosis.

Methods: Patients with alcoholic cirrhosis and a matched control population of patients without the disease were identified in the UK's primary care Clinical Practice Research Datalink and secondary care Hospital Episode Statistics (HES) database (1990 and 2011). Health-care use in people with cirrhosis during the period prior to disease diagnosis was described and compared to that of the control population before a defined index date using Poisson regression. We also specifically examined co-morbidities present in patients as potential explanations to healthcare utilisation trends.

Results: 2,479 patients with cirrhosis and 24,790 controls were identified for analysis. For the 10-year period leading up to alcoholic cirrhosis diagnosis, there was a significantly higher rate of primary care visits in cases of cirrhosis than in controls (IRR 1.52, 95% CI (1.51 to 1.53)), with an average excess of 6.6 consultations per person year. The hospitalisation rate was also over two times higher for people with alcoholic cirrhosis than controls (IRR 2.49, 95% CI (2.42 to 2.54)). People with alcoholic cirrhosis were more likely than controls to present with morbidities reported to be partly attributable to alcohol. The most frequent morbidities in cases versus controls were intentional injuries (35.9% versus 11.9%) and cardiovascular diseases (23.2% versus 15.6%), followed by diabetes (12.8% versus 5.3%), digestive diseases (6.1% versus 1.2%) and epilepsy (5.0% versus 1.1%). Multivariate analyses showed that digestive diseases (OR 5.4, 95% CI 4.4-6.7), epilepsy (Odds ratio 4.4, 3.5-5.5) and injuries (OR 4.0, 3.7-4.4) had the strongest association with subsequent development of alcoholic cirrhosis.

Conclusion: Up to 10 years before alcoholic cirrhosis is diagnosed, patients have more frequent encounters with primary and secondary care than the general population, especially for conditions which are partly attributable to alcohol (e.g. injuries, epilepsy, digestive diseases). These results show that through monitoring of healthcare attendances, it may be possible to identify patients who may develop alcohol-related liver cirrhosis, and therefore intervene, at an earlier stage in the disease course.

Disclosure of Interest: None declared

OP206 ANTICOAGULANT TREATMENT AND DECOMPENSATION RATE IN PATIENTS WITH LIVER CIRRHOSIS

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Introduction: Anticoagulant treatment in patients with liver cirrhosis (LC) is still controversial. Recent studies demonstrated that anticoagulant treatment could reduce decompensation and mortality rates in cirrhotic patients. Our aim was to evaluate decompensation rate in patients with LC and atrial fibrillation treated with acenocoumarol for thrombotic events prophylaxis.

Aims & Methods: The study group included patients diagnosed with compensated liver cirrhosis and atrial fibrillation treated with an oral anticoagulant (acenocoumarol), admitted in a tertiary center between January 2011 and December 2011. The control group included consecutive patients diagnosed with LC, matched by age, etiology and liver stage disease with the study group. All patients were regular follow-up since December 2014 or until first hepatic decompensation (ascites, hepatic encephalopathy, variceal bleeding) occurred.

Results: The study included 78 patients diagnosed with compensated LC and atrial fibrillation, mean age 62.36 ± 11.27 years at diagnosis, 48 (61.53%) males. The majority of the patients were diagnosed with alcoholic LC- 41 patients (52.56%). The control group included 78 cirrhotic patients who received no anticoagulant treatment. There were no differences regarding baseline characteristics and LC severity between the two study groups. Mean follow-up period was 82.5 ± 3.25 month. During the follow-up period 48 patients (30.7%) developed hepatic decompensation in both study groups of whom 5 died. The cumulative decompensation rate was 17.9% in the study group and 38.6% in the control group, respectively ($p < 0.0001$). The rate of decompensation was higher in the first year in both groups. There were two cases of epistaxis in the study group, and 4 cases of variceal bleeding in both groups, with no other major bleeding side effect to anticoagulant treatment.

Conclusion: Anticoagulant treatment in patients with LC is relatively safe, and may improve patient outcome and decrease decompensation rate, despite association of atrial fibrillation.

Disclosure of Interest: None declared

OP207 DISTURBANCES OF GASTRIC EMPTYING, INTESTINAL ABSORPTION, PERMEABILITY AND GUT HORMONES IN PATIENTS WITH CHRONIC LIVER DISEASE: POTENTIAL MECHANISMS UNDERLYING POOR ORAL INTAKE AND MALNUTRITION

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Introduction: Malnutrition is common in patients with chronic liver disease. Disturbed gastrointestinal function as well as poor appetite are thought to be the likely underlying mechanism for malnutrition in these patients. Although delayed gastric emptying and increased intestinal permeability have been reported in patients with liver cirrhosis, their relationship to gut hormones, small intestinal absorption and gastrointestinal symptoms remains unclear.

Aims & Methods: The aim was to evaluate the inter-relationship between gastric emptying, intestinal permeability, glucose absorption, gastrointestinal hormones glycaemia and post-prandial appetite in patient with chronic liver disease. **Methods:** Comprehensive physiological studies were performed in 20 patients with liver cirrhosis (16M:4F, 55.7±1.8 years, 10 Childs A, 7 Childs B, 3 Childs C, 12 alcoholic liver disease, 8 hepatitis C), and data were compared to those from 10 healthy controls (5M:5F, 39.0±6.4 years). After an overnight fast, all subjects underwent assessment of (i) gastric emptying of a mixed meal using scintigraphy, comprising of 50g beef patty (labelled with ^{99m}Tc calcium phytate) and 150mL glucose drink (labelled with 3MBq ^{67}Ga-EDTA), (ii) intestinal permeability using a dual sugar test (1g rhamnose and 7.5mL lactulose added to glucose drink), (iii) intestinal glucose absorption by 3-O-methyl-glucose absorption test (3g added to glucose drink), (iv) blood glucose and gut hormones (insulin, glucagon-like peptide-1, and peptide YY) were measured over 240minutes, and (v) post-prandial gastrointestinal symptoms using visual analogue scales (VAS).

Results: Compared to healthy controls, gastric emptying was delayed in 35% of patients with liver cirrhosis with overall prolonged meal retention (26.7±4.4% vs 12.3±2.9% retention at 100min, $p = 0.04$). Intestinal permeability was significantly increase in patients with cirrhosis. Patients with liver cirrhosis also had significantly higher intestinal permeability (63.8±6.1 vs 3.9±1.2, $p < 0.0001$), post-prandial blood glucose ($p = 0.02$) and plasma GLP-1 levels ($p = 0.018$), but attenuated rise in post-prandial plasma insulin ($p < 0.001$) and 3-OMG ($p = 0.004$). More importantly, there was a significant delay in the recovery of post-prandial appetite VAS ($p < 0.001$) at 4 hours. Small intestinal glucose absorption, as assessed by area under the curve of plasma 3-OMG, correlated inversely with both gastric half emptying time (t1/2) (r = -0.6, p = 0.025) and intestinal permeability (r = -0.76, $p = 0.001$).

Conclusion: Subjects with chronic liver diseases have a wide range of gastrointestinal dysfunction, characterising by delayed gastric emptying, impaired small intestinal barrier, reduced intestinal glucose absorption, and persistent elevation of appetite suppressing gut hormone, GLP-1. Together, these factors are the contributors of delayed recovery of post-prandial appetite, which in turn lead to a viscous cycle of nutritional deprivation, gut dysfunction, malabsorption and malnutrition. Early recognition and management of gut dysfunction, therefore, are important in patient with chronic liver diseases.

Disclosure of Interest: None declared

OP208 EFFECT OF DIFFERENT THERAPEUTIC MODALITIES ON SYSTEMIC, RENAL AND HEPATIC HEMODYNAMICS IN CIRRHOTIC PATIENTS WITH SPONTANEOUS BACTERIAL PERITONITIS

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Introduction: Spontaneous bacterial peritonitis (SBP) is a major risk factor for hepatorenal syndrome (HRS). One third of patients with SBP will develop HRS despite appropriate treatment with non-nephrotoxic antibiotics. Albumin infusion has been shown to prevent renal impairment and reduce mortality in high risk patients with SBP. However, albumin is expensive, has limited supply, and is a potential risk of infection transmission.

Aims & Methods: The study aimed to compare the effect of different therapeutic modalities on systemic, hepatic and renal hemodynamics and clinical outcome in high-risk patients with SBP. Two hundreds cirrhotic patients with SBP and bilirubin >4 mg/dL or creatinine >1 mg/dL were enrolled. Patients were randomized to receive albumin, terlipressin, low-dose albumin plus terlipressin, or midodrine. Systemic, renal and hepatic hemodynamics were estimated at baseline, 3 and 10 days of treatment. Renal impairment was diagnosed when the blood urea nitrogen or serum creatinine levels increased by more than 50% of the pretreatment value.

Results: SBP resolved in most of patients in all groups ($p > 0.05$). Cardiac output (CO) decreased and systemic vascular resistance (SVR) increased significantly in Terlipressin and albumin plus terlipressin groups compared to albumin group after 3 & 10 days ($p < 0.05$). Also, portal flow decreased significantly in both groups after 3 & 10 days ($p < 0.001$). After 10 days, plasma renin activity, renal and hepatic arteries resistive index (RI) were significantly higher in midodrine group compared to albumin group. Midodrine group didn't show any significant changes in heart rate, mean arterial pressure, CO and portal blood flow compared to albumin group after 3 or 10 days. There was no significant difference in mortality or development of renal impairment between all groups.

Conclusion: Terlipressin, low dose Albumin plus Terlipressin and Midodrine could be used as a therapeutic alternative to standard dose albumin in high-risk SBP patients.

Disclosure of Interest: None declared

OP209 SARCOPENIA AND OBESITY AMONG LIVER TRANSPLANTATION RECIPIENTS: A BODY COMPOSITION PROSPECTIVE STUDY

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Introduction: Muscle wasting, or sarcopenia, is a condition in which severe muscle depletion is observed. Recently, many studies have shown that sarcopenia is highly prevalent before transplantation (>50%) and it is considered a risk factor for increased morbidity and mortality. After transplantation, some authors have pointed out that sarcopenia arrests and, as patients gain too much weight as fat, this results in sarcopenic obesity when both conditions co-exist.

Aims & Methods

Aims: To prospectively verify changes in body composition, prevalence of sarcopenia, obesity and sarcopenic obesity in long-term liver transplantation (LTx) recipients after surgery.

Methods: Patients were evaluated in two moments for body composition, in 2008 and 2012, in average, 3.9±3.2 and 7.5±3.1 years after LTx. Body composition data (i.e., fat-free mass and fat mass) were obtained using bioelectrical impedance (RJL Systems® Quantum, Clinton Township, MI, USA). Fat-free mass index (FFMI) and fat mass index (FMI) (kg/m^2) were calculated and, patients classified in groups according to the following combination in: sarcopenia (low FFMI and normal FMI); obesity (normal FFMI and high FMI); sarcopenic obesity (low FFMI and high FMI) and normal body composition (normal FFMI and FMI). Low FFMI (≤17.4kg/m^2 in men and 15.0kg/m^2 in women) and high FMI (≥8.3kg/m^2 in men and 11.8kg/m^2 in women) were the cutoff values used to compare parameters (Kyle et al., 2012).

Results: A total of 113 patients were evaluated (53.1±13.2 years; 58.4% male). FFMI decreased and FMI increased over the years after surgery (Table 1). Prevalence of sarcopenia, obesity and sarcopenic obesity also increased over the years, but not significantly. Sarcopenia was prevalent in 1/5 and obesity in 1/3 of patients in the long term after LTx. Although these conditions were highly prevalent in these patients, they did not coexist since only two patients (1.8%) were diagnosed with sarcopenic obesity. Less than half of the patients had normal body composition in the long-term after LTx.

Table 1: Fat-free mass and fat mass index, prevalence of sarcopenia, obesity, sarcopenic obesity and normal body composition among long-term liver transplantation recipients over four years

	Fat-free mass index	Fat massindex	Sarcopenia	Obesity	Sarcopenic obesity	Normal
2008	17.6±2.5kg/m^2	7.8±3.4kg/m^2	22 (19.5%)	34 (30.1%)	0 (0.0%)	57 (50.4%)
2012	17.1±3.6kg/m^2	8.2±3.9kg/m^2 *	24 (21.2%)	37 (32.7%)	2 (1.8%)	50 (44.2%)

Paired t and Mc Nemar test; * $p < 0.05$

Conclusion: Fat mass increased over the years after surgery and lean mass, decreased, although not significantly. Sarcopenia and obesity were highly present after LTx with increasing prevalence over the years leading to less than half of the population presenting with normal body composition. However, sarcopenic obesity was not a reality observed in these patients. As survival after liver transplantation has improved, these patients should be followed for body composition changes and early intervention.

Abstract number: OP208

Variables		Albumin N = 50	Terlipressin N = 50	Albumin plusTerlipressin N = 50	Midodrine N = 50	p
Resolution of SBP		48 (96%)	48 (96%)	47 (94%)	46(92%)	0.787
Duration of hospital stay		10.2±0.6	10.2±0.8	10.1±0.6	10.4±0.9	0.839
Renal impairment	In hospital	5 (10%)	4(8%)	4(8%)	11 (22%)	0.092
	Within 30 days	7 (14%)	7 (14%)	7 (14%)	15 (30%)	0.090
Mortality	In hospital	4 (8%)	3 (6%)	3 (6%)	9 (18%)	0.124
	Within 30 days	12 (24%)	11 (22%)	10 (20%)	17(34%)	0.377

Reference

1. Kyle UG, et al. *Clin Nutr* 2005; 24: 133–42.

Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 08:30–10:30

PROGRESS IN ENDOSCOPIC BILIARY IMAGING AND INTERVENTIONS – ROOM B3

OP210 PROSPECTIVE RANDOMIZED STUDY OF ENDOSCOPIC BILIARY STONE EXTRACTION USING EITHER A BASKET OR BALLOON CATHETER: THE BASKETBALL STUDY

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Introduction: Presently, endoscopic extraction after endoscopic sphincterotomy (ES) is recognized worldwide as the first-line treatment for bile duct stones. Stones smaller than 10 mm in diameter can usually be extracted from the bile duct after ES, without crushing them. For this purpose, a retrieval basket is generally used in Japan and Europe, but a retrieval balloon is mainly used in the USA. Both of these devices appear to show similar success rates of stone extraction. However, the efficacies of these 2 devices have not been previously compared.
Aims & Methods: The present multicenter, prospective, randomized study was performed to compare the efficacies of basket and balloon catheters for endoscopic biliary stone extraction. This study included 184 patients from 6 Japanese institutions with bile duct stones smaller than 10 mm in diameter, with no limitation in the number of stones. After the stones were identified and size of the largest stone was confirmed smaller than 10 mm with ERCP, the patients were randomly assigned to either undergo endoscopic stone extraction using a basket catheter or undergo it using a balloon catheter. The primary end point was complete removal rate of biliary stones within 10 minutes, and the secondary end point was complications related to the procedure.
Results: The patients were assigned to the basket group in 91 patients and to the balloon group in 93 patients. Baseline characteristics, such as age, male/female ratio, number of stones, size of stones, and diameter of the bile duct, were not significantly different between the basket and balloon groups. Stone extraction was successful within 10 minutes in 81.3% (74/91) of patients in the basket group and in 83.9% (78/93) of patients in the balloon group (P = 0.5584). Among the patients with failed extraction within 10 minutes, complete stone extraction was successful after 10 minutes using the same device in 3 and 0 patients, and was successful with exchange of the device in 9 and 9 patients in the basket and balloon groups, respectively. Complete extraction failed at the initial session in 5 and 6 patients in each group. The main reasons for failed extraction were that the basket could not grasp small stones in the basket group and the balloon passed aside a stone impacted in the corner pocket at the lower end of the bile duct in the balloon group. The complication rates were 6.6% and 11.8% in the basket and balloon groups, respectively (P = 0.3092), and they included bleeding (2.2% vs. 6.5%), pancreatitis (3.3% vs. 4.3%), and cholangitis (1.1% vs. 1.1%).
Conclusion: Basket and balloon catheters showed similar efficacies for endoscopic biliary stone extraction. (Clinical trial registration number: UMIN000010486)
Disclosure of Interest: None declared

OP211 A MULTICENTER RANDOMIZED TRIAL OF ENDOSCOPIC PAPILLARY LARGE BALLOON DILATION ALONE VERSUS ENDOSCOPIC SPHINCTEROTOMY FOR REMOVAL OF BILE DUCT STONES: MARVELOUS TRIAL

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Introduction: Removal of large common bile duct (CBD) stones by endoscopic papillary large balloon dilation (EPLBD) with endoscopic sphincterotomy (EST) has been proven safe and effective. Little evidence supports the benefits of a preceding EST in reducing complications. Recent studies suggest that large CBD stone removal by EPLBD alone without EST may be safe and effective.
Aims & Methods: This multicenter randomized trial was conducted at 19 institutions in Japan to compare the efficacy and safety of EPLBD alone versus EST for removal of large CBD stones (UMIN-CTR number, 000010012).
Between February 2013 and January 2015, 181 patients over 60 years of age with large CBD stones (≥10 mm) and dilated distal CBD (≥12 mm) were randomly assigned to groups that underwent EPLBD alone or EST. The primary outcome was the rate at which complete stone removal was achieved in the first session, and secondary outcomes included complete stone clearance rate, use of lithotripsy, stone removal time, early complications, and procedure cost.
Results: After randomization, 10 patients were excluded because of not fulfilling the inclusion criteria (n = 4), incorrect diagnosis (n = 4), withdrawal of consent (n = 1), and biliary cannulation failure (n = 1). 7 patients who did not receive the allocated treatment were also excluded. Finally, data from 164 patients were analyzed (82 in each group). Patient characteristics such as age, sex, ASA score, stone number, stone size, CBD diameter, and periampullary diverticulum were similar in both groups. The rate of complete stone removal in the first session was significantly higher in the EPLBD alone group than in the EST group (92.7% vs. 80.5%, $P = 0.037$). The complete stone clearance rate was similar in both groups (100% vs. 96.3%, $P = 0.245$). The use of lithotripsy was significantly less frequent in the EPLBD alone group than the EST group (28.0% vs. 46.3%, $P = 0.023$). Stone removal time was similar in both groups (36.1 min vs. 40.3 min, $P = 0.464$). The overall early complication rate was 9.8% in each group. The rate of post-ERCP pancreatitis was similar in both groups (4.9% vs. 6.1%, $P = 1.000$). No perforation occurred in either group. Hemorrhage occurred in 1 patient in the EST group. The procedure cost was significantly lower in the EPLBD alone group (USD $1354 ± 730 vs. $1619 ± 834, $P = 0.032$).
Conclusion: EPLBD alone without EST is safe and more effective than EST for the treatment of large CBD stones.
Disclosure of Interest: None declared

OP212 PEDIATRIC BIOPSY FORCEPS VS SPYBITE FORCEPS COMPARISON AT THE DIAGNOSIS OF BILIARY STRICTURES: A RANDOMIZED STUDY

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Introduction: The accuracy of histological diagnosis for biliary strictures is low and is increased using at least two ERCP-samples collections techniques (brushing, biopsies and puncture). In this context, the effectiveness of the Spybite forceps is unknown.
Aims & Methods: To compare the histological diagnosis performance of standard pediatric biopsy forceps (PS) vs Spybyte biopsy forceps (SB) in the biliary strictures by any cause diagnosis.
Methods: Open label randomized prospective controlled trial (February 2009 - January 2011). Participants: The consecutive patients with biliary strictures detected in ERCP. Intervention: A brushing cytology of strictures was done in all patients during ERCP and immediately after the biopsies were randomly obtained by SP or SB. Main outcome measures: Diagnosis performance according to forceps biopsy type. Secondary outcomes measures: Feasibility of the access into the bile duct (number of passes), endoscopist (capability to obtain tissue) and nurse (watching the biopsies in a sample jar) impression of the quality and number of samples, according to the biopsy forceps type. The biliary stricture diagnosis was confirmed by the clinical follow up during 1 year and the histology report from the surgery.
Results: 101 patients with biliary strictures were included, (Age: 72.57 ± 13.20; 41♂) 71 malignant strictures, 86% extrahepatic strictures; SP group: 44; Sb group 57. We achieved ≥4 forceps access into the bile duct in 84%; 1-3 tissue pieces in 48.4% and > 3 in 51.6%. The number of samples was greater with SP than SB (≥3: 79.5% vs 54.4%; p = 0.008) and the tissue samples were considered good by the endoscopist in 53.5% and 55.4% by the nurse. The histological analysis of ERCP-samples were: Lack or insufficient tissue 21.2%, normal biliary epithelium 23.2%, inflammatory 25.3% dysplastic 15.2% (low grade: 8.1%; high grade: 7.1%), tumor 15.2%. The correct diagnosis was done in 59.4% (n = 60); SP: 65.9% vs. SB: 54.5%; p = 0.16. The biliary access (> 3 passes) was better with SP (93.1 vs 84.1%; p = 0.048). The impression of quality samples was better with SP for the endoscopist (p = 0.186) and the nurse (SP 77.3% vs. SB 38.6%; p = 0.001).
Conclusion: The histological performance (cytology + biopsy) of biliary strictures by ERCP is 59.4% without differences in forceps type. The access and obtaining tissue in biliary strictures is better with the standard pediatric biopsy forceps.
Disclosure of Interest: None declared

OP213 EFFECT AND IMPACT OF PROBE-BASED CONFOCAL LASER ENDOMICROSCOPY (PCLE) IN THE DIAGNOSIS AND MANAGEMENT OF INDETERMINANT BILIARY STRICTURES

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Introduction: Extrahepatic cholangiocarcinoma (ECCA) remains a highly fatal disease that is difficult to diagnose due to poor yields from standard tissue sampling methods. pCLE has been shown to improve the accuracy of diagnosis of ECCA, potentially expediting diagnosis, saving unnecessary further testing and allowing earlier initiation of treatments.

Aims & Methods: The aims of this study were to assess the diagnostic and therapeutic impact of pCLE on the management of patients with indeterminate biliary stricture, specifically comparing ERCP with tissue sampling (TS) vs. ERCP with pCLE and TS.

The FOCUS trial was a prospective multicenter evaluation of the performance of pCLE in the diagnosis of indeterminate biliary strictures. A retrospective analysis of data was performed. During the FOCUS trial, managing physicians were asked prospectively to give a presumptive diagnosis on the basis of ERCP images with pCLE information and ERCP images with pCLE and TS. Answers were recorded and compared to final diagnosis. The final diagnosis was established by positive tissue sampling or surgical pathology in cases of malignant disease, and by negative tissue sampling, negative imaging (no mass) and a benign clinical course at 6 months of follow-up. Furthermore, treatment decisions were also recorded by the managing physician, based respectively on information with and without pCLE. Treatment recommendations were considered ***"appropriate"*** if the recommended treatment corresponded to the final diagnosis or ***"inappropriate"*** if the recommended treatment did not correspond to the final diagnosis. Additional testing required for diagnosis were recorded. Time to correct diagnosis (TCD) was measured as time until positive tissue diagnosis was established OR time until a correct presumptive diagnosis was made (based on pCLE and/or TS). In cases of incorrect presumptive diagnosis in cases with malignant disease, TCD was made was deemed time to correct diagnosis. In cases of benign disease, time to correct diagnosis was considered 6 months if no presumptive diagnosis was made.

Results: 107 of the 121 patients from the FOCUS trial were evaluable.

Overall TCD was reduced from 71 days without pCLE to 15 days with pCLE. In patients with negative TS, the TCD was reduced to 89 days when pCLE information was applied.

The addition of information from pCLE to a standard approach with ERCP + TS alone increased the appropriateness of treatment management decisions from 59% to 74% (15%) and reduced the need of additional diagnostic procedure by 15%, without impairing the rate of inappropriate treatment recommendations.

In patients with indeterminate tissue sampling, the ERCP + pCLE + TS sampling approach increased the number of appropriate recommendation by 22% as compared with the standard approach and decreases the number of additional procedures by 24% without increasing the number of inappropriate procedure recommendations.

Conclusion: pCLE appears to have a beneficial effect on the diagnosis and treatment of indeterminate biliary strictures. Use of pCLE appears to decrease TCD and may reduce the number of extra diagnostic procedures required to establish a diagnosis.

Disclosure of Interest: None declared

OP214 A U.S. MULTI-CENTER FIRST HUMAN USE EXPERIENCE USING THE FULLY DISPOSABLE, DIGITAL SINGLE-OPERATOR CHOLANGIOPANCREATOSCOPE (DSOCP)

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Introduction: A new fully disposable catheter-based digital single-operator cholangiopancreatoscope (DSOCP) has recently received U.S. FDA clearance. It has a complementary metal-oxide semiconductor (CMOS) chip for high resolution, magnification, and wider field of view; a thin copper cable provides digital transmission and the lack of a separate fiberoptic probe may enhance tip articulation.

Aims & Methods

Aim: Document indications, interventions, success, and qualitative impression of the digital image. The DSOCP (SpyDS^{TM} Boston Scientific, Marlborough, MA) has 4-way tip deflection, 10.5F tip, 1.2mm working channel, and 120 degree field of view. Data from a limited release of DSOCP to five centers with expertise in cholangioscopy was collected. Technical success was defined as achieving the intended diagnostic or therapeutic intent. Each expert qualitatively assessed the digital image and ease of use on a visual analog scale (VAS) of 0 to 10.

Results: Since February 2015, five institutions performed 124 DSOCP and 121 were evaluable. Indications: indeterminate extra- (n = 54) or intrahepatic biliary stricture (n = 17), extra- (n = 20) or intrahepatic (n = 3) stones, cystic duct stones (n = 6), extra- (n = 12) or intrahepatic ductal dilatation (n = 1), pancreatic duct stones (n = 7), and pancreatic stricture (n = 1). Eight of these patients underwent DSOCP to assess cholangiocarcinoma extent. Technical success was achieved in all cases. Directed tissue sampling using Spybite^{TM} forceps (Boston Scientific) was obtained in 53 cases. Thus far, 32 patients have established neoplasia; 22/24 (92%) without a prior tissue diagnosis of neoplasia were confirmed by SpybiteTM forceps. One or more benign findings in patients with strictures or ductal dilatation included concentric stenosis or normal/erythematous changes (n = 17), low papillary mucosal projections (n = 9), coarse granular mucosa (n = 8), and nodular mucosa (n = 8). One or more neoplastic findings included "tumor vessels" (n = 14), infiltrative stricture (n = 14), villous or nodular mass (n = 9), and finger-like villous projections (n = 6). Two patients with DSOCP impression of neoplasia underwent surgery and were found to have benign disease. For biliary and pancreatic stones, complete ductal clearance has been achieved in 34/36 (94%). Stone fragmentation required electrohydraulic lithotripsy (n = 8) and laser lithotripsy (n = 18) and each of these cases had prior incomplete clearance. DSOCP also identified unsuspected stones or confirmed ductal clearance (n = 8). Two have ongoing therapy. The mean VAS for image quality and ease-of-use was 9.5. Complications: pancreatitis (n = 1), abdominal pain (n = 1), cholangitis (n = 1).

Conclusion: 1) This first human use report using the digital single-operator cholangiopancreatoscope demonstrates high technical success in a variety of complex pancreaticobiliary disorders. 2) The rate of obtaining confirmatory tissue sampling using directed Spybite sampling was over 90% in patients without a prior diagnosis of neoplasia. 3) The rate of ductal stone clearance is nearly 100%. 4) DSOCP provides enhanced image resolution and tip articulation and in expert hands may improve the ability to target difficult biliary and pancreatic stones, as well as, intraductal pathology for tissue sampling.

Disclosure of Interest: R. Shah Consultancy: Boston Scientific Endoscopy, I. Raijman Consultancy: Boston Scientific Endoscopy, R. Hawes: None declared, B. Gumustop: None declared, M. Hasan: None declared, B. Brauer: None declared, N. Fukami: None declared, D. Pleskow Consultancy: Boston Scientific Endoscopy

OP215 CAN ENDOSCOPIC PAPILLECTOMY BE CURATIVE FOR EARLY ADENOCARCINOMA OF THE AMPULLA OF VATER ?

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Introduction: According to the TNM classification of ampullary tumors, pT1 adenocarcinoma is limited to the ampulla of Vater without infiltration of the duodenal muscularis propria. The risk of lymph node metastasis (N+) rounds 20% in Western surgical series. The Japanese classification subdivide pT1 lesions in d0 tumours, confined to the sphincter of Oddi (risk N+ = 0%), and d1 tumours invading the duodenal submucosa (risk N+ = 30%). Japanese surgeons consider a d0 lesion without vascular embols, as an early cancer that should be cured by a local resection. At the moment, no series has evaluated if endoscopic papillectomy (EP) is curative in this situation.

Aims & Methods: To evaluate in which cases an endoscopic papillectomy could be considered as curative in ampullary adenocarcinoma.

From May 1999 to July 2014, patients with ampullary tumors (adenoma +/- adenocarcinoma), staged as uT1 at endoscopic ultrasound, undergone EP and were prospectively included in a database. Histopathological data, follow-up (FU) of patients and factors that predict lymph node metastases were analyzed retrospectively.

Results: 172 patients with ampullary tumors undergone EP during the study period. Adenocarcinoma was present on the resected specimen in 25 cases (mean age 70 years). A complementary pancreaticoduodenectomy (PD) was proposed in case of positive resection margins (R1), vascular embols, or submucosal invasion. In 11 cases (Group 1), the invasion was limited to the Oddi's sphincter (d0). In 14 cases (Group 2) there was an invasion of the duodenal submucosa (d1).

Group 1 (n = 11): Five patients (45%) had negative margins of resection (R0), no vascular embols and normal biopsies at the post resection control. No recurrence was evidenced during FU (mean 56 months (18-96)). Six patients (55%) had positive resection margins, one with vascular embols. A complementary PD was done in 3 patients (1 d1N-, 1d1N+, 1 without residual tumor). Three patients had contraindications or refused surgery and were followed. There was no cancer recurrence or disease related death in two cases (FU: 36 and 72 months). One patient had a cancer recurrence and was finally operated on 6 months later (pT3N+).

Group 2 (n = 14): Ten patients (71%) were R1 and four (29%) R0. Vascular embols were present in 5 cases (36%). Eight patients had an additional PD; 6 were N + (62%) +/- residual adenocarcinoma (n = 4; 50%) and two were free of tumor. The other six patients had contraindications or refused surgery. During FU (mean 24 months (12-48)) the cancer recurred in 3 patients (1N+, 1 local recurrence, 1 M+ liver), 2 patients died from complications of chemotherapy and one remained alive without recurrence at 24 months.

Tumor size (P = 0.027) and infiltration of the submucosae (P = 0.033) were found to be significantly related to lymph node metastasis.

Conclusion: In agreement with the Japanese classification, this study confirms that the prognosis of T1 carcinoma of the ampulla of Vater is very different whether or not submucosal invasion is present. EP can be considered as curative when the resection specimen evidence an adenocarcinoma limited to the Oddi's sphincter, no vascular embols, and R0 resection. In other cases, an additional PD should be discussed.

Disclosure of Interest: None declared

OP216 PROSPECTIVE RANDOMIZED TRIAL OF WIRE-GUIDED PAPILLECTOMY VERSUS CONVENTIONAL PAPILLECTOMY FOR AMPULLARY TUMORS

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Introduction: Concerns about endoscopic snare papillectomy (ESP) include technical difficulties and the risk of procedure-related pancreatitis. To maintain pancreatic duct access for stent placement after ESP, wire-guided ESP was introduced.

Aims & Methods: The aim of study was to compare the success rate of inserting a pancreatic stent, post-procedure pancreatitis rates, procedure time, and complete resection rates between wire-guided endoscopic snare papillectomy (WP) and conventional ESP (CP) procedures.

Methods: This was a multi-center, prospective, randomized study. Forty-five patients with ampullary tumors were assigned randomly to the WP group (a pancreatic stent was placed along a previously inserted guidewire immediately after snare resection) or the CP group (post-resection pancreatic stent insertion).

Results: A total of 51 patients were enrolled, 25 in the WP and 26 in the CP group. Complete resection was achieved in 24 patients (96%) in the WP group and 21 patients (81%) in the CP group ($p = 0.094$). A pancreatic stent was placed successfully in all patients in the WP group but in only 18 patients (69%) in the CP group ($p = 0.003$). Post-papillectomy pancreatitis occurred in 3 (11%) patients in the WP and 3 (12%) patients in the CP groups ($p = 0.960$). In the CP group, 3 of 8 (37.5%) patients without stents developed pancreatitis compared with 0 of 15 patients with stents ($p = 0.032$). One patient without a pancreatic stent experienced severe pancreatitis.

Conclusion: The WP method is a useful technique used to insert a pancreatic stent after an endoscopic papillectomy, compared with CP. However, there was no significant difference in the post-procedure pancreatitis or complete resection rates between the two methods.

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Disclosure of Interest: None declared

OP217 A PLEA FOR SELECTIVE USE OF STAGING LAPAROSCOPY FOR POTENTIALLY RESECTABLE PERIHILAR CHOLANGIOCARCINOMA: AN ANALYSIS OF 265 PATIENTS

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Introduction: Staging laparoscopy (SL) for potentially resectable perihilar cholangiocarcinoma (PHC) may detect unresectable disease and therefore prevent unnecessary laparotomy. The diagnostic yield, however, remains unclear with varying results reported in the literature and a possible decrease over years with improvement of imaging techniques.

Aims & Methods: The aim of the present study was to identify predictors of unresectable disease at SL that can be used to select patients who may benefit most from this procedure. Data of patients with suspicion on potentially resectable PHC who underwent SL between 2000 and 2014 in an academic medical centre were retrospectively analysed. The yield and accuracy (sensitivity) of SL were calculated by dividing total number of avoided laparotomies by the total number of laparoscopies or by all patients with unresectable disease, respectively. Factors that were potentially associated with unresectable disease at SL were investigated.

Results: A total of 265 patients underwent SL and unresectable tumours were detected in 39 patients (yield 15%). Eighty-three patients had unresectable disease upon laparotomy. Overall accuracy of SL was 32% with the highest sensitivity to detect peritoneal metastases (72%). Factors associated with unresectable disease at SL were Blumgart T-stage ($P = 0.007$), tumour size ($P = 0.03$), suspicious hilar lymph nodes ($P = 0.03$) and suspected metastases ($P < 0.001$) on imaging without the possibility for diagnosis by percutaneous puncture. On multivariable analysis, Blumgart T3 stage (odds ratio [OR] 2.5; $P = 0.02$), tumour size $\geq$5 cm (OR 3.6; $P = 0.04$) and suspected metastases on imaging (OR 6.5; $P < 0.001$) were revealed as independent predictors for unresectable disease at SL. The observed yield in the study cohort increased from 6% (no predictors) up to 14-43% (1 predictor), 46-100% (2 predictors) and 100% (3 predictors).

Conclusion: Staging laparoscopy in PHC should be targeted at 'high-risk' patients with Blumgart T3 stage, large tumour size or suspected metastatic lesions on imaging without the possibility for diagnosis by percutaneous biopsy.

Disclosure of Interest: None declared

OP218 MINILAPAROTOMY CHOLECYSTECTOMY VERSUS LAPAROSCOPIC CHOLECYSTECTOMY WITH HARMONIC SCALPEL – A PROSPECTIVE, RANDOMISED MULTICENTER TRIAL

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Introduction: Laparocopic cholecystectomy (LC) is the gold-standard operative technique for the treatment of symptomatic gallstone disease. However, minilaparotomy cholecystectomy (MC) has shown to have similar early recovery after surgery. Monopolar cauterization hook is most commonly used for dissection in LC because of the ease of securing haemostasis and low costs. Ultrasonic dissection (UsD) has later shown to be safe and effective in LC. Furthermore, we were the first to apply UsD in MC (1). A review of literature and our previous results suggest that UsD applied to either MC or LC leads to a shorter convalescence, less postoperative pain and complications compared to classic dissecting approaches. To our knowledge, there are no trials comparing the use of UsD in MC vs LC.

Aims & Methods: 99 patients with non-complicated symptomatic gallstone disease were randomized to MC (n = 51) or LC (n = 48) over a period of 2-years (2013-2015). UsD was used in both groups. The study was a prospective, randomised, multicentre trial and the procedures, anaesthesia protocol and postoperative care were standardized. Operative time, time at the operation theatre, perioperative bleed, complications and conversions were recorded. Postoperative pain was assessed at 1h, 2h, 3h, 4h after surgery using an 11-point numeric rating scale (NRS). Nausea, the amount of analgesics and antiemetics used, day surgery success and the length of hospitalization were recorded. Patients were interviewed at 24h after the surgery by phone.

Results: Demographic variables were similar in both groups. There was no difference in the time at the operation theatre (minutes): 116 (SD, 26) in the MC group, vs 125 (37) in the LC group, (p = 0.230), or operative time (minutes): 67 (26) in the MC group, vs 68 (26) in the LC group, (p = 0.81). No complications occurred in either group and conversion rate was alike (1 in MC vs 3 in LC, p = 0.28). Postoperative pain (NRS) was similar: at 1h in MC 3.5 (2.2) vs in LC 3.3 (2.4), (p = 0.52), at 2h (2.3 (1.8) vs. 2.4 (2.0), p = 0.91), at 3h (2.2 (1.7) vs 1.6 (2.1), p = 0.10), and at 4h (1.7 (1.8) vs 1.5 (1.8), p = 0.54) after surgery. Day surgery success rate (66% in MC vs 77% in LC, p = 0.31) and length of hospitalization (1.4 (0.6) vs 1.3 (0.5) days, p = 0.40) was similar. There was no difference in pain at 24h after surgery during rest, but LC patients reported less pain at normal activity (3.9 (2.3) vs 2.9 (2.4), p = 0.05) and quick movement 8.8 (2.3) vs 3.2 (2.6), p = 0.005. The use of analgesics during the first 24h was similar in both study groups.

Conclusion: UsD can be safely and effectively applied to MC with no significant difference compared to LC using UsD.

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Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 08:30–10:30

ABSTRACTS ON FIRE: UPPER GI CANCER-MECHANISMS AND CLINICAL ASPECTS – HOTSPOT

OP219 A PHASE II MULTICENTER PROSPECTIVE STUDY OF THE TRASTUZUMAB COMBINED WITH 5-WEEKLY S-1 AND CDDP THERAPY FOR PATIENTS WITH METASTATIC OR UNRESECTABLE HER2-POSITIVE GASTRIC CANCERS

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Introduction: S-1 and CDDP therapy was considered the standardized primary treatment for patients with metastatic or unresectable gastric cancers based on the results of SPIRITS trial. According to ToGA study, the combination therapy with trastuzumab and cisplatin plus capecitabine or 5-fluorouracil has been used as a standard regimen for metastatic or unrespectable HER2-positive gastric cancer. Regarding the effectiveness of trastuzumab combined with triweekly S-1 and CDDP therapy, it was reported that overall survival (OS) was 16.0 months, and 1-year OS rate was 67.9% in HERBIS-1 study. However, no studies have evaluated the efficacy and safety of trastuzumab combined with the 5-weekly S-1 and CDDP therapy, for HER-2 positive gastric cancer.

Aims & Methods: This study (UMIN000005792) was conducted between July 2011 and June 2014. Patients with metastatic or unresectable HER2-positive gastric cancer received S-1 (80-120mg per day) orally on days 1-21, cisplatin (60mg/m^2) intravenously on day 8, and trastuzumab (8mg/kg for first cycle on day 8, and 6 mg/ kg for subsequent cycles by every 3 weeks) intravenously. The primary end point was 1-year OS rate, and secondary end point included OS, progression-free survival (PFS), response rate (RR), and toxicity profiles.
Results: A total of 22 patients were enrolled. Two patients were ineligible for the study, and we analyzed 20 patients (16 men and 4 women; median age, 66 years old). 1-year OS rate was 66.8%, the confirmed RR was 38.4%, the median PFS was 7.5 months, and OS was a state of non-arrival.We recorded grade 3 or 4 adverse events including anorexia (30%), neutropenia (30%), general fatigue (20%), anemia (15%), nausea (15%), diarrhea (15%), and thrombocytopenia (10%).
Conclusion: Trastuzumab combined with 5-weekly S-1 and CDDP therapy was effective treatment for patients with metastatic or unresectable HER-2 positive gastric cancers. The toxicities in the patients were manageable level in the patients. 1-year OS rate in our study was nearly equal to that in HERBIS-1 study.
Disclosure of Interest: None declared

OP220 THE ASSOCIATED FACTORS FOR THE DEVELOPMENT OF METACHRONOUS GASTRIC CANCERS AFTER ENDOSCOPIC SUBMUCOSAL DISSECTION FOR EARLY GASTRIC CANCERS

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Introduction: *Helicobacter pylori (H. pylori)* is known as a major carcinogen for gastric cancer. In addition, there is evidence of an increased risk of gastric cancer related to gender, tobacco smoking, obesity, and so on. However, regarding the development of secondary gastric cancers after endoscopic resection for early gastric cancers, there are still many debates even about whether *H. pylori* is an independent risk factor. Furthermore, the other risk factors for the development of secondary gastric cancers have remained unclear.
Aims & Methods: The aim of this study was to clarify the associated factors for the development of metachronous gastric cancer in patients who underwent endoscopic submucosal dissection (ESD) for the early gastric cancers. Secondary gastric cancers detected within 1 year after ESD for early gastric cancers were considered synchronous rather than metachronous in this study. The patients with early gastric cancers treated by ESD between June 2003 and November 2012 at our institution were enrolled. The exclusion criteria were as follows: patients with a history of gastrectomy, patients with additional gastrectomy after ESD for early gastric cancer, and patients with a follow-up period of less than 12 months. In addition to the investigation of the development of secondary gastric cancers, the associated factors for the development of metachronous gastric cancers was also calculated by Cox hazard regression analysis. The estimated factors were age (<60 or ≥ 60 years), gender, BMI (<25 or ≥ 25 kg/m^2), *H. pylori* eradication, and current tobacco smoking and drinking (on the day of diagnosis of first gastric cancer). We further investigated the detailed relationship between tobacco smoking and the development of metachronous gastric cancers by pack-years (PY), classified into never, PY <20, and PY ≥ 20.
Results: A total of 539 patients (mean age = 69.4 years) were analyzed with a mean follow-up of 53.6 months. There was no missing value about the estimated factors except for PY, which had 7 missing values (1.3%). The 5-year cumulative incidence of secondary gastric cancers was 13.0% with 18 cases within 1 year and 53 cases after 1 year from the initial ESD. The rates of *H. pylori* eradication, current smoking, and current drinking were 39.3%, 42.3%, and 27.5%, respectively. Multivariate analysis exhibited that age ≥ 60 years (4.04 [1.22-13.3]) and current smoking (2.11 [1.19-3.76]) were the independent risk factors for the development of metachronous gastric cancers. There was no significant association between eradication of *H. pylori* and the development of these cancers. Regarding the detail of tobacco smoking, multivariate analysis by adjusting age, gender, BMI, eradication of *H. pylori*, and current drinking showed that PY ≥ 20 (1.52 [1.03-2.23]) was a significant risk factor for the development of metachronous gastric cancers with a dose-response relation (P for trend = 0.042).
Conclusion: In addition to age ≥ 60 years, we firstly demonstrated by multivariate analysis that tobacco smoking was an independent risk factor for the development of metachronous gastric cancers after ESD for early gastric cancers, with a dose-response relation.
Disclosure of Interest: None declared

OP221 MODULATION OF BMP4 FUNCTION BY LLAMA-DERIVED NANOBODIES: A NOVEL APPROACH TO OVERCOME CHEMORESISTANCE IN COLORECTAL CANCERS

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Introduction: Colorectal cancers (CRCs) are the most frequently occurring malignancy in western countries. Advanced stage CRCs are highly aggressive cancers characterized by chemo-resistance and poor patient outcomes. One pathway that has been shown to be disregulated in the progression of CRC is the Bone Morphogenetic Protein (BMP) pathway. BMPs are a group of about 20 growth factors for which both tumor suppressor and tumor promoting functions have been described. Albeit increased expression of BMP4 has been observed in CRCs, the exact role of BMP4 and its downstream signaling pathways with respect to cancer behavior still remains unknown.
Aims & Methods: Understanding the diverse roles of BMP4 has been hampered by the lack of highly specific BMP inhibitors. Although significant progress has been made in generating highly specific and less toxic BMP inhibitors, natural antagonists as well as chemical inhibitors are still non selective. These inhibitors present elevated off-target effects, most likely due to inactivation of other BMPs with beneficial anti-tumour effects, such as BMP6 and BMP7. Indeed, indiscriminate BMP inhibition has been shown to activate dormant metastatic breast tumour cells or increase colonic tumour burden *in vivo*. To resolve and inhibit the individual action of BMP4 in colorectal cancer, we aimed at generating potent and specific BMP4 inhibitors.
Results: We recently generated a llama-derived nanobody which selectively binds to BMP4. Its binding affinities are greater than those published for Noggin, a natural BMP antagonist, and for conventional anti-BMP4 antibodies. Nanobodies are promising clinical tools with a growing number of benefits compared to conventional antibodies such as low immunogenicity, cost-effective production, high stability, consistent activity and ease of manipulation. Here, we show how this BMP4-specific nanobody represents a promising therapeutic strategy for chemosensitization of colorectal cancer cells. First, a set of different CRC cell lines was tested for the expression and secretion of BMP4. We found that certain CRC cell lines specifically secrete BMP4, but not other BMPs, and these BMP4high profile is associated with enhanced chemoresistance. Next, an aggressive gene signature profile was identified by analyzing expression profiles of patient-derived BMP4high cancers in relation to malignant features and aggressive behavior of the tumors. Finally, selective inhibition of BMP4 using our anti-BMP4 nanobody rendered the aggressive CRC cells more sensitive to chemotherapy, supporting the therapeutic potential of anti-BMP4 nanobody in aggressive CRC.
Conclusion: In sum, we have developed a highly potent BMP4-specific antibody that represents a promising therapeutic strategy for sensitizing colorectal cancer cells to chemotherapy. Its novel structural format makes it remarkably suited to overcome the limitations that affect the clinical and research applications of current BMP inhibitors.
Disclosure of Interest: None declared

OP223 RISK FACTORS FOR PROGRESSION OF ENDOSCOPICALLY DIAGNOSED INTRAMUCOSAL GASTRIC CANCER

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Introduction: Endoscopic submucosal dissection (ESD) is now a widely accepted procedure as a curative treatment of early, especially intramucosal,

Abstract number: OP223

		Univariate analysis	Multivariate analysis	
	N	p-value	Hazard ratio	p-value
Age (per 10-yr increment)	181	0.677	1.71 (1.11-2.65)	0.015
Location (L)	42	0.783		
Location (M)	89		1.46 (0.57-3.74)	0.43
Location (U)	50		1.42 (0.49-4.07)	0.52
Morphology				
(Flat or Deplessed/Protruded or Flat elevated)	132/49	0.144	0.90 (0.31-2.64)	0.85
Mucosal background (Atrophy/Fundic glands)	164/17	0.112	3.96 (1.32-11.87)	0.014
Pathological diagnosis (Yes/No)	41/140	0.664	1.34 (0.58-3.10)	0.5
Sex (M/F)	148/33	0.334	1.78 (0.58-5.45)	0.31
Tumor size (per 10mm increment)	178	0.0412	1.32 (0.95-1.83)	0.1

gastric cancer. However, indication of ESD for patients with high age and/or severe comorbidity is still controversial.
Aims & Methods: In this study, we retrospectively investigated natural history and risk factors for progression of intramucosal gastric cancer (IGC) to help better understanding of indication of ESD in such patients. Records of 1462 lesions which were endoscopically and pathologically diagnosed as gastric cancer in our hospital between January 2011 and December 2014 were screened. Among them, previous records of esophagogastroduodenoscopy (EGD), which were performed after January 2006 and more than 6 month before the index EGD with conceivable pictures of the index gastric cancer, were available in 184 lesions. Among them, three lesions were diagnosed as gastric cancers with submucosal invasion based on their endoscopic findings at the time of previous EGD, and the remaining 181 lesions were endoscopically diagnosed as IGC and were in included in this study; a mean of intervals to the index EGD was 39 months as long as 22.6 months. One hundred and forty lesions were diagnosed at the time of this review of the records, and biopsies had been taken from the other 41 lesion with pathological diagnosis of adenoma (31 lesions) or cancer (10 lesions). Statistical differences were calculated using the Mann-Whitney U-test and the Fisher's exact test. Risk factors for progression of IGC to submucosal or advanced cancer were analyzed by Cox proportional hazards regression model.
Results: In the 181 lesions, 145 lesions were still IGC at the index EGD, and 36 lesions progressed to submucosal or advanced cancer. With regard to pathological diagnosis at time of index EGD, the proportion of well differentiated adenocarcinoma was significantly higher in the lesions which remained in IGC (118/145, 81.3%) than those which progressed to submucosal or advanced cancer (4/36, 11.1%)($p < 0.0001$, Fisher's exact test). Elder age (hazard ratio, 1.7; 95% confidence interval, 1.1-2.7, $p = 0.015$) and cancer at the fundic gland area (4.0; 1.3-11.9, $p = 0.014$) were identified as significant factors for the progression of IGC to invasive cancer by analysis with the Cox's proportional-hazards model.
Conclusion: IGC at the fundic gland area in elderly patients might be invasive and have indication for ESD.
Disclosure of Interest: None declared

OP224 THE EFFICACY OF THE SERUM PEPSINOGEN FOR PREDICTING THE METACHRONOUS GASTRIC NEOPLASM AFTER ENDOSCOPIC RESECTION FOR EARLY GASTRIC CANCER

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Introduction: The aim of this study is to evaluate the efficacy of the serum pepsinogen (PG) concentration level for predicting development of metachronous gastric dysplasia and cancer after endoscopic resection (ER) for early gastric cancer (EGC) and to evaluate other risk factors for the incidence of metachronous gastric dysplasia and cancer.
Aims & Methods: We enrolled 429 patients who were tested serum PG level at the time of ER for EGC, from January 2008 to December 2013 in Kyungpook National University medical center, Daegu, Korea, retrospectively. The baseline characteristics of the patients such as final *H. pylori* status, serum pepsinogen, pathologic findings of resected specimen after ER were analyzed for the development of the metachronous gastric neoplasm.
Results: The patients were divided on the basis of the 3 of serum concentration PG I/II ratio level. Overall, 165 patients (38.5%) were belonged into the serum PG I/II levels of ≤ 3 group and 264 patients (61.5%) were belonged into the > 3 group. During the follow-up period, 52 metachronous gastric lesions were found (10 gastric dysplasias and 42 gastric cancers). Metachronous gastric dysplasia or cancer were significantly developed in serum PG I/II ≤ 3 group ($p = 0.047$) and persistent *H. pylori* infection group ($p = 0.041$) on univariate analysis (Table 1). On multivariate analysis, persistent *H. pylori* infection (OR = 2.094, 95% CI = 1.034-4.239, $p = 0.040$), the serum PG I/II ratio ≤ 3 at the time of ER (OR = 0.027, 95%CI = 1.076-3.491, $p = 0.027$) were correlated with an increased incidence of subsequent gastric dysplasia or cancer after endoscopic resection of EGC.
Conclusion: Serum PG I/II ratio at the ER resection is a good indicator for predicting development metachronous gastric cancer after ESD for EGC and persistent *H. pylori* infection could increase the risk of metachronous gastric neoplasm after ER for EGC.
Disclosure of Interest: None declared

OP225 CLINICOPATHOLOGICAL CHANGES OF EARLY GASTRIC CANCER OVER TIME FROM SUCCESSFUL ERADICATION OF HELICOBACTER PYLORI

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Introduction: *Helicobacter pylori* (*H.pylori*) is one of important carcinogens in gastric cancer. There have been many reports that the eradication of *H.pylori* could prevent gastric cancer. However, we sometimes detect early gastric cancer (EGC) after successful eradication.
Aims & Methods: The aim of this study is to clarify the detected interval and clinico-pathological features of EGCs after successful eradication by retrospective assessment. A total of 748 EGCs were treated by endoscopic resection at University Hospital, Kyoto Prefectural University of Medicine from January 2009 to October 2014. Among them, 246 EGCs were certainly occurred in the mucosa of *H.pylori*-associated chronic gastritis (*H.pylori*-positive) and 69 EGCs were detected after successful eradication (*H.pylori*-eradicated). These 315 EGCs were enrolled in this study. Firstly, we investigated the detected interval of *H.pylori*-eradicated EGCs from successful eradication. Then, we classified *H.pylori*-eradicated EGCs into two groups: "early detection (ED) group" and "late detection (LD) group" according to their detected interval from eradication (more about this later). We compared clinico-pathological features among ED group, LD group and *H.pylori*-positive EGCs ("HP group"). Clinico-pathological features including age, gender, tumor size, location, macroscopic type, histological type were reviewed according to Japanese Classification of Gastric Carcinoma. The background gastric mucosal atrophy was assessed endoscopically according to the Kimura-Takemoto classification.
Results: The median interval from eradication to detection of EGCs was 36 months (range, 0.2-132 months). Among them, 47 EGCs (68.1%) were detected within 4 years after eradication. The number of EGCs detected within 4 years was substantially greater than those of over 4 years. Interestingly, we still detected EGCs for more than 10 years after eradication. Based on the result described above, we defined ED group as EGCs detected within 4 years after eradication and LD group as EGCs detected over 4 years. In ED group, the mean size of EGCs was significantly smaller than that found in HP group(10mm vs 12mm, P = 0.02), and the macroscopic morphology tended to be flat or depressed type(78.7% vs 65.8%, P = 0.12). In LD group, the mean age was significantly younger than HP group(65.6 y.o vs 67.9 y.o, P = 0.048). EGCs in LD group were mainly found on open type (severe) atrophic mucosa. In contrast, EGCs on close type (mild) atrophy were detected more than HP group(27.3% vs 6.9%, P = 0.006). In addition, all the histological type in LD group was differentiated predominant type.
Conclusion: In this study, the most prominent clinico-pathological feature of EGCs between ED group with HP group was the macroscopic morphological changes. After a long period having passed since eradication (like LD group),

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	Non-metachlonous lesion group (N = 377)	Metachlonous lesion group (N = 52)	Univariate P-value
Sex			0.747
Male : Female	262 (69.5%) : 115 (30.5%)	38 (73.1%) : 14 (26.9%)	
Mean age (years)	61.0 (23-82)	64.0 (45-84)	0.581
Location			0.333
Proximal	20 (9.5%)	2 (7.4%)	
Middle	52 (24.6%)	4 (7.1%)	
Distal	139 (65.9%)	21 (77.8%)	
Lesion size(mm)	15.8 (2-80)	17.3 (5-40)	0.364
Histologic type			0.832
Differentiated	360 (95.6%)	50 (96.2%)	
Undifferentiated	17 (4.4%)	2 (3.8%)	
SM invasion	22 (5.8%)	2 (3.8%)	0.451
Persistent H. pylori infection	52 (13.8%))	13 (25.0%)	0.041
Pepsinogen I/II ratio < 3	138 (36.6%)	27 (51.9%)	0.047
The change of Pepsinogen I/II ratio			0.102
Decreased	132 (35.0%)	19 (36.5%)	
Increased or not changed	245 (65.0%)	33 (63.5%)	
Follow up period (Median, Months)	46 (32-84)	38 (24-60)	0.259

different features seem to appear in detected EGCs. The endoscopist should pay great attention to these changes that occur over time after eradication therapy, and it is necessary for *H.pylori*-eradicated patient to conduct follow-up examination for a long time.
Disclosure of Interest: None declared

OP226 T1B OESOPHAGEAL ADENOCARCINOMA: RETROSPECTIVE COHORT STUDY ON PATIENT MANAGEMENT AND RISK OF METASTATIC DISEASE

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Introduction: Oesophagectomy for submucosal (T1b) oesophageal adenocarcinoma (OAC) is generally advised in order to optimize patient outcome given the risk of concurrent (occult) LN metastasis (LNM). However, not seldom, severe comorbidity precludes these patients from surgery.
Aims & Methods: Our aim was to assess the proportion patients referred for surgery, and to evaluate the incidence of metastatic disease in T1b OAC.
Methods: Between 2001 and 2011, all patients undergoing diagnostic endoscopic resection (ER) for OAC in two centres in the Netherlands were reviewed. Only patients with histopathologically proven submucosal tumour invasion were included. Based on the ER specimen, submucosal OAC's were divided into tumours which were removed radically (R0; tumour-negative vertical resection margin (VRM)) and irradically (R1; tumour-positive VRM). Subsequently, in the R0-group, OACs were classified as either low-risk (LR; submucosal invasion $<$ 500nm, G1-G2, no lymphovascular invasion) or high-risk (HR; deep submucosal invasion $>$ 500nm, and/or G3-G4, and/or lymphovascular invasion). Data on patient management (oesophagectomy versus conservative management) and outcome were assessed. Metastatic disease was defined as either LNM in surgical resection specimen, or evidence of malignant disease during follow-up (FU).
Results: 69 patients (55 male, median age 70 years) with a submucosal OAC were included, of which 23 patients underwent an endoscopic R1-resection, and 46 a R0-resection. Of the R0-resections, 14 were classified as LR, and 32 as HR. Oesophagectomy was performed in 7% of the R0-LR patients, in 38% of the R0-HR patients, and in 57% of the R1-group. None of the 14 R0-LR patients developed metastatic disease after a median FU of 60 months. In the R0-HR group, evidence of metastatic disease was found in 16% of patients (2/12 oesophagectomy patients, 3/20 non-surgical patients). In the R1 group, metastatic disease was diagnosed in 30% of patients (4/13 oesophagectomy patients, 3/10 non-surgical patients). Despite oesophagectomy, 2 surgical patients developed distant metastasis. During FU, 19 (44%) of the 43 non-surgical patients died: 5 due to disease progression (median survival 18 months), and 14 due to unrelated causes (median survival 32 months).
Conclusion: In superficial submucosal OAC (G1-G2, no LVI, radical resection), the risk of metastatic disease is very low: endoscopic treatment should thus be preferred. In deep submucosal OAC (and/or G3, and/or LVI, and/or R1-resection), the rate of metastatic disease is lower than reported in earlier surgical series. Moreover, oesophagectomy does not always cure disease. Given the reasonable disease-free survival and high background mortality, conservative management of these patients seems to be a valid alternative for surgery in selected cases.
Disclosure of Interest: D. Schölvinck: None declared, H. Künzli: None declared, S. Meijer: None declared, K. Seldenrijk: None declared, J. Bergman Financial support for research: Olympus Endoscopy, Cook Medical, Boston Scientific, Gi Solutions Covidien, Erbe, Ninepoint Medical, Consultancy: Gi Solutions Covidien, Boston Scientific, Cook Medical, B. Weusten Financial support for research: Cook Medical, Boston Scientific, Gi Solutions Covidien, C2 Therpeutics, Consultancy: C2 Therapeutics, Boston Scientific

OP227 LINE1-PCR: A NEW, CLINICALLY APPLICABLE SEQUENCING TOOL FOR THE DETECTION OF GENOMIC INSTABILITY IN GASTROINTESTINAL MALIGNANCY

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Introduction: Several gastrointestinal (GI) cancers involve the development of genomic instability during their progression. One manifestation of this is copy number aberrations (CNAs) such as amplifications and deletions- also a potential biomarker of progression from preneoplastia. Although technologies exist to recognize CNAs they may not give sub-chromosomal resolution, are too expensive to implement clinically or require technical expertise and therefore are still not automatable. Repeat genomic sequences such as LINE1 are ubiquitous. We hypothesized that these could be used to give an accurate measure of genomic instability by PCR using a single primer pair. The inherent low level of diversity in the repeats would allow us to align amplicons uniquely to the reference genome. From this we could derive sub-chromosomal copy number changes and demonstrate genomic instability.
Aims & Methods: 1) To use LINE1-PCR as a reliable, fast and simple test using a single primer pair to determine copy number changes in gastrointestinal cancer. 2) To compare the resolution of LINE1 PCR with whole genome sequencing (WGS) for the detection of clinically relevant copy number changes. A consensus sequence covering a number of LINE1 subfamilies was used to perform a two round barcoding PCR reaction optimized for next generation sequencing. To optimize the analysis of the number of raw sequences obtained 15 germline blood samples for which results were available for whole genome sequencing (WGS) were chosen. Criteria for determining the optimal number of reads with minimal variation were determined. 36 oesophageal adenocarcinoma tumour samples which had already undergone WGS then underwent LINE1 PCR and were quantitatively compared to WGS for CNA detection. An additional 51 non dysplastic Barrett's samples were also sequenced along with and 32 matched blood samples as controls. All sequencing was performed on a MiSeq (150 bp single end read) (Illumina, USA) sequencer.
Results: Comparison of CNAs between WGS and LINE1-PCR demonstrated an average detection rate of 93% (range 100-90%) for copy number changes over 0.5Mb. A score of genomic instability derived from a count of the number of $>$0.5Mb CNAs was able to distinguish tumour samples from diploid and non dysplastic samples (mean CNAs of control and tumour samples: 4.25 (range: $0-8.0$), and tumour samples 64.5 (range: $4-162$) respectively; Student's t-test p value 0.0015). Tumour samples with low CNAs (n = 4), detected by LINE1-PCR, were also confirmed to be low CNA samples as determined by WGS. The preparation for all samples from tissue collection to MiSeq submission was 3.5 hours regardless of the sample number. The current cost per sample for the entire workflow is £12. The minimum total DNA input is 2ng for FFPE and 0.5ng for frozen tissue.
Conclusion: LINE1-PCR is a fast and simple method for the determination of genomic instability. Its strength lies in its ability to localise CNAs at a comparable resolution to WGS as well as give an overall index of genomic instability with a markedly cheaper and faster workflow making it ideal for the clinic. We envisage that this new technique will be of use in the diagnosis of other malignant and premalignant diseases both within and outside of the GI tract.
Disclosure of Interest: None declared

OP228 SURGERY PLUS POSTOPERATIVE CHEMOTHERAPY AND/OR RADIOTHERAPY FOR T4 ESOPHAGEAL CANCER: TREATMENT OUTCOMES AND PROGNOSTIC FACTORS

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Introduction: Esophagectomy is the mainstay of treatment for patients with T1-T3 esophageal cancer. However, some patients are intraoperatively diagnosed as T4 esophageal cancer. Here we discuss the effectiveness of esophagectomy in these patients.
Aims & Methods: The aim of this study is to clarify the usefulness of esophagectomy in patients who were diagnosed as T4 esophageal cancer intraoperatively. Fifty-four patients (17%) were diagnosed as T4 disease intraoperatively among the 324 patients of thoracic esophageal cancer who underwent esophagectomy at our institution, between 2001 and 2012.
Results: The invasive organ was the mediastinal pleura (n = 23), the diaphragm (n = 11), the major airway (n = 12), the lung (n = 8), the pericardium (n = 7), the aorta (n = 6), and others (n = 8). Eighteen patients had invasive organs in two and more. Among these 54 patients, 16 (30%) received R0 resection, 20 (37%) received R1 resection, and the other 18 (33%) received R2 resection. As postoperative treatment, 27 patients received chemoradiotherapy, 13 received chemotherapy, and 5 received radiotherapy, while the other 9 received surgery alone. The overall median survival was 17months, and the overall 5-year survival was 26%. By univariate analysis, an improved survival was associated with tumor location (upper thoracic), residual tumor (R0/R1), postoperative treatment (present), lymphovascular invasion (absent), and the number of lymph nodes metastasis ($\leqq$ 2). Age, gender, site of other organ with invasion, number of other organs with invasion, histology, and tumor differentiation each did not affect survival. By multivariate analysis, the residual tumor (R0/R1 vs. R2: hazard ratio 0.230; 95% confidence interval 0.107–0.494; P = 0.0002), postoperative treatment (present vs. absent: hazard ratio 0.095; 95% confidence interval 0.034–0.267; $P < 0.0001$) and the number of lymph nodes metastasis ($\leqq$2 vs. 3 $\leqq$: hazard ratio 0.251; 95% confidence interval 0.112–0.538; P = 0.0003) were each an independent prognostic factor. The 5-year survival rate of those patients achieving R0/R1 was 32%, compared with 17% for R2 (P = 0.0243). The 5-year survival rate of those patients who received postoperative treatment was 32%, compared with 0% of those who received surgery alone (P = 0.0007). Of the 9 patients who received surgery alone, none survived more than two years.
Conclusion: Esophagectomy might be effective in patients achieving R0/R1 surgery, even if it is diagnosed as T4 esophageal cancer during the surgery. Furthermore, postoperative treatment may offer improvement in the prognosis for such patients with T4 esophageal cancer.
Disclosure of Interest: None declared

OP229 LONG NONCODING RNA COLON CANCER-ASSOCIATED TRANSCRIPT 2 PROMOTES TUMOR METASTASIS AND REGULATES EPITHELIAL-MESENCHYMAL TRANSITION IN ESOPHAGEAL SQUAMOUS CELL CARCINOMA

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Introduction: Esophageal squamous cell carcinoma (ESCC) is a common cause of cancer death worldwide[1]. Long noncoding RNAs (lncRNAs) have been reported to be of crucial importance in the progresses of many diseases, and lncRNA colon cancer-associated transcript 2 (CCAT2) which was firstly found overexpressed in colorectal cancer was reported to be up-regulated in ESCC too[2, 3]. Epithelial-mesenchymal transition (EMT) is a process by which epithelial cells switch from the epithelial phenotype to the mesenchymal phenotype, accompanied with the ectopic expressions of EMT-related genes[4]. EMT is a pivotal event for most cancer cells to acquire metastasis ability, as well as for ESCC cells[5]. However, previous studies have not shown any connections between lncRNAs and EMT in ESCC.

Aims & Methods: In the present study, we mainly focused on the functional changes caused by knockdown of CCAT2 and the EMT-related genes expressions in ESCC cells. Expression of CCAT2 was analyzed in 50 ESCC tissues and 5 ESCC cell lines by quantitative reverse-transcription polymerase chain reaction (qRT-PCR). Over-expression and RNA interference (RNAi) approaches were used to study the biological functions of CCAT2 in ESCC cells. Cell migration and invasion were evaluated by transwell assays. Tail vein injection of cells was used to investigate metastasis in nude mice. Protein levels of EMT related genes were determined by western blot analysis and immunohistochemistry. Differences between groups were tested for significance using Student'st-test (two-tailed).

Results: CCAT2 expression was significantly up-regulated in ESCC tissues ($p < 0.001$) and cell lines ($p < 0.01$) compared with corresponding normal counterparts. What's more, highly expressed CCAT2 was associated with larger tumor size and advanced pathologic stage. Further studies found that the knockdown of CCAT2 markedly decreased the migration and invasion of ESCC cells *in vitro* and *in vivo*. Moreover, down-regulation of endogenous CCAT2 enhanced the expression of E-cadherin and decreased the expressions of N-cadherin and vimentin in ESCC cells.

Conclusion: Our study presents the first evidences that CCAT2 contributes a lot to the metastasis of ESCC by regulating the expressions of EMT related genes, which may lead to the development of a novel diagnostic marker and therapeutic strategy for ESCC.

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Disclosure of Interest: None declared

OP230 SEVERE ATROPHIC GASTRITIS IS A SIGNIFICANT RISK FACTOR OF METACHRONOUS MULTIPLE GASTRIC CANCER: A MULTICENTRE RETROSPECTIVE COHORT STUDY BY THE OSAKA GUT FORUM

M. Kato[1], T. Nishida[2], K. Yamamoto[3], S. Kitamura[4], T. Yamada[5], S. Egawa[6], M. Komori[7], N. Kawai[8], A. Nishihara[9], F. Nakanishi[10], M. Nakahara[11], H. Ogiyama[12], A. Mukai[13], Y. Hayashi[14], M. Tsujii[7,14], T. Takehara[14], on behalf of Osaka Gut Forum
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Introduction: Endoscopic submucosal dissection (ESD) has been a standard therapy for early gastric cancer (EGC) at negligible risk of lymph node metastasis in Japan, due to its secure local control with maintaining Quality Of Life by preservation of stomach. On the other hand, patients are at high-risk for developing metachronous multiple gastric cancers (MMGC) arising from remnant gastric mucosa. We have reported that the cumulative incidence rate of MMGC was constant and eradication therapy for *Helicobacter pylori* (HP) did not reduce the incidence of MMGC at least for three years after ESD (M. Kato et al. Gut 2013).

Aims & Methods: The aim of this study was to elucidate the detail of development of MMGC by extending the observation period and analysis of association between various factors and MMGC incidence. This is a retrospective cohort study from 12 hospitals. From April 1999 to December 2010, total 1109 consecutive patients with EGC who underwent ESD for the first time and achieved curative resection with observation period 12 months or more were included in this study. Cumulative incidence of MMGC after ESD was analyzed using Kaplan–Meier methods. The association between background factors at initial ESD (age, sex, degree of atrophic gastritis, presence or absence of synchronous multiple gastric cancer, classification of Japanese guideline for gastric cancer of initially resected lesion, and presence or absence of eradication of HP and development of MMGC) was analyzed using Cox's proportional hazards model. The degree of atrophic gastritis of background mucosa was evaluated by review of endoscopic images at initial ESD based on Kimura-Takemoto classification.

Results: Median observational period was 52.3 (IQR 37.3 – 72.6) months. The cumulative incidence increased linearly and did not reach plateau at least for five years after ESD. Three, five, and seven-year cumulative incidence rate of MMGC were 5.2%, 9.8%, and 13.9%, respectively. In univariate analysis, atrophic gastritis revealed to have a statistic significance ($p = 0.0148$) and male gender revealed to have statistic tendency ($p = 0.059$) concerning MMGC development. In multivariate analysis, only degree of atrophic gastritis revealed to be an independent risk factor (Odds ratio 1.7 [95%CI 1.1–2.8], $p = 0.0138$). In our cohort, HP eradication did not reveal to have significant association with MMGC development.

Conclusion: MMGC incidence increases constantly for at least 5 years after curative ESD. The degree of atrophic gastritis is an independent risk factor for MMGC development. Careful endoscopic surveillance is needed especially for patients with severe atrophic gastritis.

Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 11:00–12:30

MANAGEMENT OF SEVERE AND REFRACTORY ULCERATIVE COLITIS – ROOM B2

OP231 THE AVAILABILITY OF CALCINEURIN INHIBITORS AND INFLIXIMAB IN ACUTE SEVERE COLITIS HAVE REDUCED COLECTOMY RATES IN 283 CHILDREN ADMITTED DURING 1990-2012

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Introduction: One third of children admitted with acute severe colitis (ASC) fail intravenous corticosteroids (IVCS) and require salvage therapy. While colectomy was originally the only available salvage treatment, cyclosporine and then tacrolimus (Cys/Tac) have been used since 1996, followed by infliximab (IFX) in 2004, as second line medical treatment prior to colectomy. However, no data to date have shown whether these interventions actually managed to reduce colectomy rates in children, during the admission or thereafter.

Aims & Methods: We aimed to explore trends in colectomy rate in pediatric ASC before and after the introduction of Cys/Tac and IFX, using the largest pediatric cohort of ASC to date. 283 children treated with IVCS for ASC during 1990-2012 were included (from the prospective ($n = 128$) and retrospective ($n = 99$) OSCI studies and another 55 retrospectively reviewed patients from Jerusalem and Liverpool). Patients were followed for 1 year (46% males, age 12.1 ± 3.9 years, disease duration 2 (IQR 0-14) months, baseline PUCAI 69 ± 13 points). Data accrual was similar in the 3 cohorts, collected using the same standardized case report forms at admission, 3 days and 5 days thereafter, at discharge and at 1 year. Colectomy rates were compared between 3 periods: 1990-1996 (era1: pre medications; $n = 68$), 1997-2004 (era2: Cys/Tac and colectomy; $n = 45$), 2005-2012 (era3: IFX, Cys/Tac and colectomy; $n = 170$). No child in our cohort has been treated with IFX prior to 2005.

Results: Total 1-year colectomy rates were 40/68 (59%) during era1, 17/45 (38%) during era2, and 31/170 (18%) during era3 ($P < 0.001$). Since IVCS failure rates were different between the eras, we then focused on those failing IVCS to standardize the analysis. Of the 283 children, 89 (31%) failed IVCS and required second line therapy during admission (44 primary colectomy, 9 Cys/Tac and 22 IFX; total colectomy 56). The 3 era groups were similar in 12 pre-treatment basic variables at admission (e.g. PUCAI, CRP, albumin, disease duration etc) except for age and ESR. The rate of colectomy in those requiring salvage therapy during the admission was significantly reduced from 100% (51/51) in era 1, to 62% (8/13) in era2 and 33% (14/42) in era3 ($p < 0.001$). At 1 year after discharge, 123 children (43%), were treated with second line therapy (44 primary colectomy, 12 Cys/Tac and 53 IFX; total colectomy 88). The rate of colectomy was again significantly reduced from 100% (40/40) of children requiring salvage therapy in era1 to 77% (17/22) in era2 and 51% (31/61) in era3 ($p < 0.001$).

Conclusion: We show for the first time that the introduction of Cys/Tac and then infliximab sharply reduced the need for colectomy during admission and 1-year thereafter in pediatric ASC.

Disclosure of Interest: S. Choshen: None declared, A. Griffiths Financial support for research: Abbvie, Janssen, Lecture fee(s): Abbvie, Janssen, Consultancy: Abbvie, Janssen, H. Finnamore: None declared, M. Auth: None declared, E. Shteyer: None declared, D. Mack Financial support for research: Abbvie, Consultancy: Abbvie, Janssen, J. Hyams Consultancy: Janssen Abbvie Celgene Avaxia Takeda, D. Turner Financial support for research: Janssen, Abbvie, Ferring, Lecture fee(s): Janssen, Abbvie, MSD, Consultancy: Janssen, Abbvie,

OP232 TACROLIMUS FOR INDUCTION AND MAINTENANCE THERAPY IN PATIENTS WITH REFRACTORY ULCERATIVE COLITIS

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Introduction: In recent years, the calcineurin inhibitor, tacrolimus has been introduced to induce remission in patients with active ulcerative colitis (UC), which is refractory to corticosteroids. However, hitherto the efficacy of tacrolimus as maintenance therapy has not been investigated.

Aims & Methods: The major objective of this investigation was to see the clinical potential of tacrolimus as remission maintenance therapy following remission induction. We started with 40 patients in clinical remission with UC clinical activity index (CAI) $\leq$4 according to Lichtiger, all patients had received tacrolimus induction therapy. These 40 patients were divided into 3 groups for maintenance therapy with azathioprine (n = 13), tacrolimus (n = 13) or tacrolimus + azathioprine (n = 14), and were followed for at least one year. CAI, Ulcerative Colitis Endoscopic Index of Severity (UCEIS) and the duration of tacrolimus therapy were applied to assess treatment outcomes. Relapse was defined as patient requiring remission induction therapy by increasing the blood trough tacrolimus level $\geq$ 10 ng/ml, intravenous corticosteroid or a biologic. All patients were diligently observed for adverse side effects.

Results: The average duration of tacrolimus therapy was 402 $\pm$ 167 days in the tacrolimus group, 87 $\pm$ 12 days in the azathioprine group, and 240 $\pm$ 166 days in the tacrolimus + azathioprine group. The recurrence rates after induction of remission in the tacrolimus, azathioprine, and tacrolimus + azathioprine groups were respectively 28%, 32%, and 33% at 300 days, while the respective rates were 24%, 49%, and 55% at 600 days, showing no statistically significant differences. Further, nephropathy occurred in 11 patients, and renal failure in 5 patients, both were thought to be side effects of tacrolimus induction therapy. In patients who experienced renal failure, the dose of tacrolimus was reduced or discontinued. Additionally, headache was experienced by one patient.

Conclusion: In the present study (albeit in small subgroups of patients), tacrolimus alone appeared to be effective for remission induction as well as maintenance therapy in UC patients. Patients who are intolerant to azathioprine should benefit from tacrolimus maintenance therapy. However, the therapeutic efficacy of tacrolimus may be compromised by its renal toxicity, which needs to be regularly monitored in patients who are on long-term tacrolimus.

Disclosure of Interest: None declared

OP233 ACETARSOL SUPPOSITORIES ARE AN EFFECTIVE AND WELL TOLERATED TREATMENT FOR REFRACTORY PROCTITIS: A COHORT STUDY

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Introduction: Although conventional treatments are generally effective in the treatment of proctitis, a significant minority of patients do not respond – developing so-called "refractory proctitis". This is an incredibly debilitating and disabling condition. The use of acetarsol suppositories, which are derived from organic arsenic, was first described 1965 (Connell, 1965). The mechanism of action is unknown. Data concerning clinical efficacy and tolerability of acetarsol suppositories are limited to two small studies (Connell, 1965, Forbes, 1989).

Aims & Methods: A retrospective analysis was performed on patients with inflammatory bowel disease treated with acetarsol suppositories between 2008 and 2014 at Addenbrooke's Hospital, Cambridge, UK. Patients were identified through a hospital pharmacy database. All patients who were prescribed and received acetarsol suppositories during this period were included. Clinical response was defined as resolution of symptoms (frequency, bleeding and pain) back to baseline at the time of next clinic review. Serum arsenic levels were not routinely measured.

Results: 39 patients received acetarsol suppositories between March 2008 and July 2014 (29 UC, 9 Crohn's disease, 1 indeterminate colitis). Demographic and prior treatment details are shown in Table 1. The standard dose of acetarsol was 250mg twice daily per rectum for 4 weeks; 95% of patients received this regimen.

Clinical response was observed in 26 patients (66.7%). Of the 11 patients who had endoscopic assessment before and after treatment, 9 (82%) showed endoscopic improvement and 5 (45%) were in complete remission (p = 0.0004, median assessment at 8 months post treatment). The only clinical parameter that correlated with clinical response was the number of previously failed immunomodulators (p = 0.01, mean 1.35 in responders and 2.46 in non-responders).

One patient developed a macular skin rash one week after commencing acetarsol suppositories, which resolved within 4 weeks of drug cessation. Skin biopsy confirmed superficial perivascular dermatitis, consistent with a drug rash.

Table 1: Baseline characteristics of patients

	Total
Number of patients	39
Mean age, years (± standard deviation)	39.3 (± 14.8)
Sex	
Male	16 (41%)
Female	23 (59%)
Ulcerative colitis	29 (74%)
Proctitis	8 (21%)
Crohn's disease	9 (23%)
Proctitis	0
Mean duration of disease, years	6.9 (± 5.0)
Mean follow-up, years	6.4 (± 3.4)

Conclusion: Acetarsol was effective for 2 out of every 3 patients with refractory proctitis. This cohort had previously failed a broad range of topical and systemic treatments, including anti-TNFα therapy. The clinical efficacy was reflected in significant endoscopic improvement. Adverse effects of acetarsol were rare.

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Disclosure of Interest: None declared

OP234 INTRINSIC DEFECTS IN THE EPITHELIAL STEM CELL COMPARTMENT COULD CONTRIBUTE TO THE PERPETUATION OF ULCERATIVE COLITIS

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Introduction: Ulcerative colitis (UC) is a chronic remitting and relapsing inflammatory bowel disease that affects the superficial mucosal barrier. Remission is characterized by clinical and endoscopic resolution of the disease; however, the transcriptional signature of remitting UC mucosa reveals long-lasting changes in the epithelial barrier[1].

Aims & Methods: The aim of our work was investigating whether primary defects are present in the epithelial stem cell (ESC) compartment of UC patients. To this end, we used a recently established human epithelial cell culture system[2]. Biopsy samples from the sigmoid colon of 11 non-IBD controls and 8 UC patients were collected. Isolated crypt units were in vitro cultured in matrigel, and ESCs were expanded as 3D spheroids called organoids. These were induced to differentiate into the main intestinal epithelial lineages, and total RNA from stem and differentiated organoids was extracted for transcriptional analysis.

Results: Our results show that stem organoid cultures derived from control and UC biopsy samples follow similar differentiation programs with comparable regulation of stem (i.e., Lgr5, AXIN2), proliferation (i.e., Myc, Ki67), and epithelial markers (i.e., MUC2, ANPEP). Microarray analysis, however, revealed a small panel of genes differentially expressed by organoid samples generated from UC patients compared to non-IBD individuals. UC-derived organoids showed a marked up-regulation of genes that are characteristic of the proximal gastrointestinal tract (e.g., lysozyme, an anti-microbial protein). Conversely, they displayed reduced transcription of genes commonly expressed by colonic epithelial cells (e.g., ZG16, a component of the mucus). Interestingly, several genes of this signature were found permanently altered in the intestinal mucosa of colitic patients in remission.

Conclusion: Overall, our findings demonstrate that sigmoid ESCs of colitic patients show an expression signature that may reflect the presence of intrinsic changes in UC epithelium. Notably, the acquisition of a ''proximal'' phenotype, including alterations in the nature of epithelial antimicrobial response and mucus composition, could contribute to the perpetuation of the disease over time.

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Disclosure of Interest: None declared

OP235 HISTOLOGICAL AND ENDOSCOPIC ASSESSMENT IN ULCERATIVE COLITIS: RESULTS FROM THE PURSUIT TRIAL

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Introduction: UC disease activity & severity is based on combined endoscopic & clinical assessments. Histologic assessment may provide more accurate measurement of disease activity than endoscopic assessment;correlation between endoscopy & histology is not understood.

Aims & Methods: To assess which features of the Geboes histological score are associated with endoscopic healing. PURSUIT-SC was a Phase 2/3 study conducted to evaluate induction therapy with SC GLM. Pts with Mayo scores of 6-12 inclusive, including endoscopic subscore >2 were randomized to placebo (PBO)/PBO, GLM 100mg/50mg (before Ph3 dose selection only), GLM 200mg/100mg, or GLM 400mg/200mg at wks0 & 2. Colonic biopsies were collected from a subgroup of pts, who consented to participate in the biopsy substudy. At wk0&wk6, pts had 2 adjacent biopsy specimens both obtained within 15-20 cm of the anal verge.A single, blinded pathologist reviewed each biopsy & used the Geboes classification system to assess the following histological features:structural change only, chronic inflammatory infiltrate, lamina propria eosinophils, lamina propria neutrophils, neutrophils in the epithelium, crypt destruction, & erosions & ulcers. Endoscopy assessments were made using the local Mayo endoscopic sub-score(as determined by local site investigators);subscores of 0 or 1 were defined as endoscopic healing. Results were summarized at wks0&6.

Results: Among 89pts consenting to the substudy, 343 biopsies, including 166 paired biopsies from wk0&6 were collected. Among the 343 biopsies, the endoscopy score distribution for scores of 0, 1, 2, or 3 were 4%, 20%, 45% & 30%, respectively. Overall, pts with endoscopic scores of 0 & 1 had very similar histological features. Histological features associated with endoscopic healing included: absence of histological evidence of ulceration & erosion, no evidence of crypt destruction, & only minimal neutrophil infiltration of the epithelia (<5%). For subsequent analysis, these pts were considered to have ''histological healing'' (histological healing by this definition does not mean complete histological normalization). ''Histological healing'' rates at wk6 by Mayo endoscopy scores of 0, 1, 2&3 were 100% (14/14), 68.1% (47/69), 19.9% (31/56), & 16.3%(17/104), respectively. Pts with histological healing had lower degrees of structural changes, chronic inflammation compared to those who did not have histological healing. There was 88% concordance rate of histological healing between multiple biopsies done at the same treatment visit. This rate was higher than observed with individual components of the Geboes score. ''Histological healing'' was associated with lower rates of rectal bleeding & decreased stool frequency vs pts without histological healing.

Conclusion: Absence of histological evidence of ulceration & erosion, no evidence of crypt destruction & only minimal neutrophil infiltration of the epithelia (<5%) may constitute a definition of histological healing in UC trials. This definition is highly reproducible in adjacent biopsy specimens. Pts who meet this definition are more likely to have endoscopic healing accompanied by reduced rectal bleeding & stool frequency.

Disclosure of Interest: R. Strauss Conflict with: Employee Janssen R & D, LLC, B. Feagan Financial support for research: Janssen R & D, LLC, J.-F. Colombel Financial support for research: Janssen R & D, LLC, C. Marano Conflict with: Employee Janssen R & D, LLC, S. Xu Conflict with: Employee Janssen R & D, LLC, L. Peyrin-Biroulet Financial support for research: Janssen R & D, LLC, G. De Hertogh Financial support for research: Janssen R & D, LLC, W. Sandborn Financial support for research: Janssen R & D, LLC

OP236 MODIFIED 2-STAGE ILEAL POUCH ANAL ANASTOMOSIS RESULTS IN LOWER RATE OF ANASTOMOTIC LEAK COMPARED TO TRADITIONAL 2-STAGE SURGERY FOR ULCERATIVE COLITIS

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Introduction: Surgical treatment options for ulcerative colitis (UC) depend on the indication for surgery, patient factors, and previous medical therapy. There is a paucity of evidence comparing traditional 2-stage (total proctocolectomy with ileal pouch anal anastomosis (IPAA) and diverting ileostomy, followed by ileostomy closure) versus a modified 2-stage (subtotal colectomy with end ileostomy, followed by completion proctectomy + IPAA, without diverting ileostomy) restorative proctocolectomy. This study examines the clinical outcomes following traditional vs. modified 2-stage IPAA for patients with UC in a single institution. Anastomotic leak and pelvic abscess following pouch creation were the primary outcomes of interest.

Aims & Methods: A retrospective cohort study was performed for UC patients who underwent IPAA between 2002 and 2013 at our institution. Individuals who received either a traditional or modified 2-stage IPAA were identified from our IBD Surgical Database. Demographic data, clinical data, and outcomes (peri- and post-operative complications) were collected from in-patient and out-patient chart review. Pouch leaks and abscesses were documented by clinical exam and diagnostic imaging. Statistical analyses were performed using the Pearson Chi-square test for categorical variables. Multivariate logistic regression and the Wilcoxon rank sum test were used for continuous variables.

Results: 758 UC IPAA patients were reviewed. 460 patients underwent a 2-stage IPAA procedure. 223 (48.5%) patients underwent traditional 2-stage IPAA and 237 (51.5%) patients received the modified 2-stage procedure. There was a trend towards more pre-operative systemic corticosteroid use (49.1 vs. 37.2%, p 0.01) and less azathioprine/6MP use (9.3 vs. 18.6%, p 0.01) prior to the first stage of the modified 2-stage group compared to that of the traditional 2-stage group. However, there was no difference in anti-TNF exposure between the two groups (13.1 vs. 9.9%, modified vs. traditional 2-stage groups, respectively). The modified 2-stage group had higher UC disease severity at presentation (94.5% patients with moderate/severe UC vs. 79.5%, $p < 0.01$) and the indication for the first stage of surgery was more likely to be for fulminant disease/toxic megacolon/perforation (22.8 vs. 0.9%, $p < 0.01$). There was no difference in post-operative wound infection (12.7 vs. 13.1%) or pelvic abscess (14.8 vs. 15.3%) between the modified or traditional 2-stage groups. However, the modified 2-stage group had a lower rate of anastomotic leak following pouch creation (4.6 vs. 15.7%, $p < 0.01$) and decreased post-operative length of stay (LOS) following pouch surgery (median 8 vs. 10 days, $p < 0.01$) compared to the traditional 2-stage group.

Conclusion: Ulcerative colitis patients who received the modified 2-stage IPAA (subtotal colectomy prior to IPAA pouch formation) had a significantly lower rate of anastomotic leak and shorter LOS following pouch creation, compared to the traditional 2-stage procedure.

Disclosure of Interest: E. Zittan: None declared, N. Wong-Chong: None declared, G. Ma: None declared, R. Milgrom: None declared, R. McLeod: None declared, H. MacRae: None declared, G. Greenberg: None declared, G. Nguyen Consultancy: Advisory Board for Janssen and Abbvie, K. Croitoru Financial support for research: Educational grant from Janssen, Abbvie and Takeda, Consultancy: Advisory Board for Abbvie and Takeda, A. Steinhart Financial support for research: Abbvie, Amgen, Pfizer, Millenium, Lecture fee(s): Abbvie, Janssen, Takeda, Shire, Consultancy: Advisory Board for Abbvie, Actives, Janssen, Takeda, Pharmascience, Shire, M. Silverberg Financial support for research: Janssen, Abbvie, Takeda, Prometheus, Consultancy: Janssen, Abbvie, Takeda, Prometheus, Z. Cohen Conflict with: Educational Grant from Janssen

TUESDAY, OCTOBER 27, 2015 11:00–12:30
PROGRESS IN ENDOSCOPIC OESOPHAGEAL INTERVENTIONS – ROOM 7.1

OP237 EFFECTIVITY AND SAFETY OF CAP-ASSISTED FLEXIBLE ENDOSCOPIC ZENKER'S DIVERTICULOTOMY (C-ZD) – RESULTS OF A PROSPECTIVE SERIES FROM ONE WORKING GROUP

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Introduction: Flexible endoscopic Zenker's diverticulotomy under propofol sedation has been established during the last years as an alternative to open surgery and transoral diverticulotomy with a rigid endoscope. Several endoscopic techniques have been reported. Data on cap-assisted endoscopic Zenker's diverticulotomy (c-ZD) are still limited. The aim of the present study was to evaluate efficacy and safety of c-ZD in a prospective series from one working group.

Aims & Methods: Patients (pt) with symptomatic Zenker's diverticulum (ZD) who underwent c-ZD were collected in a prospective database. For c-ZD, a transparent tip was mounted on the tip of the endoscope, and myotomy was performed using a needle-knife. Dysphagia and regurgitation symptoms (0 = no discomfort, 10 = extreme discomfort) were recorded using a visual analoge scale (VAS) prior to treatment and at 3- and 12 month follow-up (FU). Adverse events (AE) of c-ZD as well as symptomatic recurrence were registered.

Results: During the periods 07/09–03/14 (Wiesbaden, n = 82) and 04/14-02/15 (Offenbach, n = 34), a total of 116 pt with symptomatic ZD were referred to our working group. c-ZD was performed in 112/116 pt (77 men; mean age 71 ± 1 yr). Mean depth of diverticulum was 25 ± 9mm. Initially, dysphagia score was 6.5 ± 2, and regurgitation score was 5.8 ± 3. c-ZD was technically successful in all pt. (100%). Major AE occured in 3 pt (1 perforation, 1 fever >24h, both conservative management; 1 bleeding, haemostasis via rigid esophagoscopy). Subcutaneus emphysema was detected in 12 pt (10.7%; managed conservatively). Both dysphagia and regurgitation scores showed highly significant improvement (p< o.oo5) during 3- and 12-mo FU. Recurrence of symptoms was observed in 8% (n = 6; repeat c-ZD n = 5; surgery n = 1).

Conclusion: According to the results of this large prospective study, c-ZD appears to be an effective and safe treatment approach in experienced hands. Symptoms improved significantly during 3- and 12-mo follow-up, with a recurrence rate of symptoms of only 8%.

Disclosure of Interest: None declared

OP238 PROGNOSTIC VARIABLES FOR THE CLINICAL SUCCESS OF FLEXIBLE ENDOSCOPIC SEPTOTOMY OF ZENKER'S DIVERTICULUM

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Introduction: Flexible endoscopy septotomy for Zenker's diverticulum (ZD) is an alternative to endostapling. However, long-term data are sparse and studies are heterogeneous.
Aims & Methods: Aim was to assess the clinical efficacy of flexible endoscopy diverticuloscope-assisted septotomy and identify potential prognostic variables. Data from a prospective database including all patients with ZD undergoing septotomy followed up for ≥24 months were analysed. Septotomy used the diverticuloscope-assisted technique. Dysphagia, regurgitation and respiratory symptoms were scored according to frequency from 0 to 3 on a solid food diet. Clinical success was defined as the absence of symptoms or the presence of a maximum of two symptoms with score 1. Prognostic variables of clinical success were searched among age, sex, pre-treatment total symptom score, pre- and post-treatment ZD size, septotomy length. Kaplan-Meier method and Cox proportional-hazards model were used to calculate the crude and adjusted Hazard Ratio (HR).
Results: Septotomy was achieved in 89 patients. Adverse events occurred in 3 cases: perforation in 2 (2%); post-procedural bleeding in 1 (1%). Clinical success at the ITT analysis was 69%, 64% and 46% at 6, 24 and 48 months, respectively.
Prognostic variables for clinical failure were analysed at 6, 24 and 48 months of follow-up according to the time intervals in which clinical failures and recurrences were observed. No differences were found at 6 and 24 months. Independent variables for clinical failure were: septotomy length ≤25 mm at 6 and 48 months (HR 6.34 and HR 2.20); ZD size ≥50 mm at 6 months (HR 11.08); residual ZD size ≥10 mm at 48 months (HR 2.03).
Conclusion: The clinical success of FE septotomy is related to the ZD size, a decisive factor for both the completeness of myotomy and the size of the residual diverticulum. ZD size is the leading variable of the therapeutic algorithm: the maximal clinical efficacy of FE septotomy is expected for ZD measuring 30-50 mm in which a complete myotomy without a residual pouch can be achieved in a single procedure.
Disclosure of Interest: None declared

OP239 BALLOON DILATION WITH EPIDERMAL CELL SHEET TRANSPLANTATION TO ESOPHAGEAL STRICTURES FOR AVOIDING RE-STRICTURES - A NEW ENDOSCOPIC PROCEDURE FOR REGENERATIVE MEDICINE -

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Introduction: Endoscopic submucosal dissection (ESD) is a standard treatment for superficial esophageal cancinoma. However, post-ESD stricture is a major complication for treatments of widespread superficial esophageal carcinoma. We previously reported transplanting epithelial cell sheets (ECSs) immediately after extensive ESD was the safe and potential therapy to prevent esophageal strictures (1). In addition, the transplanting device of ECSs have been developed for improving the efficiency in the endoscopic procedure of transplanting ECSs (2). On the other hand, there were no effective treatments once esophageal strictures developed. We hypothesized that it is important to prevent the adhesion of tears after endoscopic balloon dilation (EBD) for avoiding the re-strictures. The newly endoscopic device, which make it possible to put ECS in the tears after EBD.
Aims & Methods: This study aims to develop a new endoscopic device and technique for transplanting epidermal cell sheets (ECSs) after the dilatation to esophageal strictures. A prototype of the endoscopic device was validated. Six pigs underwent circumferential esophageal ESD under general anesthesia. At 2 weeks after ESD, all pigs developed severe esophageal strictures. EBD with transplanting autologous ECSs was performed to two pigs (Trans group). EBD was only performed to other two pigs (BD group). Two remaining pigs were only endoscopically observed (Ctrl group). At 3 weeks after ESD, all pigs were clinically and endoscopically evaluated and scarified for further more study.
Results: The developed device has two phases, which are the transport mode and the releasing mode. The transport mode was set as suction by the syringe with the change of three-way stopcock. The releasing mode was set as air ejection with the three-way stopcock. In the bench test, the device was confirmed to work in the narrow tube. In the large animal study, transplantation of ECSs using the device in the tears after EBD were validated and successfully performed without adverse events. Next, we evaluated the feasibility of the therapy using ECSs with EBD to esophageal strictures after ESD. The pigs in the Ctrl group developed severe strictures and dysphagia (The rate of strictures: 92.2% and 87.7%) at 3 weeks after ESD. ECSs were successfully transplanted in all cases of the Trans group. The pigs in the Trans group avoided re-strictures and kept good clinical condition (The rate of strictures: 55.0% and 60.0%) On the other hand, the pigs in the BD group developed re-strictures (The rate of strictures: 71.7% and 78.2%).
Conclusion: The transplanting device and procedure of ECSs after EBD were developed. Covering the tears after EBD by ECSs could avoid re-strictures.

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Disclosure of Interest: S. Kobayashi: None declared, N. Kanai: None declared, T. Hosoi: None declared, N. Tanaka: None declared, M. Maeda: None declared, Y. Maruya: None declared, K. Kanetaka: None declared, S. Eguchi: None declared, M. Yamato Shareholder: Cell Seed Inc.

OP240 EFFICACY, SAFETY AND CLINICAL OUTCOMES OF ENDOSCOPIC SUBMUCOSAL DISSECTION USING A SCISSORS-TYPE KNIFE FOR EARLY ESOPHAGEAL NEOPLASMS

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Introduction: Endoscopic submucosal dissection (ESD) is a one of the most useful methods for the treatment of early esophageal neoplasms. Several conventional devices are used for ESD: an IT knife, hook knife, and needle knife. However, because these devices are used without being fixed to the target, there is a potential risk of complications due to an unplanned incision. To reduce the risk of complications related to ESD using a conventional knife, we used a scissors-type knife (SB knife: Akita Sumitomo Bakelite) that allows us to maintain a proper dissecting layer and prevents unexpected injury to a muscular layer. In this study, we report on the efficacy, safety and clinical outcomes of ESD performed with an SB knife for early esophageal neoplasms at our hospital.
Aims & Methods: The aim of our study was to evaluate the efficacy, safety and clinical outcomes of ESD using a SB knife for early esophageal neoplasms. ESD using a SB knife was performed on 72 lesions (47 squamous cell carcinomas, 20 high-grade intraepithelial neoplasias, 4 adenocarcinomas and 1 carcinoid tumor) in 56 patients from April 2010 to February 2015. We evaluated the en bloc resection rate, complete resection rate, size of the specimen and tumor, local recurrence rate, and complications. Complete resection was defined as an en bloc resection, where both the lateral and vertical margins were negative. In cases that underwent circumferential or semi-circumferential ESD, prednisolone was administered orally or injected into the base of ulcer after the ESD to prevent post-operative stricture.
Results: The en bloc resection rate was 100% (72/72) and the complete resection rate was 95.8% (69/72). The mean size of the resected specimens was 34.4 mm (range 11–75 mm), and that of the resected tumors was 17.3 mm (range 1–64 mm). All lesions were treated easily and safely without any unexpected incisions, and there was neither delayed hemorrhage nor perforation. Oral administration or injection of prednisolone to prevent post-operative stricture was necessary for 7 patients (9.7%) who underwent circumferential or semi-circumferential ESD, and there was no post-operative stricture in any cases. The local recurrence rate was 1.4% (1/72). In the single recurrence case, despite pathological findings that indicated submucosal invasion and vessel invasion, the patient did not undergo additional therapies because of hepatocellular carcinoma. None of the patients died of esophageal neoplasms, whereas five patients died of other diseases (mean follow-up duration, 765 days).
Conclusion: ESD using a SB knife can be adopted as an easy, safe, and technically efficient method for resecting early esophageal neoplasms.
Disclosure of Interest: None declared

OP241 LONG-TERM OUTCOMES OF ENDOSCOPIC RESECTION AND ADDITIONAL THERAPY TO SUPERFICIAL ESOPHAGEAL CANCER WITH MM OR SM INVASION

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Introduction: Recent advances in endoscopic resection (ER), such as ESD, enable us en-bloc resection of the lesions and accurate pathological diagnosis, which provide us increasing chances for resecting esophageal cancer (EC) with muscularis mucosae (MM) or submucosal (SM) invasion. However, MM or SM invasive EC have 10-50% of metastatic risks, depending on its depth, lymphovascular involvement (LI) and droplet infiltration (DI). For these cases, after ER, we perform additional therapy such as chemo radiotherapy (CRT), radio therapy (RT) or operation considering the risk of metastasis and patients' general condition.
Aims & Methods: The aim of this study is to reveal long-term outcomes of ER and additional therapy for MM and SM invasive esophageal cancer (SCC). We studied about 141 cases with MM or SM invasive esophageal cancer resected by ER (EMR or ESD), from 2003 to 2012 in Cancer Institute Hospital, Tokyo, Japan.
Results: In 141 cases (male/female 128/13, median age 66), we resected 76 cases by EMR and 65 cases by ESD, and pathological depth of invasion was MM/

SM1/SM2 85/20/36. Median observation period was 41 months (2-140). En-bloc resection rate and local recurrence rate for EMR /ESD was 47.3% /100%, 11% / 0% respectively. Of 85 cases of T1a-MM, 69 cases were observed with no additional therapy because of LI (-) and DI (-). One patient had recurrence as lymph node (LN) metastasis and received operation and CRT, surviving with no re-recurrence. The rest of 16 cases were recommended additional therapy because of LI (+) or DI (+) and 7 cases were performed additional therapy (operation/CRT 3/4). No one died of EC in T1a-MM. Of 20 cases of T1b-SM1, 11 cases were observed with no additional therapy because of LI (-) and DI (-). Of them, 2 cases had recurrence (LN metastasis and lung metastasis) and died of EC. Nine cases were recommended additional therapy, because of LI (+) or DI (+). And 5 cases were performed additional therapy (operation/CRT 1/4), although one case had recurrence (liver metastasis) and died of EC. Of 35 cases of T1b-SM2, all cases were recommended additional therapy which 23 cases were performed (operation/CRT/RT 13/6/4). Three had recurrence (2 cases of intramucosal metastasis and 1 case of LN metastasis). They were performed operation or CRT and 1 case were died of EC. Overall survival (OS) for MM/SM1/SM2 were 84.6%/71.1%/84.6% in 3 year and 81.5%/64.6%/84.6% in 5 year. In OS, additional therapy group was significantly superior to no additional therapy group ($p < 0.05$) among the cases we recommended additional therapy. Comparing OS, survival benefit was not different between operation and CRT as additional therapy. In total 7 cases had metastatic recurrence during the observation period and 4 cases died of EC.

Conclusion: The long-term outcomes of ER with additional therapy was satisfactory. With appropriate consideration for additional therapy, ER will be a good therapeutic choice for MM or SM invasive EC.

Disclosure of Interest: None declared

OP242 LONG-TERM OUTCOMES OF ENDOSCOPIC SUBMUCOSAL DISSECTION FOR SUPERFICIAL ESOPHAGEAL SQUAMOUS CELL CARCINOMA

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Introduction: Endoscopic submucosal dissection (ESD) is now widely accepted as a strategy to treat superficial gastrointestinal cancers including superficial esophageal squamous cell carcinomas (SESCCs).

Aims & Methods: The aim of this study was to analyze the long-term outcomes of esophageal ESD and to assess the feasibility of the technique as a therapeutic procedure. A retrospective cohort study was conducted in which a total of 132 consecutive patients with 177 SESCCs that underwent ESD at NTT Medical Center Tokyo between January 2007 and March 2012 were analyzed. Patients with persistent recurrence after previous endoscopic or chemoradiation therapy (CRT) before 2007 were excluded. Long-term outcomes were investigated in patients with more than 3-year follow-up. Treatment outcome, clinical course after ESD, rates of overall survival and newly developed malignancies were evaluated as long-term outcomes.

Results: The mean age of the patients and the median observation time were 64 years (range, 46-90 years) and 61months (range, 36-86 months), respectively. Regarding the histological depth, EP/LPM, MM/SM1, and SM2 or deeper were 83.0% (147 lesions), 13.0% (23 lesions), and 4.0% (7 lesions), respectively. The *en bloc* resection rate was 100% and no significant bleeding occurred, and perforation with mediastinal emphysema was observed in 5 patients (2.8%). None of the patients developed local recurrence, and metachronous SESCCs (we defined it as those detected more than one year after the ESD) were detected in 15.3%of patients (27 lesions, comprising 25 EP/LPM lesions and 2 MM/SM1 lesions, respectively). All of these metachronous lesions underwent additional ESDs. Among the 23 MM/SM1 lesions, 17 lesions including 2 cases with lymphatic vessel infiltration were closely followed up without additional treatment at the patient's decision, 4 lesions including 3 cases with lymphatic vessel infiltration underwent CRT, and 2 lesions underwent additional surgery. Among the 7 lesions with SM2 or deeper invasion, 2 lesions were closely followed up without additional treatment, 2 lesions underwent CRT, and 2 lesions underwent additional surgery. None of the patients developed regional lymph node or distant metastasis during the observation period. The 5-year overall and disease-specific survival rates were 96.4% and 100%, respectively. Cancers other than SESCCs developed in 54 out of 132 cases (40.9%) during the observation period, among which 25 cases (40.7%) were head and neck cancers.

Conclusion: ESD seems to be a feasible, effective curative treatment for SESCCs. All patients should be closely followed after ESD. It is important to follow up for not only metachronous SESCCs but also other malignancies including head and neck cancers.

Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 11:00–12:30
IMPROVING COMFORT AND OUTCOMES IN COLONOSCOPY – ROOM E1

OP243 NEW LOW-VOLUME BOWEL CLEANSING SOLUTION (NER1006) VS TRISULPHATE, POLYETHYLENE GLYCOL 3350 + ASCORBATE OR SODIUM PICOSULPHATE/MAGNESIUM SALT: THREE ONGOING MULTICENTRE RANDOMISED PARALLEL GROUP PHASE III STUDIES IN 1914 PATIENTS UNDERGOING COLONOSCOPY

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Introduction: Effective colonoscopy or colonic surgery requires a clean bowel. An optimal bowel preparation would have a low volume without compromising efficacy/safety. NER1006 is a new oral low-volume polyethylene glycol (PEG) solution with ascorbate, which achieved high-quality bowel cleansing in a phase II study of screening colonoscopy subjects. The phase III programme aims to establish the efficacy, safety and tolerability of NER1006 in a large population of adult patients undergoing colonoscopy.

Aims & Methods: Three multicentre, randomised, colonoscopist-blinded parallel group studies in male/female patients aged 18-85 years are underway. Main inclusion criteria: patients undergoing screening, surveillance or diagnostic colonoscopy. Main exclusion criteria: past history (≤12 months) or current episode of severe constipation; known or suspected ileus; gastrointestinal obstruction; gastric retention; bowel perforation; toxic colitis or megacolon; ongoing severe acute inflammatory bowel disease; previous significant gastrointestinal surgeries; regular use of laxatives or colon motility altering drugs (>2-3 times/week) in the 28 days prior to screening visit and/or laxative use within 72 hours prior to bowel preparation administration. NOCT (NCT02254486) will randomise (1:1) 620 patients in the USA to NER1006, 2-day split dosing regimen (to start the evening of the day before colonoscopy) or trisulphate solution (regimen per label). MORA (NCT02273167; 2014-002185-78) will randomise (1:1:1) 810 patients in Europe to NER1006, 2-day evening/morning split-dosing regimen and 1-day morning on day of colonoscopy regimen or PEG3350 + ascorbate (regimen per label). DAYB (NCT02273141; 2014-002186-30) will randomise (1:1) 484 patients in Europe to NER1006, 1-day, day before-only split dosing regimen (to start the evening of the day before colonoscopy) or sodium picosulphate/magnesium salt (regimen per label). Study duration: up to four clinic visits/patient for up to 40 days. Each study has two alternative primary endpoints: 1. Overall bowel cleansing success rate of NER1006 is non-inferior to that of comparator using the Harefield Cleansing Scale (HCS); 2. 'Excellent plus Good' cleansing rate in the colon ascendens of NER1006 is non-inferior to that of the comparator using the segmental cleansing scoring system of the HCS. Central readers will score colonoscopy videos. Key secondary endpoints include: adenoma and polyp detection rates in the colon ascendens and overall.

Results: As of March 2015, number of patients randomised were 559/620 at 12 US sites for NOCT, 251/810 at 30 sites in Belgium, France, Germany, Italy, Poland, Spain and UK for MORA, and 127/484 at 20 sites in Germany, Italy, Netherlands, Poland, Spain, and UK for DAYB. The studies are due to complete by September 2015.

Conclusion: Quality of bowel preparation is an important factor for a successful colonoscopy however the volume of lavage solution required to achieve efficacy and tolerability is often a barrier. The findings from these pivotal phase III studies of a new low volume bowel preparation may provide a better understanding of what is required in an optimal bowel preparation.

Disclosure of Interest: B. Tayo Conflict with: Employee of Norgine, M. DeMicco: None declared, R. Bisschops: None declared, S. Schreiber: None declared, L. Clayton Conflict with: Employee of Norgine

OP244 WATER EXCHANGE IS THE LEAST PAINFUL COLONOSCOPY INSERTION TECHNIQUE COMPARED WITH WATER IMMERSION AND CO2 INSUFFLATION: A META-ANALYSIS

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Introduction: Some studies suggested that, in some settings, carbon dioxide insufflation (CO_2) decreased abdominal pain and discomfort during colonoscopy. The effect of CO_2 on insertion pain is controversial: two meta-analyses showing a decrease in pain during colonoscopy by CO_2 compared with air insufflation assigned pain score recorded immediately after the procedure, or recalled pain recorded afterwards, as pain during colonoscopy. The meta-analyses did not address the need for sedation. Separate randomized controlled trials (RCTs) have shown water-aided colonoscopy techniques, water immersion (WI, removal of water predominantly during withdrawal) and water exchange (WE, removal of water predominantly during insertion) to significantly decrease insertion pain and the need for sedation compared with CO_2.

Aims & Methods: We performed a meta-analysis to determine which technique would produce the lowest real-time maximum insertion pain and lowest recalled pain at discharge, with interest also in some procedural outcomes. Medline, PubMed and Google searches (January 2011-May 2015) were done to identify appropriate RCTs that compared WE or WI with CO_2. Keywords were: water-aided colonoscopy, water exchange, water immersion, carbon dioxide colonoscopy, pain. Reviews, case reports and abstracts were excluded. Primary endpoints were real time maximum insertion pain and recalled pain at discharge. Secondary end-points were success of unsedated or minimally sedated

colonoscopy, cecal intubation rate, cecal intubation time. Fixed or random effect models were used as appropriate based on homogeneity or heterogeneity of data according to I2 statistic.
Results: 4 RCTs were identified. A total of 1501 procedures were analysed: 638 WE, 320 WI and 543 CO_2. Sex, age, BMI and previous abdominal surgery were comparable. Data are presented as Odd ratio (OR), mean difference and 95% confidence interval (CI). Meta-analysis shows that, compared with CO_2, WE achieved the lowest real-time maximum insertion pain score: -0.79 (-1.22,-0.36), $p = 0.003$. Compared with CO_2, both WE [-0.89 (-1.58,-0.19), $p = 0.01$] and WI [-0.46 (-0.9-0.02), $p = 0.06$] significantly decreased recalled insertion pain score at discharge. Compared with CO_2, proportion of procedures completed without sedation or with minimal sedation was in favour of WE [1.81 (1.19-2.75), $p = 0.005$]; WI [1.07 (0.67-1.70), $p = 0.78$]. Compared with CO_2, WE achieved significantly higher cecal intubation rate: 2.18 (1.3-3.6), $p < 0.005$. CO_2 and WI were comparable: 1.10 (0.3-3.4), $p = 0.9$. WE and WI were associated with a longer cecal intubation time than CO_2: 3.6 (2.6-4.1) and 2.8 (1.9-3.6), $p < 0.005$, respectively.
Conclusion: Compared with water exchange, which is the least painful insertion technique, insufflation with CO_2 does not decrease colonoscopy real-time insertion pain. Both WI and WE reduce recalled insertion pain at discharge. Water exchange significantly enhances completion of unsedated or minimally sedated colonoscopy, lessening patients' burdens; and achieves significantly higher cecal intubation rate, but at the expense of a prolonged insertion time.
Disclosure of Interest: None declared

OP245 BLUE WATER INFUSION DURING COLONOSCOPY DOES NOT INCREASE SIGNIFICANTLY THE ADENOMA DETECTION RATE COMPARED TO STANDARD COLONOSCOPY : RESULTS OF A PROSPECTIVE RANDOMIZED COMPARATIVE STUDY INVOLVING 984 PATIENTS IN 8 CENTERS: THE « GRAND BLEU » STUDY

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Introduction: Standard colonoscopy with air insufflation (SC) is currently the standard to detect colorectal lesions. However, the tandem colonoscopy studies reported a rate of missed adenomas between 16 and 24%. Different techniques have been developped to reduce this missed rate and the BWIC showed interesting results. This trial aimed to compare the efficacy of blue water infusion colonoscopy (BWIC) versus SC in terms of adenoma detection rate (ADR).
Aims & Methods: We designed a prospective comparative study in 8 regional gastroenterology units. Depending on the randomization, the patient received either a SC or a BWIC using warm water with 0.5/1000 indigo carmine blue. All the lesions detected (adenoma, SSP) were resected or biopsied for pathology confirmation.
Results: From Feb 2013 to Aug 2014, we recruited 983 patients with a validate indication of colonoscopy. 491 patients received a SC and 492 a BWIC by 17 endoscopists. The number of polyps, adenoma, SSP and invasive cancer detected was respectively 880, 371, 31 and 7 in the BWIC group versus 677, 293, 23 and 2 in the SC one ($p = 0.002$, $p > 0.1$). Regarding the ADR, no significant difference appeared between SC and BWIC with respectively 37.8 and 40.9% ($p = 0.32$). The mean number of adenoma and SSP detected per colonoscopy was 0.64 and 0.82 ($p = 0.11$) respectively in SC and BWIC. Time of cecal intubation was significantly longer with BWIC with 11.8 vs 7.9 min ($p < 0.0001$).
Conclusion: BWIC is effective to detect adenoma but not significantly superior to SC. In this regional study, a high ADR was observed, underlining the colonoscopy efficacy of the current screening strategy.
Disclosure of Interest: None declared

OP246 ASCENDING COLON EXPLORATION BY RETROVIEW: TECHNICAL FEASIBILITY AND DIAGNOSIS PERFORMANCE

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Introduction: The right colon lesions not visualized during the standard colonoscopy have been associated to interval cancer. The proximal fold side exploration of the ascending colon by retroview reduces the likeliness of losing those lesions. The shorter colonoscope diameter would make easier the cecal retroflexion with lower complication rate.
Aims & Methods: To determine the technical feasibility of the cecal retroflexion, the diagnosis performance and complication rate of the ascending colon exploration by retroview with a shorter colonoscope diameter.
Methods: Prospective study in a paired sample. There were included all the consecutive total colonoscopies performed by expert endoscopists during four months. The recruited patients were examined using two endoscopic **Methods:** conventional and retroview colonoscopy. We collected the visualized and resected lesions on both exploration types.
Technique: Conventional exploration of the ascending colon: Colonoscope insertion and colonoscope withdrawal in forward view from the cecum until the hepatic flexure. Retroview exploration: 1) Colonoscope re-insertion from the hepatic flexure and cecal retroflexion maneuver; and 2) Colonoscope withdrawal in retroview until the hepatic flexure. Exclusion criteria: incomplete endoscopies by any cause (obstruction, endoscopic therapy, right colon resection). All procedures were done with a Colonoscope PENTAX-i10L EC34 (Insert Ø: 11.6, Channel: 3.8, Deflection up/down: 180/180, left/right: 160/160).
Results: We included 323 colonoscopies done in the same number of patients. Age: 61.1 ± 18.2 years; 46% women. There were excluded 20 by incomplete examination. The cecal retroflexion was feasible in 76.6% ($n = 232$). In these procedures, in the right colon, were detected 42 polyps: 40 Paris Is (32 sessile and 8 semi-pedunculated) and 2 Ip, which accounted for 29.4% of 142 colonoscopies with polyps throughout the colon. Histology: 32 adenomas and 10 sessile serrated polyps without dysplasia. 28 polyps were detected and removed during the conventional exploration in forward view while 14 polyps (33.3% of all resected polyps in the ascending colon) were detected additionally only by colonoscope withdrawal in retroview. In the ascending colon, the adenoma detection rate (ADR) was significantly higher in the retroview exploration: 18.10 vs. 12.07%; $p = 0.001$. There were not complications.
Conclusion: The cecal retroflexion was feasible in greater than 75% of colonoscopies and were not registered associated complications. Over 30% of the ascending colon polyps were detected only by colonoscope withdrawal in retroview. This technique significantly increased the ADR in the right colon.
Disclosure of Interest: None declared

OP247 THE UTILITY OF EARLY COLONOSCOPY IN THE MANAGEMENT OF ACUTE LOWER GASTROINTESTINAL HEMORRHAGE

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Introduction: Differences in the safety of bowel preparation and procedures between early and elective colonoscopy have not been extensively studied. In addition, the clinical advantage of early colonoscopy in the setting of acute lower gastrointestinal bleeding (LGIB) remains uncertain. Although, there were two randomized controlled trials comparing early and elective colonoscopy for LGIB, but there were terminated before the prespecified sample size had been reached.
Aims & Methods: We aimed to investigate the safety and effectiveness of early colonoscopy in acute LGIB. We retrospectively studied 538 patients who were emergently hospitalized for acute LGIB. We used propensity score matching to adjust for differences of baseline characteristics between patients who underwent early (≤ 24 h of admission) or elective colonoscopy (> 24 h). Outcomes included rates of adverse events during bowel preparation and colonoscopy procedures, stigmata of recent hemorrhage, endoscopic therapy, blood transfusion requirement, 30-day re-bleeding and mortality, and length of hospital stay.
Results: Before propensity score matching, some differences were found between the groups. After matching using propensity scores based on 9 characteristics (elderly, sex, performance status, previous diverticular bleeding, fever, abdominal pain, diarrhea, anticoagulants, and weekend admission), 176 pairs were selected. No significant differences were found between the groups in bowel preparation-related adverse event rates (6.3% vs. 5.1%, $P = 0.645$), colonoscopy-related adverse event rates (14.2% vs. 13.1%, $P = 0.756$), blood transfusion requirement (27.8% vs. 28.4%, $P = 0.906$), or mortality (1.1% vs. 0.6%, $P = 0.562$). The early colonoscopy group had higher rates than the elective group for stigmata of recent hemorrahage (26.7% vs. 10.2%, $P < 0.001$), endoscopic therapy (25.6% vs. 9.1%, $P < 0.001$) including clipping (14.2% vs. 5.1%, $P = 0.004$) and band ligation (7.4% vs. 1.1%, $p = 0.004$), and re-bleeding (15.3% vs. 8.0%, $P = 0.031$). Length of hospital stay was shorter in the early colonoscopy group (10.3 vs. 13.3 days, $P = 0.001$).
Conclusion: Bowel preparation- and colonoscopy-related adverse event rates for early colonoscopy did not differ from those for elective colonoscopy. Although, early colonoscopy did not improve outcomes of re-bleeding, blood transfusion

requirement, or mortality, it was associated with increased rates of stigmata of recent hemorrhage and enabled more endoscopic therapy, and decreased length of hospital stay.
Disclosure of Interest: None declared

OP248 THE EFFICACY OF TREATMENT OF LOCAL RESIDUAL NEOPLASIA UNDER STANDARDIZED CONDITIONS

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Introduction: After endoscopic mucosal resection (EMR) of nonpedunculated neoplastic colorectal lesions, local residual neoplasia (LRN) has been observed in 5-54% of cases. Several treatment modalities are available to eradicate LRN. The purpose of our study is to evaluate the efficacy of LRN treatment under standardized conditions.
Aims & Methods: This prospective interventional study was conducted in two gastroenterology centers between October/2013 and September/2014. All patients positive for LRN at first follow-up colonoscopy performed 3months after EMR of laterally spreading tumors (LST) were included. The LRN was defined as histological presence of neoplasia in the post- EMR site. Based on endoscopic appearance, LRN was classified into 5 types: Endoscopically undetectable LRN (A), LRN $\leq$ 5mm (B), LRN $>$ 5mm with negative non-lifting sign (C), LRN $>$ 5mm with positive non-lifting sign (D), complex LRN (E). Corresponding treatment modalities were argon plasma coagulation (APC) for types A and B, re-EMR for type C, endoscopic submucosal dissection (ESD) for type D and surgery for type E. The treatment of LRN was considered complete if the post-EMR site was endoscopically and histologically negative for the presence of neoplasia at second follow-up colonoscopy performed after 6 months.
Results: Among 25 patients with 25 LRNs, 10 (40%) were females and 15 (60%) were males. Mean age was 69. 3 (range 52-80) years. Histology of original LST was LGIEN in 6(24%), HGIEN in 14(56%) and intramucosal carcinoma in 5(20%). The location of post-EMR site was rectum in 16(64%), distal colon in 6(24%) and proximal colon in 3(12%). The type of LRN according to the proposed classification was as follows: type A in 0(0%), type B in 12(48%), type C in 8(32%), type D in 5(20%) and type E 0 (0%). The histology of LRN was LGIEN in 12 (48%) and HGIEN in 13(52%). There was no mortality, perforation or delayed bleeding related to LRN treatment. Second follow-up colonoscopy was completed in 23(92%) patients. Remaining 2 (8%) patients were excluded due to loss to follow-up and anticoagulation treatment. The LRN treatment was complete in 21(91.3%) and incomplete in 2(8.7%) cases. Both persistent LRN were small residual adenomas (type B) suitable for additional APC therapy.
Conclusion: The local residual neoplasia after endoscopic mucosal resection of laterally spreading tumors can be eradicated endoscopically during one session in 91.3% of cases. Selection of appropriate treatment modality according to LRN type may be useful.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 11:00–12:30
INFLAMMATORY BOWEL DISEASE: NOT ALL IN THE GENES? – ROOM E4

OP249 AUTOPHAGY REGULATES DENDRITIC CELL MIGRATION THROUGH RAC1 – IMPLICATIONS FOR THIOPURINE THERAPY

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Introduction: The T300A variant of the *ATG16L1* gene reduces autophagy and is one of the few highly prevalent risk factors associated specifically with Crohn's disease. We have previously shown a regulatory role for autophagy during dendritic cell (DC) - T cell interactions, where the T300A allele results in enhanced contact time, T cell hyperactivation and Th17 skewing (Wildenberg et al, *Gastroenterology* 2012). Since a key element of the DC-T cell interaction is regulation of the cytoskeleton, we here further investigated the role of autophagy in DC cytoskeletal organization and function and correlated our findings to thiopurine therapy in IBD patients.
Aims & Methods: Autophagy deficient dendritic cells (DC) were generated using small interfering RNA, pharmacological inhibition or *CD11cCre-Atg5*$^{fl/fl}$ bone marrow or generated from T300A allele carrier monocytes. DC phenotype and migratory capacity were analyzed using migration assays. Correlation between *ATG16L1* genotype and response to thiopurines in IBD patients was determined in two retrospective cohort studies.
Results: Reduced autophagy in DC resulted in loss of filopodia and increased membrane ruffling. This cytoskeletal phenotype was due to increases in Rac1 activity. As a result autophagy deficient DC showed increased adhesion to various substrates. In human DC, both random and directional migration were impaired *in vitro*, while in mice bone-marrow derived DC lacking autophagy show migratory defects *in vivo*. Strikingly, migration of autophagy deficient DC could be restored by the Rac1 inhibitor 6-thioguanin (6-TG), while 6-TG did not influence migration in autophagy sufficient DC. Similar data was obtained using monocytes carrying the *ATG16L1* T300A risk allele. Finally, we correlated ATG16L1 genotype and response to thiopurines in two IBD cohorts and found that the *ATG16L1* risk variant associates with response to thiopurine treatment specifically in patients with Crohn's disease but not ulcerative colitis.
Conclusion: Our results suggest that a defect in the autophagosomal regulation of active Rac1 underlies the association between *ATG16L1* and Crohn's disease through decreased myeloid cell migration. Since thiopurine can inhibit Rac1 activity, *ATG16L1* genotyping may be used to identify patients that will benefit from thiopurine treatment.
Disclosure of Interest: M. Wildenberg Lecture fee(s): Takeda, Falck, P. Koelink: None declared, K. Diederen: None declared, A. te Velde: None declared, V. Nuij: None declared, M. Peppelenbosch: None declared, M. Nobis: None declared, O. Sansom: None declared, C. J. van der Woude Financial support for research: Falk Pharma, Abbott Laboratories, Consultancy: AbbVie, Merck Sharp & Dohme, and Ferring Pharmaceuticals, G. D'Haens Financial support for research: Abbott/AbbVie, AM Pharma, Centocor/Janssen Biologics, Engene, Photopill, Setpoint, Novo Nordisk, MSD, UCB, Takeda, TEVA, Millenium, Boehringer Ingelheim, Elan, Ferring Pharmaceuticals, Dr Falk Pharma, Shire, Cosmo, AstraZeneca, GSK, and PDL, Lecture fee(s): Abbott/AbbVie, AM Pharma, Centocor/Janssen Biologics, Engene, Photopill, Setpoint, Novo Nordisk, MSD, UCB, Takeda, TEVA, Millenium, Boehringer Ingelheim, Elan, Ferring Pharmaceuticals, Dr Falk Pharma, Shire, Cosmo, AstraZeneca, GSK, and PDL, Consultancy: Abbott/AbbVie, AM Pharma, Centocor/Janssen Biologics, Engene, Photopill, Setpoint, Novo Nordisk, MSD, UCB, Takeda, TEVA, Millenium, Boehringer Ingelheim, Elan, Ferring Pharmaceuticals, Dr Falk Pharma, Shire, Cosmo, AstraZeneca, GSK, and PDL, G. van den Brink Financial support for research: Abbvie, Crucell, PPM Services, Lecture fee(s): AbbVie, Merck Sharp & Dohme, and Ferring Pharmaceuticals, Consultancy: Abbvie

OP250 ANTI-TNF-A INDUCTION REGIMEN MODULATES GUT MICROBIOTA MOLECULAR COMPOSITION WHILE INDUCING CLINICAL RESPONSE IN CROHN'S DISEASE PATIENTS: TOWARD A PERSONALIZED MEDICINE

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Introduction: IBD is characterized by an imbalance between immune response and microbiota composition. Anti-TNF-a is one of strongest therapeutically options with high immune modulation potential. No information exists on how and whether anti-TNF-a modulates gut microbiota composition.
Aims & Methods: Aim of our study was to evaluate gut microbiota composition in Crohn's disease patients before and after 6 weeks of anti-TNF-a therapy (mean age 41). Fecal samples were collected in 6 consecutive CD patients, (3 Infliximab, 3 adalimumab) and stored at -80°C. No antibiotic were performed 4 weeks before starting anti-TNF-a therapy or during the active treatment. Clinical response was defined as a decrease of 2 points at Harvey Bradshaw Index (HBI) compared to baseline, while clinical remission was consider for HBI <4.
Results: Bacteria amplicons were detected in all samples.Six weeks after anti-TNF-a therapy, Bacteroidetes decreased in 2 patients (one of the 2 in clinical remission) and remained stable in 4 patients. Roseburia spp increased in one patient (not in clinical remission), Ruminococcus spp decreased in 2 patients (in one not responder to treatment). F. Prausnitzii increased in 3 patients (one in clinical remission). Enterobacteriaceae increased in 3 patients (one not responder to therapy). Chao index increased in 5 patients of six after 6 week. Patients non-responder to anti-TNF by 12 weeks did not show increase in Bacteroidetes at 6 weeks.
Conclusion: Anti TNF-a treatment is associated to active modulation of intestinal microbiota while inducing clinical response. Reduction of Enterobacteriacaee and Ruminococcus were associated to clinical response to antiTNF-a, together with increase in Bacteroidetes and F. Prausnitzii. Further studies are required considering a major number of patients.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 11:00–12:30
NEW DEVELOPMENTS IN DETECTION AND MANAGEMENT OF COLORECTAL NEOPLASIA – ROOM E3

OP251 PREVALENCE OF SERRATED POLYPS; A EUROPEAN OVERVIEW

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Introduction: Serrated polyps (SP) are suggested to be precursors of colorectal cancer via the serrated neoplasia pathway and should be removed during colonoscopy. However, the true prevalence and distribution of SP is largely unknown, impeding guidance for standards in detection, resection and surveillance.
Aims & Methods: We aimed to evaluate and compare the prevalence of SP subtypes in several European countries. Cohorts of patients that underwent colonoscopies between 2009-2014 were eligible to be included in the analysis, as in

Abstract number: OP251

Country	UK	Spain	Italy	Italy	Netherlands	Netherlands	Poland
Cohort type	gFOBT screening	FIT screening	FIT screening	Case-mix	Case-mix	Primary colonoscopy screening	Primary colonoscopy screening
Cohort size (n)	205.949	6.091	17.623	1.809	2.645	1.426	12.361
Age in years (range)	60-75	50-70	60-70	50-93	50-94	50-75	50-65
Male gender (%)	58	55	55	50	53	51	47
Samples assessed by gastrointestinal pathologist	All	All	NA	All	All	All	All
Cecal intubation (%)	97	97	91	91	96	99	98
Adequate bowel preparation (%)	97	98	94	85	89	92	92
≥1 adenoma (%)	43.3	47.1	47.8	31.5	42.0	29.4	32.3
≥1 SP (%)	15.1	19.5	17.6	14.1	24.7	27.2	26.6
≥1 proximal SP (%)	4.7	6.7	9.5	6.5	11.6	12.2	9.7
≥1 large SP (%)	1.2	2.5	2.1	1.9	2.2	2.6	1.1
≥1 SSA/P (%)	NA	3.2	3.3	5.0	8.2	4.8	2.2
≥1 SP ≥10 mm and/or ≥1 proximal SP >5mm (%)	2.1	5.0	7.8	3.4	4.4	4.3	NA
Serrated polyposis (%)(after follow-up)	NA	0.8	NA	NA	0.5	0.4	0.1

NA = not assessed

this era the neoplastic risk of SPs was known. To warrant firm estimates, only prospective cohorts of >1000 colonoscopies were included. Patients <50 years were excluded, to warrant more homogenous data. Aggregated data were collected per center. Cohort type, cecal intubation rate (CIR), adenoma detection rate and quality of bowel preparation were recorded to evaluate the quality of colonoscopies. The prevalence of SP subtypes was assessed in all cohorts, subcategorized for histology, location and size. Clinically relevant SP that could be assessed without the need of an accurate histopathologic differentiation was defined as: SP ≥10 mm and/or SP >5 mm located proximal to the splenic flexure.

Results: Seven prospectively collected cohorts from five European countries were included for analysis (table). All cohorts were representative for routine practice. The unadjusted CIR was >90% in all cohorts and bowel preparation was adequate in ≥85% of patients. In 6 cohorts, all lesions were assessed by gastrointestinal pathologists, while in one cohort the expertise of the pathologist was not registered. The prevalence of any SP ranged from 14.1-27.2% (median 19.5), of proximal SP from 4.7-12.2% (median 9.5), of large SP from 1.1-2.6% (median 1.9), of sessile serrated adenoma/polyps from 2.2-8.2 (median 4.1) and of clinically relevant SP from 2.1-7.8% (median 4.3).

Conclusion: The prevalence of SP is variable among European countries, probably due to inconsistency in detection, reporting and/or histopathological differentiation of SP subtypes. Awareness and training is needed to facilitate optimal and more consistent practice. The median prevalence of SP subtypes, as found in this study, could be used as a guidance for detection standards among Western countries.

Disclosure of Interest: None declared

OP252 UNDERSTANDING ADR PERFORMANCE IN "BOWEL SCOPE" - THE NHS FLEXIBLE SIGMOIDOSCOPY SCREENING PROGRAMME

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Introduction: A new arm of the NHS Bowel Cancer Screening Programme began in 2013. One-off flexible sigmoidoscopy (FS) is to be offered to all 55 year olds. Six pilot sites were chosen to start this screening programme, with roll out to the rest of the country planned by 2016. A benchmark adenoma detection rate (ADR) for endoscopists within the programme is being discussed.

Aims & Methods: The NHS Bowel Cancer Screening System database was interrogated for all FS performed at the pilot sites May 2013-May 2014. Data were extracted at procedural level. Participants aged 55 were included in analyses. Overall ADR was calculated. Data of endoscopists with ≥30 procedures were reviewed, and funnel plot analyses produced for ADR, and gender adjusted observed to expected adenoma detection ratio (GAADR). GAADR was calculated using the population risk of adenoma detection in females and males to predict how many adenomas each endoscopist should find based on case mix, and calculating the ratio of predicted to observed adenomas detected. Mean negative withdrawal time (time taken to withdraw the scope when no adenoma/cancer was detected) for each endoscopist was calculated and considered in three groups – those with GAADR <0.85, 0.85 to <1.1, and ≥1.1.

Results: 8582 subjects underwent FS, of which 8494 (99.0%) were aged 55. 4420 (52.0%) were male, 4074 (48.0%) female. Adenomas were detected in 507 males (11.5%) vs 273 females (6.7%, $p < 0.001$).

44 endoscopists performed ≥30 FS. These endoscopists performed 8256 FS (range 32-476). Overall programme ADR was 780/8494 (9.2%). GAADR mean 0.99 (range 0.00-2.05). Funnel plots were produced with control lines at 95% and 99.8%. The first demonstrates ADR, the second shows GAADR by endoscopist, and demonstrate the majority of endoscopists performing with these controls. Where a single outlier existed in ADR performance, review of GAADR showed that endoscopist continued to underperform even after adjusting for case mix by gender.

Increased mean negative withdrawal time (WT) was associated with higher GAADR (2.63min when GAADR <0.85, 3.02min when 0.85 to <1.1, and 3.25min when ≥1.1).

Conclusion: These data show in 55 year olds in the Bowel Scope programme, ADR is 9.2%. ADR between endoscopists varies. There is a significant gender difference in ADR, and as such, a gender adjusted ratio could be used when analysing individual endoscopists' performance should their ADR be below a defined benchmark. The funnel plots show that most endoscopists perform within an acceptable range, and highlights those that may need further investigation. More analysis of WT is needed, as well as consideration of the impact of depth of insertion on GAADR.

Disclosure of Interest: None declared

OP253 RISK FACTORS CANNOT EXPLAIN THE SEX-SPECIFIC DIFFERENCE IN DETECTION RATES OF COLORECTAL ADENOMAS AND ADVANCED ADENOMAS

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Introduction: It is insufficiently investigated whether the sex-specific difference in incidence and age of onset of colorectal cancer (CRC) is explained by the impact of risk factors.

Aims & Methods: We analyzed the impact of known risk factors on adenomas and advanced adenomas in men and women in a CRC screening cohort.

Results: This prospective cross-sectional study included 25,409 patients. Mean age was 61 years (SD 8.3) and 50.8% were women. A multivariate model showed that risk factors mediated only 8.6% of the 58% relative gender difference in adenoma and 14.2% of the 56% in advanced adenoma detection rate revealing male sex as strongest risk factor for colorectal lesions. The only sex-specific independent risk factor for adenomas (men OR 1.46, CI 1.29, 1.64, women OR 1.76, CI 1.53, 2.06) and advanced adenomas (men OR 1.06, CI 0.80,1.42, women OR 2.08, CI 1.52,2.83) was smoking. Independent risk factors for adenomas were BMI (OR 1.35 per IQR, CI 1.25-1.47) and triglyceride level (OR 1.03 per IQR, CI 1.00-1.06); for advanced adenomas physical activity (none vs regular: OR 1.54, CI 1.18-2.00, occasional vs regular: OR 1.17, CI 1.00-1.38), cholesterol level (OR 1.13 per IQR, CI 1.02-1.25), blood glucose level (OR 1.05 per IQR, CI 1.01-1.09) and alcohol score (OR 1.09 per IQR, CI 1.01-1.18).

Conclusion: Smoking is the only sex-specific risk factor for premalignant colorectal lesions. Although some risk factors significantly influence the prevalence of colorectal lesions, this does not explain the higher prevalences in men.

Disclosure of Interest: None declared

OP254 RISK OF COLORECTAL CANCER AFTER REMOVAL OF HIGH-RISK ADENOMAS

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Introduction: Recommendations for surveillance after removal of high-risk adenomas are mainly based on risk of advanced adenoma recurrence, not on risk of colorectal cancer (CRC).
Aims & Methods: We aimed to assess the association between high-risk adenoma features and CRC risk. We included individuals with high-risk adenomas removed from 2000 to 2008 in the CRC screening program in Poland. Individuals were followed for CRC through the National Cancer Registry until December 31, 2013. High-risk adenoma group was defined as that with adenomas with villous histology or high-grade dysplasia or ≥10 mm in size or with ≥3 adenomas. We compared CRC incidence by size of adenoma (≥10 mm vs. <10 mm), histological type (villous component vs. tubular), grade of dysplasia (high-grade vs. low-grade) and number of adenomas (1-2 vs. ≥3). We estimated hazard ratios (HR) and 95% confidence intervals (CI) using proportional-hazard regression models adjusted for age, sex and family history of CRC (adenoma characteristic model). Then, we grouped individuals according to their most advanced lesion and estimated the adjusted HR for CRC risk (clinical model).
Results: In total of 10,317 individuals were included, with 74,765 person-years. We identified 49 patients with CRC during follow-up. Size ≥10 mm and high-grade dysplasia were associated with CRC risk; adjusted HR 2.18 (95%CI 1.17-4.06, P = 0.014) and 2.52 (95%CI 1.40-4.55, P = 0.002), respectively (Table). No association was found for the number of adenomas and histology type. The clinical model confirmed that high-grade dysplasia and size ≥10 mm were associated with risk of CRC; adjusted HR 5.32 (95%CI 1.96-14.44, P = 0.001) and 2.71 (95%CI 1.03-7.12, P = 0.044), respectively.

Table: Risk Factors for CRC*

	Adenoma characteristics model[$]		Clinical model[†]	
Variable	**HR[95%CI]**	**P**	**HR[95%CI]**	**P**
Age				
40-49	1.00		1.00	
50-54	1.87 [0.23-15.54]	0.562	1.84 [0.22-15.30]	0.572
55-59	3.85 [0.51-28.88]	0.189	3.88 [0.52-29.04]	0.187
60-66	5.03 [0.68-37.17]	0.114	5.04 [0.68-37.26]	0.113
Size				
<10mm	1.00			
≥10mm	2.18 [1.17-4.06]	0.014		
Grade of dysplasia				
Low	1.00			
High	2.52 [1.40-4.55]	0.002		
Most advanced lesion				
HGD			5.32 [1.96-14.44]	0.001
No HGD, ≥10mm			2.71 [1.03-7.12]	0.044
No HGD, <10mm,tubular, ≥3			1.78 [0.47-6.64]	0.391
No HGD, <10mm, villous/tubulo-villous, ≥1			1.00	

Abbreviation: HGD, high grade dysplasia. *HR reported for variables found significant in stepwise selection. [$]Sex, family history of CRC, number of adenomas and histological type were tested for inclusion in the model. [†]Sex and family history of CRC were tested for inclusion in the model.

Conclusion: The highest risk of CRC after removal of high-risk adenomas was associated with high-grade dysplasia or size ≥10mm.
Disclosure of Interest: None declared

OP255 SAFETY AND EFFICIENCY OF COLD POLYPECTOMY FOR DIMINUTIVE OR SMALL COLORECTAL POLYPS

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Introduction: Cold Polypectomy (CP) is becoming more widely used for the removal of diminutive or small colorectal polyps. Moreover a few studies reported the possibility of CP for polyps even in patients who are currently receiving antiplatelet or anticoagulant therapy. However, the safety and efficiency of CP have not been fully evaluated.
Aims & Methods: The aim of this study was to clarify the safety and efficiency of CP. 237 consecutive patients with colorectal polyps < 10mm were removed by Cold Forceps Polypectomy (CFP) or Cold Snare Polypectomy (CSP) between June 2014 and March 2015. In principle, polyp < 5mm was removed by CFP and one < 10mm by CSP. All polyps were evaluated by using a high-definition endoscope with magnification before CP to exclude invasive cancer. Polypectomy sites after CP were observed attentively with same method to assess the presence of residual polyp tissue. We retrospectively assessed the characteristics of polyps, retrieval rate, histological result, and complications.
Results: A total of 506 polyps in 237 patients (160 males and 77 females, 4.2% on antiplatelet or anticoagulant agents) were removed by CP (155 for CFP and 351 for CSP). Their mean age was 66.6 ± 10.7 years. The mean number of polyps per patient was 2.1 ± 1.8. The morphology of polyps was as follows: sessile, 216 lesions (42.7%); semipedunculated, 198 lesions (39.1%); slightly elevated, 92 lesions (18.2%). Among the 506 polyps, 312 (61.7%) were located in the right colon and 194 (38.3%) in the left colon. The mean polyp size was 3.7 ± 0.9 mm in the CFP group and 6.1 ± 1.9 mm in the CSP group, respectively. The retrieval rate was 96.2%. Histopathological evaluation showed that advanced adenoma (AA) was detected in 36 lesions (7.1%), of which 2 were removed by CFP and 34 by CSP. All of AAs were achieved complete histological resection. Neither delayed bleeding nor perforation occurred, and moreover no patient was admitted to hospital owing to other complication such as abdominal pain or discomfort after CP in our series.
Conclusion: CP is safety and effective technique for removal of diminutive or small polyp. Especially, patients receiving anticoagulants or antiplatelet agents may benefit from CP. The appropriate selection of device in accordance with polyp size is important to achieve the complete resection.
Disclosure of Interest: None declared

OP256 ACROMEGALY AND COLONIC POLYPS REVISITED: TIME TO CHANGE THE GUIDELINES?

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Introduction: Previous studies (including an important study from our own unit published nearly 20 years ago) have highlighted an increased risk of pre-malignant colonic polyps in patients with acromegaly (1). Current clinical guidelines suggest colonoscopic surveillance for these patients. Advances in detection and treatment of acromegaly may have influenced polyp prevalence in this group, and may mean revision of current guidelines is needed.
Aims & Methods: We aimed to re-evaluate polyp prevalence in a more recent cohort of patients with acromegaly undergoing colonoscopy at the Royal London Hospital.
We interrogated our database to identify patients with acromegaly undergoing surveillance colonscopy between 2010 and 2015. In these patients we reported detection of premalignant and malignant lesions.
Results: We identified 89 patients (41 males, age range 36-82, median age 64) who had undergone colonoscopy. In this cohort we identified 16 patients (18%) with at least one adenomatous polyp. Of these polyps, 69% were tubular adenomas and 31% were tubulovillous adenomas. Polyps in only two patients displayed high-grade dysplasia, the remainder displayed low grade dysplasia. No cancers were found.

	1996 cohort	2015 cohort
Tubulovillous adenoma detection rate	26%	6%
Maligancy	5%	0%
Any premalignant or malignant lesion	30%	18%

Conclusion: In comparison to the 1996 cohort we show a significantly (p = 0.04) lower detection rate of precancerous lesions in our patient group. In fact adenoma detection rates are similar to those seen in healthy colonoscopic screening populations. The reasons for this are likely complex but may in part be accounted for advances in the diagnosis, management and monitoring of acromegaly. Consideration may be given to revisiting surveillance guidelines in these patients.

Reference

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Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 11:00–12:30
DIAGNOSIS AND TREATMENT OF GI MOTILITY DISORDERS – ROOM E5

OP257 PREVENTION AND TREATMENT OF ADVANCED DENTAL EROSION DUE TO GASTRO-OESOPHAGEAL REFLUX

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Introduction: Approximately 60% of patients presenting to dentists with dental erosion have significant gastrooesophageal reflux (GERD)[1]. The paucity of typical GERD symptoms complicates the initial diagnosis, as well as the appraisal of a response to preventative measures. No treatment studies have been reported, except a small pilot study[2] and the natural history of GERD in these patients is unknown.

Aims & Methods: Detailed dental and endoscopic assessments and exclusion of other causes of dental erosion were performed in 72 successive male and female patients of mean age 34 years presenting to dentists with significant dental erosion, who had increased GERD by 24-hour multichannel intraluminal pH-impedance measurement (pH-MII). None had previously had proton pump inhibitor treatment and their median Reflux Disease Questionnaire score (interquartile range) was 3 (1-5). All were subsequently treated with esomeprazole 20mg twice-daily. After a median follow-up of 1 year, pH-MII was repeated off-PPI and dental erosion was reassessed for progression.

Results: At follow-up, reflux had normalized in 27 (38%) of patients with dental erosion. Normalization of reflux occurred in similar numbers of patients with (41%) and without (37%) progression of erosion. No progression of erosion was observed in 53 (74%) of patients treated with esomeprazole 20 mg twice-daily. None of the baseline demographic, clinical, endoscopic or pH-MII characteristics were significantly associated with progression of dental erosions at follow-up.

Conclusion: In a subset of patients with oligosymptomatic GERD and dental erosion, reflux appears to normalize after a median follow-up of one year. Progression of erosion did not occur in the majority of patients with esomeprazole 20 mg twice-daily. No baseline characteristics were predictive of progression of erosion. As no treatment guidelines for this increasingly encountered group of patients with GERD-associated oral pathology exist, we currently recommend preventative twice-daily proton pump inhibitor treatment with biannual expert dental and pH-MII evaluation.

References

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2. 2.Wilder-Smith CH, et al. *Am J Gastroenterol.* 2009;104:2788-2795.

Disclosure of Interest: None declared

OP258 DIGESTIVE SYMPTOMS AFTER SLEEVE GASTRECTOMY: USEFULNESS OF ESOPHAGEAL HIGH-RESOLUTION MANOMETRY WITH IMPEDANCE

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Introduction: Sleeve gastrectomy (SG) has become the most frequent bariatric surgery perfomed in western countries. Digestive symptoms are less frequent than after gastric banding, but the volume reduction of the gastric cavity may lead to GER or food intolerance. Gastric stasis and post-prandial regurgitations have been shown to occur after SG (1).

Aims & Methods: The goal of this retrospective study was to evaluate the impact of esophageal high resolution manometry together with impedance (HRMI) on the management of upper GI symptoms occuring after SG.

Twenty-four patients (18 women), mean age 39 years-old (range 38-58) underwent HRMI (Manoscan, Given Imaging, Duluth, GA) within a mean delay of 3 months (range : 2-50) after SG. All but 4 patients had upper GI symptoms at the time of HRMI. The procedure was performed with 10 swallows of 5 ml water in supine position, repeated swallows of 2 ml of water, and with the rapid ingestion of 200 ml of water in the sitting position. The analysis of HRM was performed according to the Chicago classification. Intra-gastric pressure (IGP) was also measured after ecah swallow. Thirteen patients also underwent an abdominal CT scan with filling of the stomach with gastrobubbles, and 3D reconstruction, to measure the volume of the sleeve. Results are expressed as mean (SD), and comparisons between groups performed by ANOVA.

Results: An increase IGP during 5 ml-swallows was observed in 18 patients (75%) : when present, this IIGP occurred in 30 to 100% of swallows (mean 35%). This IIGP was not correlated to the presence of digestive symptoms, weight loss, to the residual volume of the gastric pouch as measured by 3D-CT scan, nor to the time between the surgery and the HRMI.

Reflux episodes were detected by impedance in 47% of cases, and occurred between 10 and 100% of 5 ml-swallows (mean 20%). Patients with reflux episodes detected by impedance had more often GER symptoms (63% vs 10%, $p < 0.02$), less vigorous esophageal peristaltis (mean DCI = 1307 (663) mmHg.cm.s vs 3510 (629), $p < 0.03$), and a smaller gastric pouch volume (138 (28) ml vs 232 (31), $p = 0.054$). There was no correlation between IIGP and reflux episodes.

Conclusion: Increased intra-gastric pressure during 5 ml-swallows is very frequent after SG : it indicates a decrease of the compliance of the gastric pouch, but seems independant of digestive symptoms, since it may be present in asymptomatic subjects after SG. Reflux episodes are also very frequent and are significantly associated with typical GERD symptoms, hypotonic esophageal peristalsis and a smaller volume of the gastric pouch. HRMI may thus be uselful for the diagnosis of GERD after SG.

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Disclosure of Interest: F. Mion Financial support for research: Given imaging, Consultancy: given imaging, S. Marjoux: None declared, E. Pelascini: None declared, J.-R. Risson: None declared, M. Robert: None declared, S. Roman Financial support for research: Given imaging, Consultancy: Given imaging

OP259 PER-ORAL ENDOSCOPIC MYOTOMY FOR ACHALASIA. HOW ARE THE PATIENTS DOING AFTER MORE THAN TWO YEARS?

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Introduction: Per-Oral Endoscopic Myotomy (POEM), for the treatment of achalasia, combines the benefits of a minimally invasive approach with the long term efficacy of a surgical procedure. The short-term efficacy of POEM has been the object of various publications. However, only scanty data on the long-term follow-up are available nowadays. We report on a consecutive series of patients with achalasia who underwent POEM more than 2 years ago.

Aims & Methods: A total of 252 patients underwent POEM in a single tertiary referral endoscopy center between 2011 and April 2015. Sixty-four patients (mean age 47.5 years, 24 males) were treated more than 2 years ago and were included in the study.

After POEM patients underwent a close follow-up, including high-resolution manometry, EGD, pH-metry and timed barium swallow (TBS). Data on the clinical history, procedure and follow-up were prospectively collected and analyzed. Clinical success was defined by and Eckardt score < 4. ANOVA and Fisher's Exact test were used to identify factors related with clinical failure.

Results: Forty-two patients (68.8%) have a 2-year follow-up, 16 (26.2%) a 3-year follow-up and three (4.9%) a 4-year follow-up. Three patients (4.7%) were lost-at-follow-up.

At the last follow-up visit (mean 26.7 months), POEM was successful in 53/61 patients (86.9%). Clinical success decreased with time, being 98.4%, 95.2%, 91.7%, 90.0% and 83.3% at the 3-month, 6-month, 1-, 2-, and 3-year follow-up, respectively. Symptoms recurred in 8 patients, in 3 cases within the first year, in 3 cases after 2 years, in 1 patient after 3 years. Pneumatic dilation (PD) was proposed as initial rescue therapy in case of recurrence. Two patients refused PD and preferred surgery. Four patients underwent PD (30mm balloon); in 2 patients (50%) symptoms persisted after PD and additional sessions were scheduled. Two patients are still awaiting PD. During follow-up, esophagitis was diagnosed in 16.9% of patients (10/59 with EGD). Altered esophageal acid exposure was seen in 51% of patients (26/51 with pH-metry); 19.7% of patients complained with heartburn. In all the cases, esophagitis and heartburn completely disappeared with medications.

At univariate analysis, no differences were observed in patients with or without a successful treatment in terms of gender, age, type of achalasia, total length of myotomy, post-operative LES pressure (4sIRP). In case of clinical success, the myotomy on the gastric side was significantly longer than in cases with symptoms recurrences (3.5cm vs 2.75cm, $p < 0.05$). At postoperative TBS, patients with recurrences had a larger esophagus (5.0cm vs 2.8, $p < 0.001$), and an higher column of barium at the end of the barium swallow (12.8cm vs 4.3cm), after 1 minute (11.7cm vs 3.4cm), 2 minutes (11.8cm vs 3.1cm), and 5 minutes (10.7cm vs 2.4cm) ($p < 0.001$).

Conclusion: Our study confirms the efficacy of POEM for the management of achalasia also at a mid-term-follow-up. However, success rate seems to decrease with time. Achalasia is a chronic illness, and the efficacy should be especially evaluated at long term. A long myotomy (>3cm) on the gastric side is likely associated with better outcomes

Disclosure of Interest: None declared

OP260 PER ORAL ENDOSCOPIC MYOTOMY: A PROSPECTIVE EVALUATION OF 86 CONSECUTIVE CASES

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Introduction: Per oral endoscopic myotomy (POEM) is an endoscopic alternative to laparoscopic myotomy. Herein, we report single-center mid-term results of POEM in the Czech Republic.

Aims & Methods: Since 2012, a total of 87 POEM procedures have been performed in 86 patients (38 women, 48 men, mean age 46). All patients had a

diagnosis of achalasia (n = 85) or jackhammer esophagus (n = 1) based on endoscopic, manometric and radiologic examinations. A follow up at 3, 6, 12 and 24 months was completed in 66, 60, 41 and 12 patients. The primary outcome was treatment success defined as an Eckardt score < 3. Three months after POEM, high resolution manometry and 24-hours pH metry monitoring were performed.
Results: A. PROCEDURE: POEM was successfully completed in all patients. The median length of the procedure was 70 minutes (range 32-145). The median myotomy length was 13 cm (8-19). In 42 patients (49%), capnoperitoneum had to be decompressed and 45 patients (52%) experienced a subcutaneous emphysema which resolved spontaneously. Fever was present on the first postoperative day (POD 1) in 9 patients (10%). Eighty five patients (99%) were discharged on the POD 2 or 3 and only one patient required prolonged hospitalization due to thoracic drainage of haemothorax. We observed the following minor complications: inadvertent mucosotomy 9x (treated with clips), respiratory instability during POEM 2x, bleeding at the entry site 2x, difficult entry site closure 2x (necessary to use high resolution clips) and large subcutaneous emphysema 2x.
B. TREATMENT RESULTS: 3, 6, 12 and 24 months after POEM, treatment success (Eckardt score < 3) was achieved in 65, 57, 41 and 10 patients (98%, 95%, 100% and 83%), median score pre- vs. post-treatment 7 vs. 0 at 3, 6 and 12 months, and vs. 1 at 24 months; $p < 0.001$. The median percentage of overall symptomatic improvement was 90%. Quality of life significantly improved (median score 104 before POEM vs. 130, 137, 139 and 138 at 3, 6, 12 and 24 months after POEM, $p < 0.001$). Manometric parameters (IRP and LES pressure) normalized in a majority of patients.
Heartburn has been present in 24% of patients and 19% of patients have been treated with proton pump inhibitors. Three months after POEM, a mild reflux esophagitis (LA A) was diagnosed in 19 patients (29%) and a pathological gastro-esophageal reflux (DeMeester score > 14) was detected in 24 (36%) patients.
Conclusion: POEM is a safe and effective treatment modality in patients with achalasia with excellent mid-term results which seems durable. Although post-POEM gastroesophageal reflux is present in 36% of patients, it causes no or mild symptoms and/or mild esophagitis in some patients.
Disclosure of Interest: None declared

OP261 EVALUATION OF ENDOSCOPIC ULTRASONOGRAPHY IN THE DIAGNOSIS OF SPHINCTER OF ODDI DYSFUNCTION

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Introduction: Endoscopic retrograde cholangiopancreatography (ERCP) with manometry is the definitive investigation for the diagnosis of sphincter of Oddi dysfunction (SOD) but caries a significant risk of pancreatitis in ~15% of cases. Endoscopic ultrasonography (EUS) has been adopted in many centres as a preliminary investigation in patients considered to have SOD. This study aimed to examine the referrals for EUS to a tertiary hepatobiliary specialist centre with a potential diagnosis of SOD.
Aims & Methods: In all cases referred for evaluation of suspected SOD between January 2012 to April 2015, data was captured for age, sex, reason behind the SOD suspicion, derangement of liver function tests (LFT), findings at EUS and subsequent SOD classification.
Results: Of 1195 EUS procedures performed in this period, 5.9% (71/1195) were referred with a suspicion of SOD due to characteristic biliary pain of whom 34% (24/71) also had suggestive imaging (abnormal US/CT/MRCP). 83% (59/71) subsequently had findings consistent with SOD. Of these, the mean age was 43 years (SD ± 14) and 81% were women (48/59). In this group, 47% (28/59) had a normal EUS, 36% (21/59) biliary duct dilatation, 1 of whom also had pancreatic duct dilatation (1.7%; 1/59), 12% (7/59) had features of chronic pancreatitis, 10% (6/59) had fatty infiltration of the pancreatic parenchyma, 2% (1/59) had a duodenal diverticulum and 2% (1/59) had air in the biliary tree. Combining compatible EUS features with LFT derangement classified 10% (6/59) as Type 1 SOD, 56% (33/59) as Type 2 SOD and 34% (20/59) as Type 3 SOD. EUS revealed alternative diagnoses in 17% (12/71) of SOD queries. Of these, 42% (5/12) had microlithiasis, 25% (3/12) a biliary stricture, 17% (2/12) had pancreatic cysts, 8% (1/12) a pancreatic stricture and 8% (1/12) a duodenal diverticulum causing their symptoms and/or suggestive imaging.

Table 1: Subgroup analysis of suspected SOD referrals

	n	%
Outcome post EUS for all referrals	**71**	
SOD	59	*83*
Non-SOD	12	*17*
SOD classification post EUS	**59**	
Type 1	6	*10*
Type 2	33	*56*
Type 3	20	*34*
Alternative diagnosis post EUS	**12**	
Microlithiasis	5	*42*
Biliary Stricture	3	*25*
Pancreatic Cysts	2	*17*
Pancreatic Stricture	1	*8*
Duodenal diverticulum	1	*8*

Conclusion: Our findings highlight the importance of EUS in the evaluation of patients with a history or imaging suggestive of SOD. While the majority had EUS features consistent with this diagnosis, a significant proportion had alternative diagnosis. Precise evaluation of suspected SOD cases therefore avoids the need and risk of ERCP with manometry in a subgroup of patients who would subsequently have received it without EUS.
Disclosure of Interest: None declared

OP262 PERCUTANEOUS TIBIAL NERVE STIMULATION: A SUCCESFULL TREATMENT FOR PATIENTS WITH ANAL INCONTINENCE (URGENCY), LEADING TO A SUSTAINED RESPONSE AND MODULATING ANAL SPHINCTER PRESSURE AND RECTAL PERCEPTION

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Introduction: Little is known about the efficacy of PTNS treatment in urge anal incontinence. Our objective was to assess the long-term symptomatic response, anorectal motor and sensory function in incontinent patients treated by PTNS
Aims & Methods: This is a retrospective analysis of prospective sequential gathered data of 100 patients with anal urge incontinence treated with PTNS in a 3 year period (2010-2013). Patients had 21 treatment sessions within 8 months. St. Marks Incontinence-score and Visual Analogue Scale (VAS)-score of well-being in relation to their incontinence were collected at baseline, after 3, 8, 10 and 20 months. All patients had a high resolution manometry (sphincter pressure and rectal sensory testing) at baseline and after 12 weeks.
Results: A successful clinical response, defined as ≥ 50% reduction of the St. Marks, resp. VAS-score was reached at end of treatment (8 months) in 74% resp. 82.2% and at one year after end of treatment (20 months) in 71.1%, resp. 80.6% of the patients ($p < 0.001$). The sphincter squeeze pressure significantly improved from 126.5mmHg at baseline to 137.6 mmHg ($p < 0.001$) at 12 weeks. The constant perception for urge changed from 101.4ml to 120ml ($p = 0.002$), the maximal tolerable volume from 155.5ml to 183.7ml ($p < 0001$) after 12 weeks PTNS treatment. A significant, although weak correlation between clinical response and improvement of rectal sensory function was observed ($p = 0.04$, Spearman coefficient = -0.25)
Conclusion: PTNS is a minimal invasive treatment, with negligible side effects and a response rate of 80%. The therapeutic effect sustains at least one year after end of treatment. The treatment leads to a significant improvement of the sphincter squeeze pressure as well as the rectal perception.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 11:00–12:30
NUTRITION AND GI DISEASES – ROOM E6

OP263 THE CLINICAL AND PHENOTYPIC ASSESSMENT OF ULTRA-SHORT COELIAC DISEASE

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Introduction: Data suggests that an additional duodenal bulb (D1) biopsy may increase the diagnostic yield for coeliac disease (CD) by up to 10%. However no consensus exists on necessity of D1 biopsy. One reason may be that it is not clear if these patients with Ultra-Short Coeliac Disease (USCD) have the same phenotype or are at risk of the same consequences as conventional CD. We aimed to assess the clinical phenotypes of patients with USCD compared to those with conventional disease.
Aims & Methods: All patients attending a specialist CD endoscopy list were invited to take part. All patients had duodenal biopsy taken as routine. Patients had standard quadrantic biopsies taken from the second part of the duodenum (D2) and at least one biopsy taken from D1. Biopsies were analysed separately according to the Marsh classification system. Marsh 3 disease was required to diagnose CD. Patients had concurrent tissue tranglutaminase (tTG) and endomysial antibodies (EMA) and total IgA. All patients with VA were followed up in the CD specialist clinic where routine hematology, biochemistry, HLA typing and DXA scans were requested. Presenting symptoms and immunology were compared for all presentations. Hematology and biochemistry results were compared to a control group of patients that had CD excluded with normal serology and histology.
Results: 1378 new presentations (62% female; mean age 50.3) underwent duodenal biopsy. 268 (19.4%) new diagnoses of CD were made (66% female; mean age 41.6). CD patients were significantly younger than controls ($p < 0.0001$). 25/268 (9.3%) of new CD patients had USCD. Univariate analysis showed fewer USCD patients had diarrhoea than conventional CD (3.8 vs 24.0%, $P < 0.0001$). Decision tree analysis to identify USCD showed the absence of diarrhoea was the single discriminating factor (Adj $P = 0.018$). Rates of osteoporosis ($p = 0.78$) and anaemia ($p = 0.14$) were equal. Ferritin deficiency ($P = 0.007$) and folate deficiency ($P = 0.003$) rates were higher in conventional CD than USCD and controls. On multivariate analysis, patients with USCD were younger than

those with conventional CD 36.6 vs. 42.1 (AOR 0.97 (0.94 – 0.998) $P = 0.03$), had lower tTG titres (AOR 0.89 (0.81 - 0.98) $P = 0.02$) and were less likely to have folate deficiency (AOR 1.17 (1.01 - 1.36) $P = 0.03$) compared to conventional disease.
Conclusion: USCD appears to represent early disease with younger age and lower tTG titres and may represent a milder form of CD with lower rates of diarrhoea and folate deficiency. Long-term follow-up of patients with USCD is required to fully assess the clinical impact of diagnosis.
Disclosure of Interest: None declared

OP264 POTENTIAL CELIAC DISEASE IN ADULTS: CLINICAL FEATURES AND NATURAL HISTORY

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Introduction: Potential celiac disease (PCD) is characterized by the positivity for serological and genetic markers with absent or minimal small intestinal damage. Little is known on PCD natural history in adults.
Aims & Methods: Our aim was to define the clinical features of adult PCD and to evaluate its evolution to overt CD in cases left on a gluten-containing diet. Seventy-seven (F/M 3.2:1; mean age 25 years) of 735 CD cases, consecutively diagnosed at our center, met the diagnostic criteria of PCD. Clinical and laboratory findings of PCD patients were evaluated at diagnosis and during a follow-up ranging from one to 10 years (mean 3 years).
Results: Sixty-one of the 77 PCD were symptomatic, whereas 16 did not complain of any symptom. Of the 61 symptomatic, 10 showed diarrhea and weight loss, while 51 had other gastrointestinal (alternating bowel habit/constipation) and extra-intestinal manifestations (anemia, osteopenia, aphthous stomatitis, hypertransaminasemia, recurrent miscarriages). IgA tissue transglutaminase (TGA) and endomysial antibodies (EmA) were positive in all but one patient with IgA deficiency (TGA IgG+). HLA typing displayed DQ2 in 73 cases, whereas 3 and 2 patients had DQ8 and DQB1*02. Duodenal biopsy showed normal mucosa in 20 and high IELs count in 57 cases. All the 61 symptomatic PCD started a gluten-free diet (GFD) with a significant clinical improvement. The 16 asymptomatic PCD remained on a gluten-containing diet and were periodically followed up by serology and duodenal biopsy. Only one patient became symptomatic and developed flat mucosa, whereas the other 15 did not develop either symptoms or villous atrophy and 4 of them became antibody-negative.
Conclusion: PCD frequency is increasing in adults, accounting for about 10% of the total diagnoses. The majority of PCD cases in adulthood is symptomatic and significantly benefits from GFD. In contrast, our study indicates that GFD is not recommended in adult asymptomatic PCD, since these patients do not tend to experience symptoms over time with a possible antibody disappearance and without progression to severe intestinal damage.

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Disclosure of Interest: None declared

OP265 HLA-DQ8 CELIAC SUSCEPTIBILITY GENE IS IMPORTANT IN THE DEVELOPMENT OF BEHAVIOURAL AND MOTILITY CHANGES ASSOCIATED WITH GLUTEN SENSITIVITY

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Introduction: Non-celiac gluten sensitivity is a frequent disorder, which shares many clinical features with irritable bowel syndrome and celiac disease, including gastrointestinal symptoms and frequent psychiatric comorbidity. Its pathophysiology is poorly understood and may involve immune and genetic factors, as 50% of these patients express celiac risk alleles. Gluten sensitization and challenge in genetically predisposed mice generates immune activation and gut cholinergic nerve dysfunction, however the *in vivo* correlates of these findings are unknown.
Aims & Methods: Our aim was to investigate the effect of gliadin sensitisation and challenge on behaviour and motility in wild type and mice expressing the human HLA-DQ8 gene.
SPF C57Bl/6 and NOD-DQ8 mice maintained on a gluten-free diet were orally sensitized with cholera toxin (CT) and gliadin weekly for 3 weeks, while control mice received CT alone. Two weeks later, mice were challenged with gliadin (2mg/mouse) or vehicle 3 times per week for 2 weeks by oral gavage. Gastrointestinal motility and behavioural profile were assessed before and after gliadin challenge. Mice were sacrificed thereafter and tissue samples were collected. Motility was assessed by bead videofluoroscopy (Reed *et al* 2014), behaviour was studied by the step-down, light preference and tail suspension tests. Statistical analysis was performed using Mann-Whitney or t-tests, as appropriate.
Results: Gliadin sensitization, without gliadin challenge, did not affect motility or behaviour in C57Bl/6 or in NOD-DQ8 mice. After gliadin challenge, no changes in motility or behaviour were observed in sensitized C57Bl/6 mice. However, NOD-DQ8 mice displayed anxiety-like behaviour, as they stepped down from an elevated platform with longer latency compared to controls and they tended to spend less time in the illuminated compartment. Videofluoroscopy showed delayed gastrointestinal transit in challenged NOD-DQ8 mice compared to controls. Although a mild reduction in the villi/crypt ratio was observed in NOD-DQ8 compared to C57Bl/6 mice, no marked inflammatory or atrophic lesion was observed. Mice with higher levels of serum anti-gliadin (AGA) IgG antibodies displayed more anxiety-like behaviour and slower transit time than mice with lower AGA titers. IgA anti-transglutaminase antibodies were not detected in any experimental group.
Conclusion: Gliadin sensitization and challenge induced anxiety-like behaviour and gastrointestinal dysmotility in NOD-DQ8 mice, but not in C57Bl/6 mice. These changes were observed in the absence of mucosal atrophy or TTG antibodies, but were associated with gliadin specific antibody responses. This study suggests that the HLA-DQ8 celiac susceptibility gene is important in the development of altered behaviour and gut dysfunction associated with gluten sensitivity. These changes occur in the absence of atrophy and thus supports the concept of an underlying "celiac light" condition in gluten sensitivity.
Disclosure of Interest: None declared

OP266 COMPARISON OF LYOPHILIZED MONO- AND THREE-STRAIN PROBIOTIC AND ALIVE MULTISTRAIN PROBIOTIC ADMINISTRATION FROM CHILDHOOD FOR PREVENTION OF OBESITY IN ADULT

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Introduction: Today it is well known the association between obesity and alteration of microbiota composition in gut. Obesity contributes to destroying microbiocenosis of intestine, and in turn dysbiosis leads to excessive energy storage via various molecular pathways including increased production of short chain fatty acid and decreased expression of fasting-induced adipose factor and AMP-activated protein kinase. Such feedback loop explains the efficacy of probiotic in obesity treatment but there is still a gap in knowledge of which probiotics are more effective. Our study was aimed to compare the antiobesity effects of intermittent introduction by short courses of lyophilized three-strain and alive multistrain probiotic.
Aims & Methods: Seven groups of rats (control, MSG- and 5 MSG + probiotic group) were included. All newborn rats except control were injected with monosodium glutamate (MSG) (4 mg/g) at 2-10th days of life. MSG + probiotic groups were treated intermittently from one-month age with lyophilized monoprobiotics *B.animalis VKL*, *B.animalis VKB*, *L.casei IMVB-7280*, mix of these three probiotic strains and alive multiprobiotic "Symbiter" containing concentrated biomass of 14 alive probiotic bacteria (*Bifidobacterium, Lactobacillus, Lactococcus, Propionibacterium)*. Anthropometric parameters (weight, body length) of rats were measured, body mass index (BMI) and index Lee were calculated, total visceral adipose tissue (VAT) was weighed, biochemical parameters of lipid metabolism and level of adipocytokines (adiponectin and leptin) in serum were estimated. The clinical studies of anti-inflammatory properties of the most effective probiotic were performed.
Results: We established the beneficial effect of all probiotics intermittent administration from childhood on obesity parameters in adult rats. The most pronounced effect was detected in group treated with alive multistrain probiotic. In this group we found the greatest lowering of body weight, BMI, index Lee, improvement of biomarkers of lipid metabolism in blood (the decrease of very low-density lipoproteins and raise of content of high density lipoproteins). The normalization of hormonal activity of VAT was observed in rats treated with multistrain probiotics: the level of leptin reduced by 14.3% ($p < 0.05$) and adiponectin raised by 89% ($p < 0.05$) compared to MSG-group. In obese humans with elevated transaminases we assessed levels of proinflammatory cytokines (TNF-α, IL1β, IL6, IL8, INFγ) and showed their decreased after multistrain probiotic treatment.
Conclusion: The comparative study suggest the beneficial role of probiotic bacteria for visceral obesity treatment and confirmed the most significant antiobesity properties of alive multistrain probiotic.
Disclosure of Interest: None declared

OP267 IMPACT OF GASTRIC EMPTYING AND SMALL INTESTINAL TRANSIT ON BLOOD GLUCOSE, INTESTINAL HORMONES, GLUCOSE ABSORPTION IN THE MORBIDLY OBESE

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Introduction: The superiority of Roux-en-Y gastric bypass over gastric banding in inducing weight loss and improving glycaemic control may relate to the

exaggerated release of gut hormones from the distal intestine which plays important roles in the regulation of appetite and blood glucose. We have shown that rapid gastric and small intestinal transit is a major determinant of changes in blood glucose, intestinal hormones, and glucose absorption after gastric bypass (Nguyen et al. *Obesity* 2014), suggesting that slower small intestinal (GI) transit may be important in the pathogenesis of obesity.

Aims & Methods: The aim is to evaluate gastric emptying and small intestinal transit of the morbidly obese and their relationship to glycaemia, incretin hormones, and glucose absorption. Gastric emptying and caecal arrival time (CAT) of a mixed meal were assessed in 27 morbidly obese (age: 50.2 ± 2.5yrs; 18F:9M; BMI: 48.6 ± 1.8kg/m^2) and 10 lean healthy (age: 38.6 ± 8.4yrs; 5F:5M; BMI: 23.9 ± 0.7kg/m^2) subjects, using scintigraphy. The mixed meal consisted of a 50g beef patty (584 kJ) labelled with 15MBq ^{99m}Tc-sulfur colloid and a 150ml glucose drink (50g of glucose, 840 kJ), containing 3MBq ^{67}Ga-EDTA and 3g 3-O-methylglucose (3-OMG, to assess glucose absorption). Blood glucose, plasma 3-OMG, insulin, glucagon, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) were measured over 240 min. Insulin resistance was also assessed by HOMA-IR score.

Results: Compared to lean subjects, gastric emptying (GE-t50: 60.7 ± 6.5 vs. 41.1 ± 7.3min; P = 0.04) and CAT (221.5 ± 9.8 vs. 148.0 ± 7.1min; P < 0.001) were prolonged in the morbidly obese, and associated with smaller rises in GLP-1 (P = 0.04), GIP (P < 0.001), insulin (P = 0.02) and 3-OMG (P < 0.001). In contrast, both fasting (P = 0.045) and post-prandial (P = 0.012) plasma glucagon concentrations were higher in the obese. Although both fasting (P < 0.01) and post-prandial (P < 0.001) blood glucose were higher in the obese, the magnitude of the post-prandial glycaemic rise was less than that in lean subjects (P = 0.03). HOMA-IR score was higher in the obese subjects (4.5 ± 0.7 vs. 1.5 ± 0.2; P = 0.01).

Conclusion: Gastric emptying and small intestinal transit are slower in the morbidly obese, which is associated with lower plasma GIP and GLP-1 but higher glucagon concentrations. Given rapid gastrointestinal transit is a major determinant of weight loss after gastric bypass surgery, the current finding of slower gastric emptying in the morbidly obese may be central to the pathogenesis of obesity and warrants further evaluation.

Disclosure of Interest: None declared

OP268 ELECTROMAGNETIC GUIDED BEDSIDE VERSUS ENDOSCOPIC PLACEMENT OF NASOENTERAL FEEDING TUBES IN SURGICAL PATIENTS: A MULTICENTER RANDOMIZED CONTROLLED NON-INFERIORITY TRIAL

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Introduction: Gastroparesis in surgical patients frequently leads to the need for enteral feeding through a nasoenteral feeding tube. Endoscopic tube placement is relatively cumbersome for patients and labour-intensive for hospital staff. Electromagnetic (EM) guided bedside placement by nurses may reduce patient discomfort, workload, and costs, but evidence from comparative studies is lacking.

Aims & Methods: In this investigator-initiated, multicenter, randomized controlled non-inferiority trial, adult patients admitted to gastrointestinal surgical wards in five Dutch hospitals requiring nasoenteral feeding, were randomly assigned (1:1) to undergo EM guided or endoscopic nasoenteral feeding tube placement. The primary endpoint was the need for reinsertion of an endoscope and/or tube (e.g. after failed initial placement or dislodgement/blockage of the tube). Successful tube placement was defined as a position of the tip beyond D2 (or in the efferent jejunal limb if applicable) on imaging followed by successful delivery of enteral feeding. The trial was designed to assess non-inferiority of EM guided placement with a pre-specified non-inferiority margin of 10% more patients requiring reinsertion. The trial is registered in the Dutch Trial Register, number NTR4420.

Results: Between March 2014 and March 2015, a total of 154 patients were enrolled (88% after gastrointestinal surgery, 12% managed non-operatively). Reinsertion of an endoscope and/or tube (primary endpoint) occurred in 27 of 80 patients (34%) in the EM guided group and 31 of 74 patients (42%) in the endoscopic group (absolute risk difference -8%, upper limit of one-sided 95% CI 5%, p for non-inferiority = 0.01). No significant differences were noted in success rates of primary tube placement (56 [71%] vs. 52 [70%], RR 1.01 (95% CI 0.82-1.24), p = 0.93) or tube related complications, such as dislodgement and blockage (43 [54%] vs. 36 [49%], RR 1.11 (95% CI 0.81-1.51), p = 0.52). Conscious sedation was used in none of the 79 (0%) patients undergoing EM guided placement vs. 61 of 69 (88%) patients undergoing endoscopy. Although the level of discomfort (visual analogue scale) was higher in the EM guided group (median [IQR] 3.9 [2.0-6.6] vs. 2.0 [0.2-5.6], p = 0.009), pain, social embarrassment, anxiety and total burden were not significantly different between the two groups and EM guided placement received higher recommendation scores than endoscopy (median [IQR] 8.2 [4.8-9.9] vs. 5.5 [2.3-7.8], p = 0.008).

Conclusion: EM guided bedside placement of nasoenteral feeding tubes by nurses was non-inferior to endoscopic placement and may therefore be considered the preferred technique for nasoenteral feeding tube placement in surgical patients.

Disclosure of Interest: A. Gerritsen Financial support for research: This study was supported by Stichting Agis (Amersfoort, the Netherlands), Stichting Achmea Gezondheidszorg (Leiden, the Netherlands) and CORPAK MedSystems UK (Gatwick, United Kingdom). The sponsors had no influence on the design of the study; neither did they have any influence on the data collection, interpretation or decision to publish the results. The authors have no individual agreements, affiliations with or involvement in any of these organizations., T. de Rooij: None declared, M. Dijkgraaf: None declared, O. Busch: None declared, J. Bergman: None declared, D. Ubbink: None declared, P. van Duijvendijk: None declared, G. W. Erkelens: None declared, P. Kruyt: None declared, D. J. Bac: None declared, C. Rosman: None declared, A. Tan: None declared, I. Q. Molenaar: None declared, J. Monkelbaan: None declared, E. Mathus-Vliegen: None declared, M. Besselink: None declared

TUESDAY, OCTOBER 27, 2015 11:00–12:30

NEW INSIGHTS INTO THE PATHOPHYSIOLOGY AND PATHOGENESIS OF FUNCTIONAL BOWEL DISORDERS – ROOM B3

OP269 THE ROLE OF ZONULIN IN NON-CELIAC GLUTEN SENSITIVITY AND IRRITABLE BOWEL SYNDROME

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Introduction: Zonulin, the human homolog of the zonula occludens toxin secreted by *Vibrio cholera*, is the only known endogenous modulator of epithelial tight junctions (TJs) and intestinal permeability. Intestinal bacterial infections and gluten evoke zonulin release in the intestinal milieu and in the bloodstream. A role for zonulin has been demonstrated in different diseases such as celiac disease (CD). Increased intestinal permeability has been reported in Non-Celiac Gluten Sensitivity (NCGS) and Irritable Bowel Syndrome (IBS) although the mechanisms involved are not clear. Zonulin serum levels and its diagnostic value in NCGS and IBS remain undetermined

Aims & Methods: In the present study, we aimed at characterizing zonulin serum levels in patients with NCGS (n = 27) and IBS-D (n = 15) compared with CD (n = 15; positive control) and healthy controls (n = 15; HC, negative control). ELISA assay was used to evaluate zonulin serum levels; qPCR was used to evaluate zonulin gene expression in the colonic mucosa. Clinical data, abdominal symptoms and bowel habit were recorded and analysis of HLA alleles was performed. Zonulin serum levels were evaluated in a subgroup of NCGS patients during gluten containing diet (GCD) and gluten free diet (GFD).

Results: CD patients showed significantly higher zonulin serum levels compared to HC (0.033 ± 0.004 vs 0.007 ± 0.001 ng/mg total proteins, p < 0.0001) and to IBS-D patients (0.012 ± 0.002 ng/mg total proteins, p < 0.001). NCGS showed significantly higher zonulin serum levels compared to HC (0.030 ± 0.006 vs 0.007 ± 0.001, p < 0.05) and IBS-D (p < 0.05). IBS-D patients showed higher zonulin serum levels and colonic mRNA expression compared to HC. Zonulin levels were positively correlated with the titer of anti-TTG antibodies (r:0.6; p < 0.05) and anti-DGP antibodies (r:0.6; p < 0.05). A decrease in zonulin serum levels was observed during GFD compared to GCD (p = 0.06) and a comparable decrease was observed for AGA IgG levels (p = 0.06). Only HLA-DQ2-positive patients showed a significant decrease in zonulin serum levels during GFD compared to GCD (p < 0.05). A significant difference was observed in zonulin serum levels during GFD between HLA-DQ2-positive patients and HLA-DQ2/DQ8 negative ones (p < 0.05).

Conclusion: Zonulin serum levels are increased in IBS-D and NCGS, in addition to CD. A positive and significant correlation was found between zonulin serum levels and both anti-DGP and anti-TTG antibody titers. A comparable decrease of AGA IgG and zonulin serum levels was observed during GFD. Interestingly, only HLA-DQ2-positive patients showed a significant decrease of zonulin serum levels during GFD compared to GCD. Our data suggest that a zonulin-dependent TJ dysfunction may play a role in the pathophysiology of IBS and NCGS, particularly in a subset of patients.

Disclosure of Interest: None declared

OP270 PRINCIPAL COMPONENT ANALYSIS (PCA) WITH REPLICATION CONFIRMS FOUR INDEPENDENT ETIOLOGICAL FACTORS IN IRRITABLE BOWEL SYNDROME (IBS)

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Introduction: Multiple variables have been identified that separate IBS patients from healthy controls, including visceral hypersensitivity, motility, stool consistency abnormality, and psychological traits. It is not yet known if these variables are separate or mutually dependent.

Aims & Methods: We aimed to determine whether the variables discriminating a large sample of IBS patients from a demographically similar group of healthy individuals cluster together in distinct patterns that suggest independent pathophysiological factors in IBS. We tested 530 IBS patients (Rome II or III criteria+ physician diagnosis; 79.4% females; mean age = 35.8 years) and 337 control subjects without gastrointestinal problems (78.7% females; mean age = 34.7 years). Subjects completed psychological and gastrointestinal symptom questionnaires, as well as barostat tests to measure bowel sensory thresholds with the ascending method of limits (AML) method and the colonic motility index at rest,

after the AML, after recovery, and after a standard meal. In the control group, barostat testing was only conducted in a sub-set of 41 individuals. All variables that significantly ($p < 0.05$) differentiated IBS and control subjects (listed in the Table) were entered into PCA analysis (a statistical method useful for discovering independent dimensions among inter-correlated variables) with varimax rotation. The PCA was run twice, on randomly divided equal-size halves of the total IBS sample, to examine the stability of the generated model.
Results: Significant differences between IBS and control subjects were found on all test variables except motility post-meal, which was excluded from the PCAs. The initial PCA, on half the total IBS sample, yielded 4 factors that were easily identifiable as representing psychological functioning, motility, visceral sensitivity, and abnormal stool consistency, and collectively explained 63.9% of the total variance (see Table). The replication PCA conducted with the other half of the IBS sample yielded the same 4 factors with similar loadings, confirming the IBS factor structure, and explained 63.4% of the variance.

Numbers in table are factor loadings: Factors scoring < 0.35 have been set to 0 for clarity

	Factors:			
Psychological Functioning	**Motility**	**Visceral Sensitivity**	**Abnormal Stool Consistency**	
Hard stools by Rome II and III	0	0	0	-0.776
Soft stools by Rome II and III	0	0	0	0.798
Motility Index (baseline)	0	0.827	0	0
Motility Index (distension)	0	0.692	0	0
Motility Index (recovery)	0	0.816	0	0
AML Pain Threshold	0	0	0.939	0
AML Urge Threshold	0	0	0.934	0
Catastrophizing	0.659	0	0	0
RPSQ Somatization	0.621	0	0	0
BSI Depression (BSI-18)	0.838	0	0	0
BSI Anxiety (BSI-18)	0.838	0	0	0
Neuroticism (NEO-PI)	0.724	0	0	0

Conclusion: Our findings of four robust and replicable factors in our large IBS sample confirm that psychological variables, motility, visceral sensitivity and stool consistency abnormalities are all independent and prominent etiological contributors to IBS. [Supported by grant RO1 DK31369]
Disclosure of Interest: None declared

OP271 DIFFERENTIAL EXPRESSION OF MIRNAS IN THE JEJUNAL MUCOSA OF IBS-D IS INVOLVED IN INTESTINAL EPITHELIAL BARRIER DYSFUNCTION THROUGH MODULATION OF SPECIFIC TIGHT JUNCTION PROTEINS

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Introduction: miRNAs play a crucial role in the control of intestinal epithelial barrier function by modulating stability and translation of mRNAs encoding tight junction proteins. We have previously shown differential mRNA expression associated to ultrastructural abnormalities of the epithelial barrier, mast cell activation and symptoms in IBS-D patients. However, the role of miRNAs modulating intestinal dysfunction in IBS-D has not been fully addressed.
Aims & Methods
Aims: to identify dysregulated miRNAs in the small bowel mucosa of IBS-D patients and to identify targets specifically involved in intestinal epithelial barrier function.
Healthy controls (n = 31) (HC) and non-allergic, non-celiac, IBS-D patients (n = 45) were studied. Total RNA and protein from jejunal tissue were analyzed to identify potential candidates by: a) miRNA/mRNA profiling, by RNAseq and nCounter analysis; b) Pathway analysis and upstream regulator identification; and c) miRNA and target validation by nCounter nanostring analysis, qPCR and Western blot.
Results: Thirty-two miRNAs and 3086 mRNAs were differentially expressed (FDR < 0.05) between HC and IBS-D. Pathway and network analysis identified miR-125b as playing a central role by targeting genes involved in molecular functions and pathways relevant for modulation of epithelial barrier function like tight junction and cytoskeleton signaling pathways. Validation of selected genes showed consistent up-regulation in 7 out of 9 mRNAs involved in epithelial barrier function (Table 1). Moreover, six miRNAs (including miR-125b) identified as down-regulated in IBS-D in our miRNA profiling experiment were also highlighted as predicted to be inhibited based on the expression pattern of their targets. Down-regulation of all six miRNAs was validated by qPCR ($P < 0.05$). Bioinformatic analysis of putative miRNA binding sites by TargetScan identified miR-125b and miR-16 as potentially regulating expression of cingulin (*CGN*) and claudin 2 (*CLDN2*). Consistently, expression of these two proteins was up-regulated in IBS-D samples (*CGN* fold-change 1.5; $P < 0.01$; *CLDN2* fold-change 1.7; $P < 0.01$). Down-regulation of both miRNAs negatively correlated with bowel habits ($r > -0.55$; $P < 0.01$) and mast cell numbers ($r > -0.52$; $P < 0.01$) while up-regulation of *CGN* and *CLDN2* protein positively correlated with bowel habits ($r < 0.60$; $P < 0.001$).
Conclusion: Modulation of the intestinal epithelial barrier function in IBS-D involves both transcriptional and post-transcriptional mechanisms. These molecular mechanisms include miRNAs as master regulators in controlling the expression of TJ proteins and are associated with major clinical symptoms and mast cells.
Disclosure of Interest: None declared

OP272 AUTOMATING THE ANALYSIS OF HIGH-RESOLUTION COLONIC MANOMETRY DATA

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Introduction: The introduction of high-resolution manometry to record colonic motor patterns has helped to quantify and define both normal and abnormal colonic motor patterns in health (1) and disease (2). However, the recording also generates large quantities of data that makes manual analysis both time consuming and subject to bias, and therefore the findings are difficult to standardize amongst different research groups.
Aims & Methods: We have used colonic manometry data recorded for two previous publications (1, 2). Data were recorded with a 72 sensors (spaced at 1cm intervals) fibre-optic manometry catheter from 12 healthy controls (5 men; median age 51 years; range 27 - 69 yrs) and 14 patients (2 men; median age 52 years; range 24 - 76 years) with scintigraphically defined STC. The manometric recordings were taken for two hours pre and post a 700cKal meal. The approach used in this work was adapted from a technique developed in the field of meterorology (3), and effectively identifies wave forms in adjacent channels of data and determines the likelihood that the wave forms are associated with one-another; it therefore identifies propagating events. Utilising the baseline-corrected data from each study, the automated analysis applied a cross wavelet transform between each pair of adjacent sensors, for each region in the colon (proximal, descending and sigmoid colon). The technique averages the phase of the transformed data over the duration of each period, weighted by the amplitude of the transformed data. The result is then averaged over all pairs of adjacent channels per region. The value for each region, in each of the groups (health and patients) was then averaged across each of the subjects within each group. The end result indicates a distribution of propagating activity (antegrade / retrograde) over the propagation-velocity and frequency of the propagating activity.
Results: The group mean data for each region in healthy controls and patients with slow transit constipation is shown in fig 1. In health (post meal) motor activity in the proximal and descending colon is characterized by predominantly antegrade propagating events that occurs at > 1 per min and travel at ~0.5cm/s. In contrast in the sigmoid colon, propagating activity is

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	RNAseq			nCounter		
Gene	**Mean Reads**	**Fold-change**	**FDR- adjusted P-value**	**Mean Counts**	**Fold-change**	**FDR- adjusted P-value**
CDH1	5220	1.8	0.00001***	10283	1.8	0.0002***
CELF1	524	1.3	0.003**	768	1.5	0.0001***
CGN	2188	1.5	0.0001***	1048	1.4	0.05*
CTNNA1	2875	1.5	0.002**	4671	1.6	0.007**
CTNNB1	1998	1.4	0.01*	5892	1.3	0.01**
F11R	3013	1.8	0.0001***	2429	1.6	0.007**
JAM2	119	-1.3	0.03*	278	1.2	0.34
JAM3	70	1.5	0.02*	113	1.3	0.06
PLEKHA7	692	1.8	0.002**	465	1.6	0.01**

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	vehicle	antibiotic treatment	2 wkspost antibiotic discontinuation	4 wkspost antibiotic discontinuation	6 wkspost antibiotic discontinuation
GI motility(geometric centre)	7.50 ± 0.33	8.63 ± 0.08*	8.24 ± 0.15*	8.49 ± 0.38*	7.81 ± 0.25
muscle tension(EFS, 40Hz)	126 ± 12	45 ± 8*	43 ± 11*	93 ± 14	102 ± 10
damage of the ENS (score)	-	+++	++++	++	+
GDNF mRNA levels (ΔC_T)	7.3 ± 0.2	1.7 ± 0.5*	2.3 ± 0.3*	2.7 ± 0.2*	2.5 ± 0.5*

*$P < 0.05$ *vs* vehicle

predominantly retrograde, occurring at 2-4/min, traveling at speeds between 0.5-8cm/s. No dominant post-prandial propagating activity is seen in the patient data.
Conclusion: This automated technique clearly defines both regional differences of propagating activity within the healthy human colon, and differences between patients with slow transit constipation and healthy controls.

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Disclosure of Interest: None declared

OP273 SEARCHING FOR GENES WHERE THE SUN DON'T SHINE: A PILOT GENOME-WIDE ASSOCIATION STUDY (GWAS) OF STOOL FREQUENCY IN A SWEDISH POPULATION-BASED SAMPLE

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Introduction: Normal gut function, including regular defecation, is of key relevance to human wellbeing. This is evident, for instance, from alterations of stool frequency and pattern frequently observed in functional disorders such as irritable bowel syndrome (IBS), where these are in fact regarded as intermediate phenotypes or endophenotypes of disease. While stool frequency appears to be a rather stable intra-individual phenotype from clinical observations, anecdotal evidence suggests it may have familial aggregation although this has never been scientifically investigated. We explored the potential correlation between genotype and stool frequency/pattern by studying GWAS data in relation to daily bowel function recordings in 251 Swedish healthy individuals.
Aims & Methods: 251 participants from the Population-based Colonoscopy cohort (PopCol) were included, with available genome-wide genotype (Illumina HumanOmniExpressExome+) and recorded questionnaire data including daily recordings of bowel movements (BM) scored on the Bristol Stool Form Scale (BSFS) over 1 week. 637,607 SNP markers from 247 individuals passing quality control (QC) filters were studied in relation to quantitative measures of stool frequency and pattern (BM/day, total BSFS/day) using linear regression adjusting for age and gender under an additive genetic model. Enrichment of Gene Ontology (GO) terms was performed with hypergeometric test based tools.
Results: Genome-wide association testing of bowel movement frequency and BSFS scores identified a total of 86 suggestive ($P < 5x10-5$) association signals, spread over 41 genes. Among these, strongest associations were detected respectively in the *TEAD1* gene on chr 11 ($P = 6.42x10-7$ for rs10766003) and the *PLIN3*promoter on chr 19 ($P = 6.57x10-7$ for rs3760949). Gene set enrichment analysis highlighted specific GO pathways including smooth muscle contraction, cellular response to organic cyclic compound and almost reassuringly, response to caffeine.
Conclusion: "Outside-the-box" approaches to gene-hunting in gastroenterology may provide valuable clues to human gut function and physiology, and therefore improve our understanding of GI disease. Massive-scale efforts are required to reach adequate statistical power for the analyses of "loose" phenotypes, though these appear feasible if existing epidemiological and genetic data from several population-based cohorts are combined and exploited. We provide preliminary evidence that specific genes and associated pathways may be relevant to the control of bowel movement frequency, and establish a set of candidate targets for follow-up and replication in independent datasets.
Disclosure of Interest: None declared

OP274 ANTIBIOTIC TREATMENT INDUCES LONG LASTING EFFECTS ON MURINE ENTERIC NERVOUS SYSTEM AND IMPAIRS GUT MOTILITY

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Introduction: The most common side-effects of antibiotic treatment such as diarrhoea, bloating and abdominal pain are considered the direct consequence of intestinal dysbiosis. Indeed, a balanced gut microbiota is known to support the integrity of the enteric nervous system (ENS) which in turn controls gastrointestinal (GI) neuromuscular functions.
Aims & Methods: In this study we investigated the long-term effects of antibiotic-induced microbial dysbiosis on the ENS and we studied the impact of the spontaneous re-establishment of the gut microbiota on GI functions. C57Bl/6 mice were treated daily for 2 weeks (wks) with a cocktail of antibiotics. After 0-6 wks of antibiotic wash-out we determined a) gut microbiota composition by quantitative PCR (qPCR) on faecal DNA, b) GI motility by measuring fluorescein-isothiocyanate dextran distribution in the gut; c) changes in isometric muscle tension in ileal segments; d) integrity of the ENS by immunohistochemistry (IHC) on ileal whole-mount preparations; e) neurochemical code by qPCR and IHC; f) inflammatory damage by histological examination.
Results: Two wks of antibiotic treatment reduced the bacterial 16S rRNA genes copy number by 300-fold and resulted in a higher *Firmicutes*/*Bacteroidetes* ratio compared to vehicle-treated mice. Mice treated with antibiotics experienced delayed GI transit time, impaired electric-field stimulation (EFS)-elicited contraction, altered expression and distribution of the neurofilaments peripherin and βIII-tubulin, and deregulated expression of Substance P and nNOS (see Table). Histological examination of ileum and colon sections revealed nearly normal structure in mice after 2 wks of antibiotic administration and after 2-6 wks of antibiotic discontinuation. At the 6th week from antibiotic interruption bacterial DNA load re-established at normal levels but the composition of gut microbiota greatly diverged from the one of vehicle treated mice. As assessed by qPCR, Bacteroides and Lactobacillus groups drastically decreased in antibiotic-treated mice while the Clostridium became the predominant group. The functional and structural anomalies of the ENS still persisted 4 wks after antibiotic interruption whereas the expression of glial marker S100β and the glial derived neurotrophic factor (GDNF) did not recover.
Conclusion: In this study we strengthened the idea that antibiotic-induced GI dysmotility directly correlates with gut dysbiosis and structural and functional damage in the ENS. Therefore, fostering the recovery of gut microbiota (i.e. probiotic supplementation) could be helpful for restoring the neurochemical code of the ENS and reducing the antibiotic-induced adverse effects on GI motility.

Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 14:00–15:30
DIAGNOSTIC AND THERAPEUTIC CHALLENGES IN GORD – ROOM B2

OP275 USE OF ACID-SUPPRESSIVE THERAPY BEFORE ANTI-REFLUX SURGERY. A NATIONWIDE REGISTER-BASED STUDY IN DENMARK

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Introduction: Guidelines recommend that patients with gastroesophageal reflux disease are adequately treated with acid-suppressive therapy before undergoing anti-reflux surgery (ARS). Little is known of the use of acid-suppressive drugs before ARS.
Aims & Methods: This study aimed to determine the use of proton pump inhibitors and histamine-receptor-2-antagonists in the year before ARS.
We performed a nationwide retrospective study of all patients aged ≥18 undergoing first-time ARS in Denmark during 2000 – 2012 using data from three different sources: the Danish National Register of Patients, the Danish National Prescription Register, and the Danish Person Register. We extracted data for prescriptions on acid-suppressive therapy (proton pump inhibitors and/or histamine-receptor-2-antagonists) within five years before ARS and prescriptions of non-steroidal anti-inflammatory drugs (NSAID) and antiplatelet drugs for the year leading up to ARS. We also extracted data for the pre-surgical procedures upper endoscopy, esophageal manometry, pH monitoring and impedance monitoring within three years before ARS.
We defined inadequate dosing as redeeming <180 defined daily doses (DDD) of acid-suppressive therapy in the year before ARS and factors associated with inadequate dosing was analyzed using logistic regression and presented as odds ratio (OR) with 95% confidence intervals (CI).
Results: The study population included 2,922 patients (median age: 48 years, 55.7% male). The annual proportion of patients redeeming ≥180 DDD of acid-suppressive therapy increased from 17.0% five years before ARS to

64.9% one year before. Of the 1,895 patients redeeming ≥180 DDD in the year before ARS, 1,121 (59.2%) redeemed ≥360 DDD. Of the 1,027 patients redeeming <180 DDD one year before ARS, 839 (81.7%) redeemed <180 DDD every year in the five years leading up to surgery.
The probability for inadequate dosing one year before surgery (<180 DDD) was significantly increased for younger patients aged 18 - 39 (OR 1.8; 95% CI: 1.4 - 2.2), patients operated in the period 2000 – 2003 (OR 1.7; 95% CI: 1.4 - 2.1), patients, who had not undergone pre-surgical manometry, pH- or impedance monitoring (OR 1.6; 95% CI: 1.3 - 2.0), and patients, who had not redeemed prescriptions on NSAID or antiplatelet drugs (OR 1.3; 95% CI: 1.1 - 1.6).
Conclusion: Compliance to medical therapy should be evaluated thoroughly before planning anti-reflux surgery since a high proportion of patients received inadequate dosing of acid-suppressive therapy prior to the operation.
Disclosure of Interest: None declared

OP276 A NOVEL PROSTANOID EP1 RECEPTOR ANTAGONIST ONO-8539 REDUCES ACID-INDUCED HEARTBURN SYMPTOMS IN HEALTHY VOLUNTEERS

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Introduction: Prostaglandin E_2 (PGE_2) is a key mediator in the processing of pain hypersensitivity via the EP1 receptor, and the previous study showed that an EP1 receptor antagonist (ZD6416) has been shown to attenuate the development of oesophageal hypersensitivity in humans [1]. Recently, we have also reported that oesophageal PGE_2 expression is associated with degree of heartburn induced by mucosal acid exposure [2-3]. In the present study, we investigated the effects of ONO-8539, a novel EP1 receptor antagonist, on the induction of heartburn symptoms by acid perfusion in healthy men.
Aims & Methods: The present prospective, double-blinded, placebo-controlled, 2-period cross-over study was performed over 3 visits in 20 healthy men. A novel prostanoid EP1 receptor antagonist, ONO-8539 (450 mg), was administered once 4 h prior to an acid perfusion test. During the test, hydrochloric acid (0.15 mol/L) was perfused into the lower oesophagus for 30 min. We evaluated heartburn symptoms during acid infusion using a validated categorical rating scale. Further, we calculated and assessed the area under the curve (AUC) as a total symptom score.
Results: Compared with placebo, ONO-8539 significantly extended the time (min) to first sensation of heartburn (5.7 ± 4.3 min for placebo and 9.7 ± 7.2 min for ONO-8539; $P < 0.05$), and ONO-8539 significantly reduced the AUC for heartburn (83.5 ± 10.2 for placebo and 56.5 ± 7.2 for ONO-8539, $P < 0.05$).
Conclusion: ONO-8539 attenuated acid-induced heartburn in healthy men. EP1 receptor plays a key role in generation of heartburn symptoms and ONO-8539 may be a novel therapeutic option for controlling these symptoms in patients with gastroesophageal reflux disease. Clinical Trials Registry no: UMIN000015753.

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Disclosure of Interest: None declared

OP277 PROTON PUMP INHIBITORS AND THE RISK OF PNEUMONIA USING A NEW ANALYTICAL TECHNIQUE: PRELIMINARY RESULTS FROM A RETROSPECTIVE COHORT STUDY USING PRIMARY CARE DATABASE

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Introduction: Research examining the association between use of proton pump inhibitors (PPIs), and risk of pneumonia has been inconsistent. Due to the difficulties associated with conducting trials, the majority of existing studies that aimed to investigate this association were observational in nature. These observational studies have been criticised due to a lack of control for unmeasured confounding. The prior event rate ratio (PERR) adjustment method, an analytical method to control for unmeasured confounding(1), may overcome this problem.
Aims & Methods: The aim of this study was to determine whether the association between PPI use and pneumonia is independent of confounding through the use of the PERR method. A cohort study was conducted using anonymised records from a primary care database between the years 1990 and 2013. Adult patients newly prescribed a PPI (exposed) were selected and individually matched, according to age, gender and year of prescription, to subjects not prescribed a PPI (un-exposed). The primary outcome was the occurrence of first pneumonia event before and after a prescription of PPI. PERR was estimated by dividing the unadjusted hazard ratio for pneumonia during the year after initial PPI prescription (of the exposed group versus the unexposed group), by the unadjusted hazard ratio for pneumonia before the PPI prescription (of the exposed versus the unexposed group).
Results: There were 1,176,632 subjects included in this study. The rate of pneumonia was higher (3.04 per 1,000 person years of follow-up) before the PPI prescription compared with the rate after a prescription for the exposed patients (2.85 per 1,000 person years of follow-up). Exposed patients were at 3.05 (95% confidence interval 2.78-3.25) times more risk of pneumonia than patients not prescribed a PPI in the period before the first PPI prescription, and 2.41 (95% confidence interval 2.20-2.63) times the risk afterwards(see table). Giving a PERR for pneumonia of 0.79.
Table unadjusted hazard ratio (95% confidence interval) before and after prescription of proton pump inhibitor .

Patients matched for dateTotal number of patients(1,176,632)	PPI exposed Number of patients588,316	Non-PPI exposed Number of patients588,316
Before PPI prescription		
Pneumonia event (%)	1790(0.30)	587(0.09)
Person years follow-up	587.69	588.02
Incidence per 1,000 per person year(95%CI)	3.04 (2.90-3.19)	0.99 (0.92-1.08)
Hazard ratio (95%CI)(PPI/non-PPI)	3.05 (2.78-3.25)	
After PPI prescription		
Pneumonia event (%)	1,675(0.28)	695(0.11)
Person years follow-up	587.43	587.97
Incidence per 1,000 per person year(95%CI)	2.85 (2.71-2.99)	1.18 (1.09-1.27)
Hazard ratio (95%CI)(PPI/non-PPI)	2.41 (2.20-2.63)	

Conclusion: The outcome of the study indicates that commencing PPI use does not increase the association between the eventually PPI exposed group and the risk of pneumonia. It is likely therefore that confounding factors present before PPI use rather than the PPI itself were the main contributors to an increased rate of pneumonia in patients who have been prescribed PPI.

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Disclosure of Interest: None declared

OP278 INVOLVEMENT OF LEPTIN IN THE SEVERITY OF REFLUX OESOPHAGITIS

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Introduction: Obesity has widely been recognized to promote a wide variety of diseases including Gastroesophageal reflux disease (GERD), Barrett's esophagus and ensuring arising of esophageal adenocarcinoma (EAC) which incidence depicts sharp rise in the western countries over the last 3 decades.[1] Leptin, adhipokine that exerts pleiotropic functions such as regulation of food intake and energy consumption as well as inflammatory response, is increased in obese individuals.[2] In humans, women's serum leptin level is about 3-fold as high as men, however there is profound male-predominance in GERD related diseases.[3, 4] On the other hand, postmenopausal women have a higher incidence of these diseases. We hypothesize that the discrepancy of the gender difference attributes to sex hormones.
Aims & Methods: Male and female wistar rats were subjected to a surgically induced GERD model. Groups of rats were treated continuously subcutaneous injection of leptin. Divided female rats underwent ovariectomy to diminish serum 17b-estradiol (E2). Intensity of GERD was assessed both macroscopically and histologically. Expression in tissue TNF-a was measured by immunohistostaining and serum leptin level was measured by ELISA.
Results: A significant increase in inflammation of reflux esophagitis was observed in leptin-administered male rats compared to control rat, followed rising of serum leptin level (injury area: $17.7 \pm 11.3\%$ vs $5.4 \pm 2.9\%$, $p < 0.01$), whereas a slight decrease in severity of reflux esophagitis was seen in leptin-injected female rats compared to controls (injury area: $2.9 \pm 1.5\%$ vs $2.5 \pm 1.0\%$). Additionally significant deterioration in esophagitis was observed in ovariectomized and leptin-applied female rats (injury area: $5.8 \pm 3.5\%$ vs $2.9 \pm 1.5\%$, $p < 0.01$). Leptin administration caused TNF-a expression in esophageal epithelium to increase in both male and ovariectomized female rats compared to respective controls.
Conclusion: We showed that high level of leptin profoundly intensified inflammation induced by acid reflux in male and ovariectomized female rats, while the leptin tended to decrease the inflammation in non-ovariectomized female rats. Sex hormones secreted from ovary such as E2 could downregulate TNF-a expression induced by leptin and strengthen an epithelial defense system in lower esophagus to ameliorate an inflammation caused by GERD.[5] Severe GERD is reported to correlate high prevalence of Barrett's esophagus and

subsequent development of EAC. [6]Thus, this molecular process might shed light to develop a new therapeutic strategy for EAC.

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Disclosure of Interest: None declared

OP279 NOVEL IMPEDANCE PARAMETERS IMPROVE THE DIAGNOSTIC YIELD OF IMPEDANCE-PH MONITORING IN GERD – A MULTICENTER STUDY

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Introduction: Recently, two novel impedance parameters evaluating esophageal chemical clearance and mucosal integrity, namely the post-reflux swallow-induced peristaltic wave (PSPW) index and the mean nocturnal baseline impedance (MNBI) have been proposed. According to the results of preliminary studies, they appear as potentially useful to improve the diagnostic accuracy of impedance-pH monitoring in gastroesophageal reflux disease (GERD).
Aims & Methods: We aimed to assess whether the PSPW index and the MNBI can improve the diagnostic yield of impedance-pH monitoring in typical GERD. Off-therapy impedance-pH tracings from 289 patients with proton pump inhibitor (PPI) responsive heartburn, 68 with erosive (ERD) and 221 with non-erosive (NERD) reflux disease, and from 50 healthy controls were blindly reviewed. The PSPW index, the MNBI, the esophageal acid exposure time, the number of total refluxes, and the bolus exposure were calculated as well as the symptom association probability (SAP+ if $\geq$ 95%) and the symptom index (SI+ if $\geq$ 50%). In particular, a PSPW was defined as an antegrade 50% drop in impedance relative to the pre-swallow baseline originating in the most proximal impedance site, reaching all the distal impedance sites, and followed by at least 50% return to the baseline in the distal impedance sites (bolus exit). Only PSPWs with bolus exit occurring within 30s from the end of reflux episodes were taken into account. For each impedance-pH tracing, the number of refluxes followed within 30s by a PSPW was divided by the number of total refluxes in order to obtain the PSPW index. MNBI was assessed from the most distal impedance channel during nighttime recumbent period. Three 10-minute time periods (around 1.00 am, 2.00 am, and 3.00 am) were selected. Time periods including swallows, refluxes and pH drops were avoided. The mean of the three measurements was calculated to obtain the MNBI.
Results: At receiver operating characteristic (ROC) analysis, the area under curve (AUC) of the PSPW index (0.977, 95% CI 0.961-0.993) was significantly greater than that of the other impedance-pH parameters ($P < 0.001$). The PSPW index and the MNBI showed the highest sensitivity in ERD (100% and 91%) and in 118 pH-positive (99% and 86%) and 103 pH-negative (77% and 56%) NERD cases. In pH-negative NERD, the PSPW index and the MNBI had the highest sensitivity in 65 SAP/SI positive (82% and 52%) and in 38 SAP/SI negative (68% and 63%) cases. NERD diagnosis was confirmed by pH-only criteria, including SAP/SI positivity, in 165/221 (75%) cases and by impedance-pH criteria in 216/221 (98%) cases ($P = 0.001$).
Conclusion: The PSPW index and the MNBI improve the diagnostic yield of impedance-pH monitoring in typical reflux disease. Impedance-pH criteria, including calculation of the PSPW index and the MNBI ensure significant diagnostic gain as compared to pH-only criteria.
Disclosure of Interest: M. Frazzoni: None declared, E. Savarino Lecture fee(s): Given Imaging, N. de Bortoli: None declared, M. Furnari: None declared, I. Martinucci: None declared, L. Frazzoni: None declared, S. Marchi: None declared, R. Conigliaro: None declared, V. Savarino: None declared

OP280 MAGNETIC SPHINCTER AUGMENTATION VERSUS TOUPET FUNDOPLICATION: A LONGITUDINAL STUDY FOCUSED ON QUALITY OF LIFE

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Introduction: Only about 1% of the patients with gastroesophageal reflux disease (GERD) are offered a surgical option. This is mostly due to the fear of potential side effects, the variable success rate, and the extreme alteration of gastric anatomy with the current gold standard, the laparoscopic Nissen fundoplication. Laparoscopic Toupet Fundoplication (LTF) and laparoscopic magnetic sphincter augmentation (LINX) seem to prevent reflux more physiologically and with a lower incidence of side-effects and reoperation rate. We present the first case-control study comparing LTF and LINX.
Aims & Methods: Between March 2007 and December 2014, 135 LINX and 97 LTF patients were compared by using the propensity score full matching method. Outcomes were measured by GERD-HRQL scores, PPI use, dysphagia rate, bloating and reoperation rate. HRQL-GERD and bloating were analyzed over the time using Generalized Estimating Equation (GEE) with logit link function. Dysphagia was analyzed using logistic or Firth logistic regression and PPI use with chi square test.
Results: At 7-year follow-up, patients in both groups had similar GERD-HRQL scores (OR 1.01 CI 0.82-1.30 $p = 0.80$) and PPI use (14% of LINX and 11% of LTF, $p = 0.7$). No significant differences were detected in the incidence of dysphagia (9% of LINX and 9% of LTF, $p = 0.89$) and bloating (OR 0.69 CI 0.21-2.28 $p = 0.54$) between the two groups. Reoperation rate was 7.4% in LINX and 2% in LTF ($p = 0.13$).
Conclusion: In two contemporary cohorts of patients matched by propensity score analysis, control of reflux symptoms was similar after both LINX and LTF. No statistically significant difference was found in the incidence of dysphagia, bloating, and reoperation rate. These results suggest a possible paradigm change and a new concept of antireflux surgery.

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Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 14:00–15:30
ENGAGING IBD PATIENTS IN THE MANAGEMENT OF THEIR DISEASE – ROOM 7.1

OP281 IMPACT OF AN EDUCATION PROGRAM ON IBD PATIENT'S SKILLS: A RANDOMIZED, CONTROLLED MULTICENTER STUDY (ECIPE)

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Introduction: Inflammatory bowel diseases (IBD) may induce difficulties in everyday life of patients. Treatment is aimed at reducing symptom burden, progression of damage and impact on quality of life. An improvement of patients' skills, in terms of knowledge, competences and behavior could have a positive impact on therapeutic efficacy, control of the disease and quality of life. The aim of our study was to demonstrate that an education program could have a significant impact on IBD patient's skills with regards to their disease.
Aims & Methods: GETAID centers, which promoted therapeutic education through the EDU-MICI program, were eligible. Patients were randomized into "educated" or "non-educated" groups for 6 months. A crossover then allowed uneducated patients to benefit from the educational program the next 6 months. Inclusion criteria were: - patients with a recent diagnosis (<6 months), - or need to optimize medical therapy. Education was performed by dedicated staff (mainly nurses) using an illustrated book, covering the different dimensions of life with an IBD. A psycho-pedagogic score (ECIPE score) was performed by a "blinded" physician (independent from the education team) at M0, M6 and M12. The primary endpoint was the variation of ECIPE score at M6. A variation of more than 20% was considered as significant. Different questionnaires, including SIBDQ, RFIPC, and WPAI were completed by patients.
Results: 263 patients were included in 18 centers (40% Male; median age: 30.8; 73% CD; 27% UC): 133 patients were randomized in the educated group and 130 in the non-educated group, with no marked differences regarding baseline characteristics. The primary endpoint was reached with a 27.8% variation [IQR: 9-47] of the ECIPE score at M6 in the educated group vs. 9% [0-20] in the non-educated group ($p = 0.0007$). Variation in ECIPE score of more than 20% was observed in 46% vs. 24% in the educated and non-educated groups, respectively ($p = 0.0003$). Within ECIPE score, variations were significant for items regarding competences and behavior, but not for those regarding quality of life. A total of 92 patients experienced an increase in ECIPE score of at least 20%. In multivariate analysis, randomization in the educated group (OR = 2.61) together with no past surgery (OR = 2.00) remained associated with an increase of ECIPE score of at least 20%. These patients who had an increase in ECIPE score of at least 20%, also significantly improved all ECIPE sub-scores (competences, behavior, quality of life) and SIBDQ, RFIPC and WPAI scores, except for the observance score.
Conclusion: This large prospective controlled multicenter study shows for the first time, that an educational program improve the skills of IBD patients, as

demonstrated by a significant increase of a psycho-pedagogic score in the educated group.
This study has been supported by a grant from MSD France and from Association François Aupetit
Disclosure of Interest: None declared

OP282 PATIENTS PERCEPTIONS OF QUALITY OF CARE AND FOLLOW-UP IN INFLAMMATORY BOWEL DISEASE

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Introduction: Quality of care (QoC) is increasingly used in evaluation of health care performance. In IBD, a better QoC is often linked to the number of patients on corticosteroid-free remission, number of hospitalizations and surgery. Factors of equal importance to patients may however be health-related quality of life (HRQoL), patient-care provider communication, access to care, autonomy and shared decisions. Recently the IMPACT study (1) revealed that IBD patients may be experiencing sub-optimal care related to some of these issues.
Aims & Methods: The aim of this study was to assess patient perceived QoC and patient centeredness in follow-up among IBD outpatients in Norway. Furthermore to identify potential clinical and epidemiological associations to QoC scores. A purposely designed questionnaire was developed, based on clinical assessment, patient input and literature review. Questionnaire items covered aspects related to specialist care, primary care and hospitalizations. Clinical and epidemiological data was gathered by interview, medical records and laboratory tests. Validity was tested with Cronbach's alpha, while descriptive analysis was used to describe the material. Associations between QoC and background variables were investigated with t-tests, chi-square and Pearson's correlation coefficient.
Results: In all, 414 patients gave informed consent to participate in the study. Of these, 411 had complete datasets, CD; n = 231, UC; n = 180, female (202/411, 49.1%). Internal consistency (Cronbach's alpha) was 0.90. In total, 86.1% (354/411) reported to be either satisfied or very satisfied with the quality of IBD follow-up. In contrast 4.1% (17/411) of patients were dissatisfied or very dissatisfied with QoC. There were no significant differences between the two diagnostic groups (Mean UC = 4.3, CD = 4.2). Moreover, no significant correlations were found between QoC scores age, calprotectin levels, CRP or number of relapses (prior 365 days). In UC, but not in CD, female gender was associated with decreased scores in general satisfaction ($p = 0.05$). In CD, elevated SCDAI score correlated negatively ($p = 0.03$), while a longer disease duration was correlated positively with QoC scores ($p = 0.04$). The highest level of dissatisfaction in IBD follow-up was related to general practitioners' (GP's) knowledge of IBD (75/411, 21.9%), and communication with primary health care after hospitalizations (26/278, 12.6%). Moreover, 19.2% (62/411) and 32.4% (75/411) of patients reported little focus on quality of life and on relatives in IBD follow-up.
Conclusion: Contrary to the findings presented in the IMPACT study, this large, multicenter study revealed that a majority of IBD patients are satisfied with IBD care and follow-up. In CD, patients with shorter disease duration and increased symptoms seem to have lower satisfaction scores. Furthermore, many patients perceive little focus on the psychosocial impact of IBD in follow-up.

Reference

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Disclosure of Interest: None declared

OP283 MEDICATION ADHERENCE IN INFLAMMATORY BOWEL DISEASE IN THE GLOBAL ALIGN STUDY: IMPACT OF CONCERNS AND PERCEIVED NECESSITY OF IMMUNOSUPPRESSANTS, 5-AMINOSALICYLATES, AND TUMOR NECROSIS FACTOR INHIBITORS

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Introduction: Relatively little is known about the relationship between patients (pts') beliefs (eg, concerns, necessity) regarding inflammatory bowel disease (IBD) therapies and medication adherence; a better understanding could enhance interventions to optimize adherence.
Aims & Methods: The global, cross-sectional ALIGN study determined pts' beliefs about, and adherence to, systemic therapies in > 7000 pts with 6 immune-mediated inflammatory diseases including Crohn's disease (CD) and ulcerative colitis (UC). Consecutive pts completed the Beliefs About Medicines Questionnaire (BMQ) and 4-item Morisky Medication Adherence Scale (MMAS-4) at a routine visit. Here, CD and UC pts were divided into 3 treatment groups (**Table**). The reference for comparisons was immunosuppressant (IS) monotherapy for CD and 5-aminosalicylate (5ASA) monotherapy for UC. Multiple random-effect linear and logistic regression analyses explored pts' beliefs regarding their therapies and associations with adherence.
Results: 1146 CD pts and 613 UC pts were analyzed. In CD, BMQ-Specific *Concern* ratings were similar for IS, 5ASA, and TNFi. In UC, TNFi (alone or combined with IS) and IS (in combination therapy) were associated with increased concerns vs 5ASA monotherapy. For CD and UC, TNFi (alone or combination) was associated with higher BMQ-Specific *Necessity* beliefs vs IS monotherapy. Older age and higher necessity beliefs were associated with higher treatment adherence in multivariable regression. Higher proportions of CD and UC pts reported high adherence (MMAS-4 = 4) to TNFi vs other therapies (73%–82% vs 29%–59%). Regression analyses revealed that, in CD and UC, adherence was significantly higher with TNFi therapy (alone or combined with IS) vs IS monotherapy; in UC, adherence was significantly higher with IS and TNFi (alone or in combination) vs 5ASA monotherapy (**Table**).
Conclusion: This large cross-sectional study indicates that concerns regarding TNFi are similar to conventional therapies in CD and UC, but are higher compared with 5ASA treatment in UC. In both CD and UC, pts express high treatment necessity beliefs for TNFi therapy, which is associated with increased adherence rates.
Disclosure of Interest: P. Michetti Lecture fee(s): AbbVie, Ferring Pharmaceuticals, MSD, and Vifor, Consultancy: AbbVie, Ferring Pharmaceuticals, Merck Serono, MSD, Nestlé Health Sciences, Takeda, UCB Pharma, and Vifor, L. Peyrin-Biroulet Lecture fee(s): AbbVie, Ferring Pharmaceuticals, H.A.C. Pharma, Janssen, Merck, Norgine, Therakos, Tillotts Pharma AG, and Vifor, Consultancy: AbbVie, Boehringer Ingelheim Inc, Bristol-Myers Squibb, Celltrion, Eli Lily, Ferring Pharmaceuticals, Genentech, Hospira, Janssen, Merck, Mitsubishi, Norgine, Pharmacosmos, Pilège, Shire Pharmaceuticals, Takeda, Therakos, Tillotts Pharma AG, UCB

Abstract number: OP283 Table: Multivariable Logistic Regression Analysis On High Adherence (MMAS-4 = 4) to IBD Treatments in CD or UC

CD			
Treatment Group	**MMAS-4 Adherence Rating**	**N**	**Odds Ratio (95% CI)**
IS monotherapy(IS ± 5ASA ± steroids)	IS (Reference) 5ASA	26262	–0.4 (0.1–1.1)
TNFi monotherapy(TNFi ± 5ASA ± steroids)	TNFi 5ASA	577122	7.3 (3.8–13.9) 1.6 (0.7–3.6)
IS-TNFi combination therapy (IS + TNFi ± 5ASA ± steroids)	IS TNFi 5ASA	27728065	1.5 (0.8–3.0) 17.5 (7.8–39.3) 1.5 (0.5–4.7)
UC			
5ASA monotherapy(5ASA ± steroids)	5ASA (Reference)	157	–
IS monotherapy(IS ± 5ASA ± steroids)	IS 5ASA	12689	6.2 (1.8–21.0) 1.9 (0.5–6.5)
TNFi monotherapy(TNFi ± 5ASA ± steroids)	TNFi 5ASA	18587	67.7 (13.8–331.1) 5.5 (1.3–22.7)
IS-TNFi combination therapy (IS + TNFi ± 5ASA ± steroids)	ISTNFi 5ASA	929446	19.2 (4.1–88.8) 185.2 (27.5–1245.6) 21.0 (3.5–126.6)

Pharma, and Vifor, E. Louis Lecture fee(s): Abbvie, Ferring, MSD, Chiesi, Mitsubishi Pharma, Hospira, and Janssen, Conflict with: Educational grants from MSD and AbbVie, as well as advisory board fees from AbbVie, Ferring, MSD, Takeda, Mitsubishi Pharma, and Celltrion, M. Silverberg Financial support for research: AbbVie, Janssen, and Prometheus, Lecture fee(s): AbbVie, Janssen, Takeda, and Prometheus, Consultancy: AbbVie, Janssen, Takeda, and Prometheus, J. Weinman Conflict with: Employee of Atlantis Healthcare, J. Sommer Conflict with: Employee of GKM Gesellschaft fuer Therapieforschung mbH, J. Petersson Conflict with: Is an AbbVie employee and may own AbbVie stock and/or options, B. Pappalardo Conflict with: Is an AbbVie employee and may own AbbVie stock and/or options, P. Nurwakagari Conflict with: Is an AbbVie employee and may own AbbVie stock and/or options, N. Selenko-Gebauer Conflict with: Is an AbbVie employee and may own AbbVie stock and/or options

OP284 INFLUENCE OF ALEXITHYMIA ON THE CLINICAL COURSE OF INFLAMMATORY BOWEL DISEASE (IBD)

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Introduction: Alexithymia is a personality trait characterized by difficulty to perceive and express emotions. Previous studies have reported a high prevalence of alexithymia in IBD patients, but its influence on the clinical course of the disease is unknown.

Aims & Methods: The aim of this study was to assess the influence of alexithymia on the clinical course of IBD patients.

Methods: A prospective observational cohort study was designed. Crohn's disease (CD) and Ulcerative Colitis (UC) patients older than 18 years of age were included. Alexithymia was evaluated using the Toronto scale (TAS-26). This scale is a self-report instrument consisting of 26 items with a response format of a five-point scale (range 26 to 130). Alexithymia was defined as a total score of > 73 points. In order to assess the clinical course of IBD, all unscheduled or emergency visits and hospitalisations related with IBD were recorded over a 18-month follow-up time. The influence of alexithymia on clinical course was analysed by logistic regression analysis.

Results: 470 patients were included; 219 (46.6%) male, mean age 44 years, range 18 to 85 years, 60.8% with UC and 39.2% with CD. The overall prevalence of alexithymia was 67.4%. Mean emergency or unscheduled visits was 1.08 (SD 1.50, range 0-14) and mean hospitalizations of 0.38 (SD 1.04, range 0-9). Higher alexithymia scores at baseline were not associated with more emergency visits (B = 0.06; 95%CI 0.93-1.21; p = 0.364) nor more hospitalizations (B = -0.02; 95% CI 0.82-1.18;p = 0.838).

Conclusion: Alexithymia is highly prevalent in IBD patients but it has no influence on the number of emergency visits and hospitalizations.

Disclosure of Interest: None declared

OP285 EVALUATION OF FERTILITY IN MEN WITH INFLAMMATORY BOWEL DISEASE

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Introduction: Inflammatory bowel diseases (IBD, Crohn's disease-CD and ulcerative colitis-UC) are chronic conditions, with the highest incidence rates during the peak reproductive years. Our aims were to compare the fertility status in men with IBD and controls (CTR) and to investigate the pathophysiology.

Aims & Methods: A multicentre, transversal groups study was performed between April 2010 and March 2014. Patients with varicocele, altered FSH, LH, prolactine (PRL) or testosterone levels (TST), pathology related to subfertility, ≥ 5 white blood cells in semen or positive culture were excluded. Age, smoking status, activity of IBD (by Harvey and Simple clinical colitis activity index), semen characteristics (million sperm/ml, progressive motility, morphology and vitality), hormone levels (FSH, LH, PRL and free TST), plasma and seminal zinc, 24 hour urinary zinc,antisperm antibodies (ASA), and plasma TNF-α were measured in each patient.

Results: Seventy-four patients [30 CD (40.4%), 22 UC (29.7%) and 22 CTRL (29.7%)] were included. Mean age was 30.5 ± 5.5 in CD, 34.0 ± 6.0 UC and 31.3 ± 5.1 CTRL (p = 0.780), smokers 14 patients in CD, 8 in UC and 8 CTRL (p = 0.221[FB1]).[h2] 86.6% of IBD patients were asymptomatic. Differences in FSH, LH and TST levels were not found. Regarding to PRL levels, the difference observed was close to statistical significance (CD 15.2 ± 6.7; UC 16.7 ± 6.6 ;CTRL 12.3 ± 4.0; p = 0.062). In sperm analysys differences in sperm/ml (CD 35 (19.7-53.0), UC 71.5 (37.7-124.2), CTRL 81 (10.0-110.0; p = 0.038) were obtained, without difference in progressive motility (CD 42.3 ± 22.9; UC 47.8 ± 19.7, CTRL 50.6 ± 16.6, p = 0.324), vitality (CD 64.1 ± 19.7; UC 65.6 ± 19.2; CTRL 71.8 ± 12.6; p = 0.300 or morphology (CD 9.9 ± 6.5; UC 9.1 ± 4.3; CTRL 7.9 ± 3.7; p = 0.422). Although, this stadistical significance was lost when the results were adjusted for age and smoking status (p = 0.162). When comparing CD and UC, we found that patients with CD had worse progressive motility-astenospermia- (CD 35.1 ± 22.1; UC 49.1 ± 19.2; p = 0.036) and sperm/ml -oligospermia- (CD 34.5 (19.2-48.0); UC 70 (34.5-127.5); p = 0.02) without differences in vitality (CD 59.5 ± 21.0; UC 67.4 ± 17.8; p = 0.205 and morphology (CD 7.6 ± 4.9; UC 8.8 ± 4.2). All ASA were negative. TNF α levels were similar in CD and UC patients, and lower in CTRL (CD 4.49 (3.65-12.2), UC 4.51 (3.9-5.385), CTRL 4.755 (3.932-6.280), p = 0.433). Patients with CD had lower seminal zinc levels than UC patients(CD 1455.0 ± 860.1 μmol/L ; UC 2193.3 ± 1152.8; CTRL 1522.9 ± 937.2, p = 0.012)without difference in serum zinc (CD 11.6 ± 2.7; UC 12.6 ± 2.6; CTRL 12.4 ± 2.4; p = 0.211) and urinary zinc (CD 10.3 ± 6.9; UC 9.9 ± 4.6; CTRL 6.5 ± 2.9,; p = 0.823). Seminal zinc showed possitive correlation with progressive motility(r = 0.243, p = 0.086)

Conclusion: Male CD patients have a worse fertility status than UC patients or control which is characterized by lower sperm count, reduced progressive motility and lower seminal zinc levels. The alterations observed do not seem to be related to ASA or ant-TNF levels in these patients.

Disclosure of Interest: M. P. Valer Financial support for research: GETECCU GRANT. FROM THE THEORY TO THE PRACTICE., D. Santos: None declared, A. Algaba Financial support for research: MERCK GRANT, M. E. Nieto: None declared, M. de Lucas: None declared, P. Lopez: None declared, M. Chaparro: None declared, I. Guerra: None declared, F. Bermejo: None declared

OP286 ADALIMUMAB AND INFLIXIMAB CLEARANCE IN NEONATES (ERA STUDY)

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Introduction: Anti-TNF-alpha (ATNF) therapy in pregnancy results in transfer of drug to the foetus. Neonatal levels and clearance of ATNF therapy are poorly understood.

Aims & Methods: We investigated neonatal ATNF levels after exposure in utero and correlated these with maternal levels, therapy duration, time to clearance and factors affecting clearance.

Pregnant IBD women exposed to infliximab (IFX) or adalimumab (ADA) were enrolled at 14 sites in Denmark, Australia, and New Zealand. Drug levels were measured by ELISA. If positive at birth, infants were tested three monthly. Demographics, disease activity, medication, and pregnancy outcomes were prospectively collected. Multivariate and logistic regression analysis determined factors correlated with drug levels at birth in mothers and newborns, time to and factors influencing clearance in newborns.

Results: Of 80 women (44 IFX, 36 ADA) recruited, 49% were on combination therapy with thiopurines. There were 3 (4%) preterm births, 3 (4%) babies who were small for gestational age and 3 (4%) with congenital malformations. There was an inverse correlation between duration since last dose and both cord drug levels (IFX: r = -0.77; ADA: r = -0.64, both p < 0.0001) and maternal levels (IFX: r = -0.80; ADA: r = -0.80, both p < 0.0001). At delivery the cord/maternal ratio was 1.96 (95% CI 1.5-2.4) for IFX and 1.21 (95% CI 0.93-1.48) for ADA. Last ATNF dose was at median gestational week (GW) 30 in IFX, (8-37) and 35 in ADA (14-41) treated mothers. Median maternal and cord drug concentrations were 2.0 (0-22.2 mcg/ml) and 5.9 (0.12-28.7 mcg/ml) for IFX and 1.5 (0-10 mcg/ml) and 2.0 (0-12.1 mcg/ml) for ADA. Concentrations were significantly lower when ATNF was stopped prior to GW 30 (p < 0.002). Cessation prior to GW 30 in 31% of mothers did not increase the risk of disease activity in the 3rd trimester or postpartum. Median time to neonatal clearance was 6 months (range 3-12) for IFX and 6 months (range 0-9) for ADA. The average decrease in neonatal ATNF concentration from birth to 3 months of age was 82% (95% CI 77-87%) for IFX and 91% (95% CI 88-94%) for ADA, p = 0.002. The number of weeks since last dose in pregnancy predicted likelihood of neonatal clearance by 3 months (p = 0.01). Child development was normal on routine infant checks and no serious infections were noted.

Conclusion: Maternal and cord ATNF levels inversely correlated with duration since last exposure. Stopping before week 30 reduced drug levels but did not prevent transfer to the neonate. The rate of ADA clearance was faster than IFX clearance within the first 3 months of life. Neonatal clearance of ATNF took up to 12 months, emphasizing the importance of avoiding live vaccines the first year. Despite recordable neonatal drug concentrations, no increased risk of infections or adverse developmental outcome was reported.

Disclosure of Interest: M. Julsgaard Lecture fee(s): Ferring, MSD, UCB, L. A. Christensen Lecture fee(s): Ferring, MSD, UCB, Takeda, AbbVie, Conflict with: Member of the advisory board for MSD, P. R. Gibson Financial support for research: Janssen, AbbVie, Ferring, Lecture fee(s): Janssen, AbbVie, Abbott, Fresenius Kabi, Astrazeneca, Consultancy: AbbVie, Janssen, Ferring, Takeda, Nestle, Danone, R. Gearry Financial support for research: AbbVie, Ferring, Lecture fee(s): AbbVie, Janssen, MSD, Consultancy: AbbVie, Janssen, MSD, J. Fallingborg Financial support for research: AbbVie, Ferring, Lecture fee(s): AbbVie, Janssen, MSD, Consultancy: AbbVie, Janssen, MSD, J. Kjeldsen: None declared, S. Wildt Financial support for research: Dr Falck Pharma, Conflict with: Member of Advisory Board: MSD and Tillots, L. Svenningsen: None declared, W. Connell: None declared, C. L. Hvas Lecture fee(s): AbbVie, MSD, Tillotts, Ferring, M. P. Sparrow Financial support for research: Ferring, Lecture fee(s): AbbVie, Janssen, MSD, Conflict with: Advisory Board: Janssen, A. Walsh Consultancy: Janssen, AbbVie, S. J. Connor Financial support for research: Ferring, Shire, Orphan/Aspen, Abbvie, Lecture fee(s): Ferring, Abbvie, Shire, Janssen, Consultancy: Abbvie, Janssen, Vifor, G. Radford-Smith: None declared, I. Lawrance: None declared, J. M. Andrews Financial

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TUESDAY, OCTOBER 27, 2015 14:00–15:30

PREVENTION AND MANAGEMENT OF PROCEDURE-RELATED GI COMPLICATIONS – ROOM E1

OP287 ENDOSCOPIC TREATMENT OF POST-SURGICAL FISTULAS INVOLVING THE GASTROINTESTINAL TRACT: A LARGE CASE SERIES

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Introduction: Post surgical fistula (PSF) or anastomotic leak is surely a dreadful event. It is generally managed with a surgical approach, which is mandatory when peritonitis, mediastinitis or severe sepsis are present. Several endoscopic devices have been introduced in the last decades, so that such a complication could be treated conservatively in selected cases without a re-intervention.

Aims & Methods: The aim was to assess the pivotal role of endoscopic treatment of PSF involving the gastrointestinal (GI) tract **Methods:** Data of all pts with a PSF involving the GI tract were prospectively collected. Information on the previous surgical approach, time, site and diameter of fistula, the endoscopic device used, technical success, the need of an additional approach, the hospital stay and the clinical outcome were recorded. The fistula was defined 'early' when occurring within 7 days, 'delayed' when later. The endoscopic treatments included: placement of a covered SEMS; over-the-scope clip positioning; fibrin glue injection (Tissucol); endo-sponge application. Single or multiple endoscopic devices were used, based on site of fistula and the therapeutic outcome. In those pts with a fluid collection cavity, drainage by either radiological or surgical approach was also performed (combined treatment).

Results: From April 2009 to September 2014, 76 pts (36 M; mean age: 63 yrs) with a PSF involving the GI tract were treated. The surgery was performed for a neoplastic (52 pts) and benign (24 pts) disease. An open or laparoscopic surgery was performed in 42 and 34 pts, respectively. Our series included fistulas after gastric-oesophageal anastomosis: 5 pts; bariatric surgery: 10 pts; gastric resections:22 pts; pancreatic surgeries: 5 pts; small bowel resections: 5 pts; colorectal resections: 24; urologic surgeries: 5 pts. The fistula was classified as early in 36/76 pts, and delayed in 40/76 pts. 35 and 24 pts were managed with only endoscopic treatment for either upper or lower GI fistula, respectively, whilst a combined approach was performed in the remaining 17 pts. Following the endoscopic therapy (single or combined) the fistula was successfully closed in 61/76 treated pts (80%) pts, without a statistically significant difference between single (48/59; 81%) and combined (13/17; 76%) treatment. The median of hospital stay was 16 days (5-180). The fistula closure was achieved in 45/53 (85%) pts managed by using only one type of device, and in 18/23 pts (78%) following a combination of devices., without a statistically significant difference. A similar success rate was achieved in pts with early (29/36; 81%) and those with a delayed (32/40; 80%) PSF

Conclusion: Endoscopic approach is successful and safe in the majority of pts with GI fistula specially when performed by skilled endoscopist. It should be always attempted before resorting in more invasive, costly and risky re-intervention. Therefore, a closed collaboration among the endoscopist, surgeon, radiologist and nutritional staff is required.

Reference

1. Manta R, Magno L and Conigliaro R, et al. Endoscopic repair of post-surgical gastrointestinal complications. *Dig Liver Dis* 2013; 45: 879–85.

Disclosure of Interest: None declared

OP288 SHOULD ANTITHROMBOTIC AGENTS BE STOPPED FOR GASTRIC ENDOSCOPIC SUBMUCOSAL DISSECTION ?

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Introduction: As usage of antithrombotic agents increases, how to manage these drugs in perioperative period becomes a great concern. Recent Japanese guideline is converted to permit gastric endoscopic submucosal dissection (ESD) without cessation of low dose aspirin because thrombosis is usually more severe than bleeding[1]. American and British guidelines also admit to continue low dose aspirin during high-risk procedure, however, there are limited data of bleeding risk. Moreover, how to manage antithrombotic agents other than low dose aspirin is hardly reported.

Aims & Methods: The aim of this study is to compare the delayed bleeding rate in the patients who take antithrombotic agents with matched controls during the perioperative period of gastric ESD. We also compare the delayed bleeding rate of continuing antithrombotic agents with that of heparin bridging or cessation of antithrombotic agents.

Patients who underwent gastric ESD with or without cessation of antithrombotic agents between January 2009 and October 2014 were reviewed. Antithrombotic agents were defined as anticoagulant and antiplatelet, such as low dose aspirin, thienopyridine derivatives or cilostazol. Delayed bleeding was defined as the cases of emergent hemostasis after gastric ESD with a sign of bleeding.

Results: A total of 2105 patients underwent gastric ESD in the relevant period. Among them, 317 patients on antithrombotic therapy were reviewed. The patients on antithrombotic agents were divided into 3 groups according to existence of cessation or bridging therapy: 42 patients (13%) without cessation (continuation group), 29 patients (9%) with cessation and bridging therapy of heparin (heparin group), and the other 246 patients with cessation and without bridging therapy (cessation group). The period of cessation was determined according to the Japanese guideline in most cases[1]. A total of 683 patients without antithrombotic therapy were selected as controls. Controls were matched with a 1:2 ratio by location of the lesion and resected size of the specimen.

Overall bleeding rate of the patients on antithrombotic agents was 11% (35/317). This rate was significantly higher than that of matched controls (4.1% 28/683). The bleeding rate of continuation group, heparin group, and cessation group was 11.9%(5/42), 13.8%(4/29), and 10.6%(26/246), respectively. No significant differences were seen in bleeding rate, procedure time, tumor size and resected specimen size among these 3 groups.

During the perioperative period, a total of 4 thrombotic events occurred only in cessation group (1.6%).

	Continuation group(n = 42)	Heparin group(n = 29)	Cessation group(n = 246)	P value
Delayed bleeding	11.9%(5/42)	13.8%(4/29)	10.6%(26/246)	0.81
Procedure time (min)	44.7 ± 26.8	58.5 ± 51.6	48.7 ± 35.4	0.68
Tumor size (mm)	21.0 ± 16.8	23.5 ± 17.0	19.7 ± 15.2	0.18
Specimen size (mm)	49.3 ± 19.7	47.8 ± 20.7	45.9 ± 16.1	0.63
Thrombotic event	0%	0%	1.6% (4/246)	0.36

Conclusion: Patients who regularly take antithrombotic agents had higher risk of delayed bleeding than controls during the perioperative period of gastric ESD. No differences were seen in delayed bleeding rate with or without cessation. Taking into account the risk of thrombosis, gastric ESD without cessation of antithrombotic agents may be feasible.

Reference

1. 1 Fujimoto K, et al. *Dig Endosc* 2014;26:1-14.

Disclosure of Interest: None declared

OP289 PREDICTING DELAYED BLEEDING AFTER PIECEMEAL ENDOSCOPIC MUCOSAL RESECTION OF COMPLEX COLORECTAL POLYPS

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Introduction: Delayed bleeding is the most common severe adverse event after p-Endoscopic Mucosal Resection (p-EMR) but factors that may predict delayed bleeding are not well-defined.

Aims & Methods: The primary objective of this study was to identify potential patient, polyp and technique-related risk factors for delayed bleeding using univariate and multivariable logistic regression analyses. A prospective p-EMR database of complex colorectal polyps included a description of the final post-EMR defect. We also aimed to analyse the inter-observer agreement between two blind assessors for 4 polypectomy defect-related factors (visible vessels, visible muscle fibres, submucosal haematoma (''cherry red spot'') and APC > 30% base). A checklist telephone call at 15 days post p-EMR documented the incidence of delayed bleeding.

Results: Of 323 patients/341 complex colorectal polyps (mean size 3.7cm), seventy-two patients (22%) had delayed bleeding (39/72 did not require hospitalisation, 22/72 required hospitalisation but no therapeutic intervention, 11/72 required blood transfusion and 1/11 had a segmental bowel resection). Univariate analysis demonstrated that delayed bleeding was associated with **patient** (female gender), **polyp** (rectosigmoid site, increasing size, Paris classification Is + IIa, Kudo pit pattern type IV, incomplete lift, previous polypectomy

attempt), **technique** (longer procedure time, mixed - saline and hyaluronate - injection solution type, greater solution volume, spiral p-EMR) and **post-polypectomy defect** (“cherry red spot” and visible muscle fibres) related factors (Table).

Factors	Category	Delayed BleedingN (%)	Odds Ratio (95% CI)	P-value
PATIENTGender	Female	34/122 (28%)	1.73 (1.02, 2.93)	**0.04**
POLYPSite	R. sigmoid/rectum	37/112 (33%)	1	**0.007**
Size (cm)	-	-	1.27 (1.12, 1.43)	**<0.001**
Paris classification	IIa /IIb	13/104 (13%)	0.51 (0.26, 1.01)	**<0.001**
Kudoclassification	IV	39/130 (30%)	2.17 (1.28, 3.68)	**0.004**
Polyp Lift	Incomplete	50/173 (29%)	2.49 (1.43, 4.36)	**0.001**
Previouspolypectomy	Yes	29/91 (32%)	2.13 (1.23, 3.70)	**0.007**
TECHNIQUE				
Procedure time (*)	-		1.18 (1.07, 1.31)	**0.002**
Solutiontype	Saline/hyaluronate	19/51 (37%)	2.57 (1.35, 4.89)	**0.004**
Solution volume(*)	-		1.15 (1.06, 1.25)	**0.001**
DEFECTSRed cherry spot	Yes	18/41 (44%)	3.31 (1.63, 6.73)	**0.001**
Visible muscle fibers	Yes	23/51 (45%)	3.87 (1.99, 7.51)	**<0.001**

(*) Odds ratios reported for a 10-unit increase in predictor variable

Multivariate analysis confirmed that delayed bleeding was associated with female gender (OR 2.2,p = .02), previous polypectomy attempt (OR 2.58,p = .006), longer procedure time (OR 1.2,p = .007), visible muscle fibres (OR 4.51,p < .001), Paris classification Is + IIa (OR 2.51,p = .002), mixed injection solution type (OR 2.53,p = .02) and spiral p-EMR (OR 1.89,p = .02). The presence of visible vessels within the polypectomy defect, the use of APC and aspirin were not found to be significant predictive variables. The inter-observer agreement for all four defect measures was moderate, with kappa values from 0.5-0.6.
Conclusion: Risk factors for delayed bleeding post p-EMR were identified. A global risk assessment may be developed using patient (female gender), polyp (previous polypectomy), technique (prolonged procedure time) and defect (visible muscle fibers) related factors.
Disclosure of Interest: None declared

OP290 MULTICENTER STUDY ABOUT HEMORRHAGE AFTER THERAPEUTIC ENDOSCOPY IN HEMODIALYSIS PATIENTS

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Introduction
Background: Therapeutic gastrointestinal endoscopy in hemodialysis patients is becoming a usual procedure, as the prevalence of maintenance hemodialysis is increasing every year, with the number of dialysis patients in Japan exceeding 300 thousand at the end of 2011 and continuing to increase. The increased risk of post-procedural hemorrhage among dialysis patients is empirically known, but has not been well documented.
Aims & Methods
Aim: We aimed to characterize hemorrhage after therapeutic endoscopy in hemodialysis patients.
Methods: Between 2009 and 2011, a nationwide multicenter survey using questionnaire was performed about hemodialysis patients undergoing therapeutic endoscopy (i.e., gastric endoscopic mucosal resection [EMR], gastric endoscopic submucosal dissection [ESD], colonic EMR/polypectomy, and colonic ESD) . For controls, non-dialysis patients who underwent therapeutic endoscopy were also included.
Results: We collected data from 113 dialysis patients and 10297 control patients at 13 medical institutions. Of the 113 dialysis patients, 46 had undergone therapeutic gastroscopy and 67 therapeutic colonoscopy. Of the 10297 control patients, 3386 had undergone therapeutic gastroscopy and 6957 therapeutic colonoscopy.
The overall incidence of post-procedural hemorrhage was 14.2% (16/113) in the dialysis group and 2.6% (272/10297) in the control group ($p < 0.001$).
By site, the incidence of hemorrhage after therapeutic gastroscopy was 23.9% (11/46) in the dialysis groupand 4.8% (160/3340) in the control group; and that after therapeutic colonoscopy was 7.4% (5/67) in the dialysis group and 1.6% (112/6957) in the control group ($p < 0.001$).
As for background factors, overall, use of antithrombotic drugs ($p = 0.03$) and pre-procedural dialysis using nafamostat mesilate ($p = 0.002$) were detected as significant factors. Multivariate analysis using logistic regression analysis revealed that duration of dialysis (in years) was also a significant factor ($p = 0.001$).
A similar analysis performed separately for gastroscopy and colonoscopy, demonstrated that post-procedural dialysis using nafamostat mesilate ($p = 0.01$) was a significant factor for hemorrhage after gastroscopy, and duration of dialysis (in years) ($p = 0.03$) was a significant factor for hemorrhage after colonoscopy.
The hemorrhage after therapeutic endoscopy tended to be of delayed onset in dialysis patients compared with control patients.
Conclusion: The risk of hemorrhagic complications after therapeutic endoscopy was significantly higher in hemodialysis patients. Dialysis itself can be a risk factor, rather than age and use of antithrombotic drugs. Increased caution is warranted in monitoring dialysis patients after therapeutic endoscopy.
Disclosure of Interest: None declared

OP291 POST POLYPECTOMY BLEEDING (PPB) IN THE ENGLISH NHS BOWEL CANCER SCREENING PROGRAMME (NHSBCSP)

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Introduction: Colonoscopies in the English NHSBCSP are offered to 60-74 year olds with an abnormal Faecal Occult Blood Test. Colonoscopies are performed at 61 Bowel Cancer Screening Centres (BCSCs) which are divided geographically between five regions of England. Polypectomy breaks the adenoma-carcinoma sequence but carries a risk of Post Polypectomy Bleeding (PPB). The NHSBCSP has a longstanding robust mechanism for capturing adverse events. Adverse Events are graded by severity using the NHSBCSP framework, based on the American Society of Gastrointestinal Endoscopy grading system.[1,2]
Aims & Methods: We aimed to (1) determine the rate of PPB, broken down by severity grading, in one region of the NHSBCSP (2) describe PPB management and outcomes and (3) explore the factors that contribute to PPB’s severity grading. This prospectively collected observational case series identified patients with PPB at 5 BCSCs within the North East Region of the English NHSBCSP from 06/12/2010 to 15/07/2014. We defined PPB as bleeding presenting following completion of the procedure and that resulted in medical consultation, admission to or prolongation of an existing hospital stay or another intervention. Patient co-morbidity, use of anticoagulation, polyp location, morphology, size, polypectomy method, time to presentation, subsequent patient management and outcome were all recorded. PPB was graded into major, intermediate or minor as per the NHSBCSP grading system.
Results: From a total population of 4,191,507, 15,285 colonoscopies were subsequently performed on 11,564 patients leading to 23,766 polypectomies. 68 patients with PPB were identified; a PPB rate of 0.44% per colonoscopy and 0.29% per polypectomy. 2.9% of cases were major due to need for surgery or admission to ITU for > 1 night; median time to presentation was 3.5 days (range 1-6 days), median hospital stay was 3 days (range 2-4) days. 42.6% were intermediate, the majority due to requiring an interventional procedure or a haemoglobin drop ≥ 2g/dL; median time to presentation was 4.5 days (range 0-19 days), median hospital stay was 2 days (range 0-6 days). Of all patients with PPB, 8.8% presented with symptoms or signs of haemodynamic compromise. 19.1% required resuscitation with intravenous fluids and/or red blood cells. Repeat endoscopy was performed in 27.9% with repeat endoscopic therapy in 10.3%. Surgery was performed in 1.47% of cases. 1.47% of patients required a second admission and were managed radiologically.
Conclusion: (1) We believe this detailed, robustly collected and prospectively categorised dataset gives a true reflection of PPB rate among experienced colonoscopists. (2) A PPB rate of 0.44% is therefore excellent when compared with other similar series. (3) Clinically significant PPB, defined as major or intermediate severity, occurred in less than half of the cases reported.

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Disclosure of Interest: None declared

OP292 ESTABLISHMENT OF OVER-THE-SCOPE-CLIPS (OTSC) IN DAILY ENDOSCOPIC ROUTINE: A LONG-TERM SINGLE CENTRE EXPERIENCE

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Introduction: Alongside with the evolution of interventional endoscopy, the need for a more sophisticated closure tool tailored to the treatment of new challenging indications has been increasing rapidly. In 2007, the first small case series (11 cases) of Over-The-Scope-Clip (OTSC, Ovesco, Tübingen) placement in the gastrointestinal tract was reported.
Aims & Methods: We here present our collected data on 223 OTSC placements in a total of 198 interventions at out institution. Follow up was focused on clinically lasting success in regard to the different indications.
Results: Acute gastrointestinal perforation (39.9%; 79/198), fistulas or anastomotic insufficiency (34.3%; 68/198), gastrointestinal bleeding (23.2%; 46/198) and diameter reduction of the gastrojejunal anastomosis after bariatric surgery (2.5%; 5/198) were the four main indications for OTSC placement.
Acute gastrointestinal perforations were located in the esophagus (10.1%; 8/79), in the stomach, (17.7%; 14/79), in the duodenum (21.5%; 17/79), in the colon (44.3%; 35/79) and in the rectum (6.3%; 5/79).

Anatomic locations of the *fistulas or anastomotic insufficiencies* were defined by their gastrointestinal origin. 20.6% (14/68) of the lesions originated from the esophagus, 29.4% (20/68) from the stomach, 1.5% (1/68) form the duodenum, 16.2% (11/68) from the small intestine, 11.8% (8/68) from the colon and 20.6% (14/68) from the rectum.
Gastrointestinal bleeding was located in the esophagus in 6.5% (3/46), in 19.6% (9/46) in the stomach, in 54.3% (25/46) in the duodenum, in 2.2% (1/46) in the small intestine, and in 17.4% (8/46) in the colon.
Overall immediate success of OTSC deployment was achieved in 84.8% (168/198) of the cases. The main causes for failure of OTSC placement (15.2%; 30/198) were non-suitable anatomic structure (30%; 9/30), rigidity of the lesion-surrounding tissue (30%; 9/30) and lesion size exceeding OTSC size (40%; 12/30). In 3 cases (1.5%; 3/198) the passage of the mounted OTSC through the upper esophageal sphincter was not possible, but OTSC-passage became successful after loading a smaller sized OTSC. In 8.1% of the cases (18/223), proper OTSC placement was not achieved and clip removal was performed during the same procedure.
At *thirty-day follow-up*, 61.1% (121/198) of the cases were granted as successful OTSC treatment, whereas 34.8% (69/198) of the cases had to be considered as failed treatment. Four percent (8/198) of the cases were either lost to follow up at 30 days or no follow was indicated. OTSC application in the stomach, duodenum or colon was shown to be favourable in order to reach success at day 30, whereas the treatment of fistulas and anastomotic insufficiency was less promising.
After one year, 42.4% (84/198) of the cases were followed up. Eighty-one per cent (68/84) of these cases were considered as permanent successful OTSC treatment. 9.5% (8/84) were declared as failure of OTSC treatment at one year follow up, whereas another 9.5% (8/84) were lost of follow up at this point.
Conclusion: In conclusion, the OTSC device has been shown to be a must-have tool when performing frequent interventional endoscopic procedures and may be a valuable tool to spare the surgeon. Yet, before a safe and purposeful OTSC application can be guaranteed, the endoscopist has to earn experience in handling the device. An issue to overcome in the near future is the removal of the clip if indicated.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 14:00–15:30
BRAIN-GUT INTERACTIONS IN HEALTH AND DISEASE – ROOM E4

OP293 FOOD-INDUCED DOPAMINE RELEASE IN EXTRA-STRIATAL REGIONS OF THE BRAIN REWARD SYSTEM PREDICTS FOOD INTAKE IN HEALTHY HUMANS

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Introduction: Several studies have tried to assess the role of dopamine (DA) in human food reward by measuring either baseline DA $D_{2/3}$ receptor availability or DA release in response to some food cue. However, results have been inconsistent and often rely on the use of pharmacological stimulation of DAergic neurons and/or scanning before and after rather than during presentation of food stimuli. Moreover, research on the role of extra-striatal DA signaling in human food reward is completely lacking to date, even though it is generally accepted that DA release in these regions is also implicated in food reward.
Aims & Methods
Aim: To assess DA release in both striatal and extra-striatal brain regions in response to food stimuli in healthy volunteers.
Methods: 7 healthy females (age = 25 ± 8.25 years; BMI = 21.62 ± 2.02 kg/m^2) underwent a single dynamic Positron Emission Tomography (PET) scanning session after intravenous administration of 183.25 ± 7.01 MBq of the highly selective DA $D_{2/3}$ PET radioligand [^{18}F]fallypride. A food reward task was initiated at 180 min post-injection and comprised a set of visual stimuli consisting of high-calorie food images, combined with the delivery of a small amount (8ml/8sec) of chocolate milkshake every 4 min. PET data were analyzed using the linearized simplified reference region model, which accounts for temporal perturbations in [^{18}F]fallypride displacement. Parametric voxel-based statistical maps, representing specific $D_{2/3}$ binding changes, were computed to subsequently localize areas within a binary mask of regions of interest with increased ligand displacement after the food reward task onset. Significant ligand displacement, representing food-induced DA release, was quantified as the number of voxels within each region exceeding a threshold of $T > 4.4$, which corresponds to $p_{FWE\text{-}corrected} < 0.05$. Data are presented as mean ± SEM.
Results: Food stimuli induced significant DA release in extra-striatal regions of the reward system (ventromedial prefrontal cortex (vmPFC, BA10), medial orbitofrontal cortex (mOFC, BA11), lateral orbitofrontal cortex (lOFC, BA47), anterior cingulate cortex (ACC, BA24 & BA32), and insula), with the largest amount of ligand displacement present in the ACC (BA24 = 28.6 ± 4.7%, BA32 = 33.5 ± 5.1%). Moreover, food-induced DA release in the left ACC and left insula strongly and significantly predicted the amount of milkshake consumed during an ad libitum drink test following the PET scan (respectively r = 0.84, p = 0.037 and r = 0.86, p = 0.027). The amount of significant food-induced ligand displacement in striatal regions was less pronounced compared to extra-striatal brain regions, with exception of the putamen (left = 24.4 ± 8.4%; right = 19.4 ± 7.0%). There was no significant DA release in the nucleus accumbens.
Conclusion: To the best of our knowledge, this study shows for the first time that food stimuli induce not only increased levels of endogenous DA in striatal regions, but also in extra-striatal brain regions of the reward system. Furthermore, this food-induced extra-striatal DA release predicted subsequent food intake. These results might be a first step towards a better understanding of the role of the brain DA system in food reward, which may facilitate the development of improved therapeutic approaches for disorders of food intake such as obesity.
Disclosure of Interest: N. Weltens: None declared, L. Cool: None declared, J. Ceccarini: None declared, J. Tack Financial support for research: Novartis, Shire, Zeria, Almirall, AstraZeneca, Janssen and Menarini, Lecture fee(s): Abbott, Almirall, AstraZeneca, Janssen, Menarini, Novartis, Shire, Takeda and Zeria, Consultancy: Almirall, AstraZeneca, Janssen, Menarini, Shire, Zeria, AlfaWassermann, Danone, GI Dynamics, GlaxoSmithKline, Ironwood, Novartis, Rhythm, Sucampo, Takeda, Theravance, Tsumura and Yuhan, K. Van Laere: None declared, L. Van Oudenhove: None declared

OP294 RNASEQ ANALYS REVEALS DYREGULATED EXPRESSION OF NOVEL GENES IN IDIOPATHIC ACHALASIA

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Introduction: Esophageal achalasia is a motility disorder characterized by the lack of esophageal peristalsis and failure of the lower esophageal sphincter to relax. The occurrence of genetic syndromic cases and data from mutant mouse models (Sprouty-2$^{-/-}$ and kit$^{-/-}$) suggest that genetic factors may play an important pathogenetic role.
Aims & Methods: This study was designed to identify novel molecular features of sporadic achalasia.
Methods: 16 (7 F; age range: 26-72 yrs) clinically, radiologically and manometrically characterized patients with sporadic achalasia were included. A group of 4 (2F; age range: 30-67 yrs) subjects undergoing surgery for uncomplicated esophageal cancer served as controls. During surgery, full-thickness tissue samples were obtained from achalasic patients and controls from immunohistochemical and molecular analysis. Total RNA (150 ng), extracted from tissues of 4 achalasia patients and 4 controls, was used for library preparation (TruSeq Stranded Total RNA Sample prep kit v2) and sequencing on HiScan SQ. Data analysis was performed with the 'edgeR' option of R-Bioconductor. Gene expression was validated by real-time qRT-PCR and immunohistochemical analysis. Variant calling analysis from transcriptome data was also performed using an internal pipeline for single nucleotide/small indels calling. Sanger sequencing was performed to validate the presence of the variants at the DNA level.
Results: Quantitative transcriptome evaluation and cluster analysis revealed 116 differentially expressed genes, with a $P = 10^{-3}$. 9 genes with a $P < 10^{-4}$ were chosen for validation and further analysis by qRT-PCR. Among the genes not previously associated to the achalasia phenotype in human samples *CYR61*,*CTGF*, *KIT, DUSP5*, *EGR1* were downregulated, whereas *AKAP6* and *INNP4B* were upregulated in patients vs. controls. Compared to control tissues immunohistochemical analysis revealed a clear increase in *AKAP6* and *INNP4B* immunostaining, whereas *KIT* immunolabeling resulted downregulated, thus confirming in humans previous data in mouse models.
Sequence analysis of the transcriptome data from the same achalasia patients revealed rare heterozygous missense variants for the type T calcium channel-encoding gene *CACNA1H*, which is expressed in murine ICC cells. The presence of the variants was confirmed in the corresponding genomic DNA.
Conclusion: Our study identified several novel genes dysregulated in achalasia patients, which provide a molecular basis to severe neuro-glial-ICC alterations. These findings may prove relevant for a better definition and identification of subsets of achalasic patients.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 14:00–15:30
TRAINING IN ENDOSCOPY – ROOM E3

OP295 DOES THE PRESENCE OF A TRAINEE COMPROMISE BILIARY CANNULATION RATES AT ECRP: RESULTS FROM A PROSPECTIVE AUDIT

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Introduction: A trainee endoscopist on the ERCP list prolongs procedure time and may increase risk of technical failure or procedural complications [1, 2]. Recent BSG guidance has identified a biliary cannulation rate of 90% as an ERCP performance indicator which may conflict with the need to train juniors. This prospective audit assessed the impact of an endoscopy trainee on the overall biliary cannulation rates.
Aims & Methods: We prospectively audited sequential ERCPs done on a ''virgin'' ampulla (no previous ERCP). Procedures were supervised by 2 experienced trainers ; trainees were present when possible(trainees were senior SpRs with limited ERCP experience) . A short-wire system was used for biliary cannulation and standard techniques used [1]. The trainee would have 6

minutes to achieve biliary cannulation, failing which the trainer would take over. Predicted ERCP difficulty was graded using accepted criteria [3]. The primary outcome was the biliary cannulation rate.
Results: One hundred and eight sequential ERCPs were prospectively audited over a period of 6 months [July 2014- Dec 2014]. Difficulty was graded as 1 (n = 69) or 2 [n = 39]. One of two trainee endoscopists was present during 61 [56%] ERCP cases; remaining cases were done by a consultant alone [n = 47, 44%]. Deep biliary cannulation was successful in 99 cases [91%]. The cannulation rate was 93% [57/61] with a trainee and 89% [42/47] without [p = 0.7229 Fishers exact test]. Median cannulation time was 6.6 minutes (range 1 – 25). There was no significant difference in cannulation times when a trainee was present [T test, p = 0.890]. Where a trainee was involved, 20/61 [32%] cannulations were achieved independently by the trainee. There were no major complications recorded in cases where a trainee was involved.
Conclusion: This audit suggested that acceptable biliary cannulation rates can be achieved on ERCP training lists, with involvement of experienced trainers and defined training parameters.

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Disclosure of Interest: None declared

OP296 STANDARDIZED TRAINING PROGRAM FOR DIAGNOSIS OF EARLY GASTROINTESTINAL CANCERS IN ASIA

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Introduction: Gastrointestinal (GI) cancers are diagnosed at advanced stage in most of the Asia Pacific countries. The development of NBI allowed endoscopists to improve recognition and characterization of early GI cancers through narrowing bandwidth of light with concentration on details of the mucosa. The Asian NBI group (ANBIG) was founded with an objective to conduct training in endoscopic diagnosis and treatment of early GI cancers in Asia using standardized training module. This is a prospective cohort study on the effectiveness of standardized training module for NBI on diagnosis of early GI cancers in Asia.
Aims & Methods: This is a prospectively collected database from workshops conducted in Asia on endoscopic diagnosis and treatment of early GI cancer by ANBIG. All the workshops were conducted in a standardized program, including pre-test, lectures on NBI diagnosis of early esophageal, gastric and colorectal cancers, case discussion, live demonstration or video presentation and hands-on training on EMR and ESD. After completion of the training course, a post-test was conducted to reassess the knowledge gained. The pre-training and post-training tests were standardized questions addressing 4 domain of knowledge, including basic knowledge of imaging, diagnosis of esophageal, gastric and colonic neoplasia.
Results: From Nov 2013 to April 2015, 15 ANBIG workshops were conducted in Asia, including China, Hong Kong, India, Indonesia, Malaysia, South Korea, Taiwan, Thailand, Mongolia and Myanmar. A total of 531 delegates had participated in these workshops and 279 of them completed the pre-test and the post-test. 26 faculties had contributed to the conduction of these training courses. Comparing the pre-training and the post-training test results, there was a significant overall improvement after the workshop training in the diagnosis of early gastric and colorectal neoplasia (Table 1). When the workshops were divided into those conducted in developed countries against those developing countries using GDP, there was generally a lower accuracy in pre-test knowledge for participants from developing countries than those in developed countries.

Table 1: - Comparison of accuracy in endoscopic diagnosis of early gastrointestinal neoplasia before and after standardized training workshops

Overall Accuracy	Pre-training	Post-training	p value
Basic NBI Knowledge	53.6%	64.6%	0.009∫
Endoscopic diagnosis of early esophageal neplasia	44.6%	52.6%	0.052
Endoscopic diagnosis of early gastric neoplasia	50.1%	65.5%	0.002∫
Endoscopic diagnosis of early colorectal neoplasia	50.8%	65.7%	0.020∫

∫ = $p < 0.05$

Conclusion: A standardized training module on image-enhanced endoscopy improved the diagnostic ability and quality for endoscopists in recognition of early gastrointestinal cancers.
Disclosure of Interest: None declared

OP297 NURSE PARTICIPATION COLONOSCOPY OBSERVATION VERSUS COLONOSCOPIST ALONE FOR POLYP AND ADENOMA DETECTION: A META-ANALYSIS

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Introduction: Colorectal cancer (CRC) is one of the most common cancers worldwide. Colonoscopy screening and removal of adenomas has been considered to be the most effective method reducing incidence and mortality of CRC [1,2].
Aims & Methods
Aims: This meta-analysis aimed to evaluate whether nurse participation (NP) colonoscopy improves polyp and adenoma detection, compared with colonoscopist alone (CA) colonoscopy.
Patients and methods: Literatures in English were searched for randomized controlled trials (RCTs) in the databases PUBMED, EMBASE, and Cochrane Library. Outcome measurements included: (1) polyp and adenoma detection rate (PDR and ADR); (2) advanced polyp detection rate; and (3) mean polyp and adenoma detection per colonoscopy.
Results: Three RCTs with a total of 1676 patients were included. Two RCTs compared NP colonoscopy versus CA colonoscopy on PDR and advanced PDR, and pooled data showed there was no significant difference in the PDR and advanced PDR between the two groups (RR: 0.95, 95% CI: 0.95-1.37; RR: 1.35, 95% CI: 0.92-1.97; respectively). Three RCTs compared NP colonoscopy versus CA colonoscopy on ADR, and pooled data showed a significant higher ADR on NP group (45.7% vs. 39.3%; RR 1.16; 95% CI, 1.04-1.30). Two trials compared NP colonoscopy versus CA colonoscopy on advanced PDR, and pooled data showed no statistical differences between the two groups (12.4% vs. 8.7%; RR 1.35; 95% CI, 0.92-1.97).
Conclusion: Nurse participation during colonoscopy can improve ADR, while no benefit for PDR and advance PDR.

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Disclosure of Interest: None declared

OP298 EXPERIENCE IN POLYPECTOMY TRAINING AND ASSESSMENT: AN INTERNATIONAL SURVEY

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Introduction: Colonoscopy is widely practised to reduce rates of colorectal cancer, although the protection it confers is not absolute. The most hazardous part of colonoscopy is polypectomy, accounting for the majority of serious complications. It is unclear whether countries around the world have highlighted polypectomy as a specific skill that needs to be taught.
Aims & Methods: The objective of the study was to assess both trainees' and trainers' experience of polypectomy training in countries around the world. Colonoscopy trainers from 19 countries worldwide were asked to provide access to local trainers and trainees who would be invited to participate in a survey. An online survey was created asking about trainees' experience of instruction and trainers' experience of teaching polypectomy skills.
Results: Data were obtained from 610 colonoscopists- 348 (57.0%) trainers and 262 (43.0%) trainees. Most (79.6%) of the trainers surveyed were involved in trainee polypectomy assessment weekly. 51.4% of those surveyed said that they used a specific framework when assessing polypectomy.
90.5% of trainees had a primary specialty of medical gastroenterology. The trainees had a breadth of colonoscopic experience, 31.7% having completed more than 500 colonoscopies and 38.2% fewer than 200 procedures. 51.1% stated that the principles of polypectomy had only been taught intermittently.

Most (64.1%, 168 respondents) trainees had never been taught the principles of endoscopic mucosal resection.
Only 53.1% of trainees had ever had their polypectomy technique formally assessed by any trainer. Of the 177 trainees who stated that they were competent at polypectomy, 70 (39.5%) had never had a formal evaluation of their polypectomy technique.
Conclusion: This study, the only in the literature, shows that polypectomy training is variable worldwide with low prevalence of formal competency assessment. There is a need to a) understand the learning curve for polypectomy, b) develop an international consensus defining optimal training methods and c) develop a framework of competency assessment. This should improve the safety of polypectomy and the effectiveness of colonoscopy in preventing colorectal cancer.
The authors would like to acknowledge the contribution of all 610 respondents and in particular the local training faculty who facilitated this study.
Disclosure of Interest: None declared

OP299 A LOCAL STRUCTURED TRAINING PROGRAM WITH IN-VIVO PIGS ALLOWS TO PERFORM RECTAL ESD WITH RESULTS CLOSE TO JAPANESE EXPERTS

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Introduction: Training in ESD requires numerous sessions to become efficient. A well-structured training program is essential, because the outcome of ESD is dependent of the experience of the endoscopist. European experts recommend such programs with animal models to overcome the initial learning curve. European experts recommended a minimum training of five ESD on animal model and observation of at least 15 live procedures before beginning ESD initially in the rectum before stomach and oesophagus. Afterwards, constant practicing of ESD is required to increase success and decrease the procedure time and complications. Despite the completion of these recommendations, first results published by european teams are far from those of Japanese experts in the rectal location.We thus decided to initiate a local training program with constant and regular exposure to gastric ESD in in vivo pigs.
Aims & Methods: Between March 2013 and April 2015, 52 pig gastric ESD were performed by two operators in a total of 14 anesthetized pigs, fasted for 48H prior to the procedure. After the 11 initial pig gastric ESD, operators felt able to begin human rectal ESD. 29 rectal human ESD for large LST were performed during the same period. The 41 next animals ESD were performed in parallel in order to keep a constant exposure to ESD cases. All procedures were performed with a hybridknife type T (Erbe medical, Germany). Glycerol mixture and physiologic serum were used for submucosal injection. In 25 human cases, the two operators took turns every hour to facilitate the procedures.
Results: Pig model: en bloc resection rate (EBRR): 98.07% (51/52); mean dissection time (DT): 47 min; mean speed of dissection (SOD): 23.3 mm^2/min; mean size of the resected specimen (SOS): 1046 mm^2.
The SOD of the 10 first ESD was significantly lower than each group of 10 next ESD: 15.7 vs 24.83-28.5-23.5-23.9 mm^2/min; $p < 0.05$).
Only 1 perforation (1.8%) occurred and 10 (19.2%) per procedure bleedings imposed the use of a coagulation forceps.
Human rectal ESD: EBRR: 100% (29/29); R0 resection rate: 93.1% (27/29); mean DT: 193.4 min; mean SOD: 12.70 mm^2/min; mean SOS: diameter 1: 56.57 mm, diameter 2: 43.85 mm, surface: 193.4 mm^2; perforation rate: 10.3% (3/29) all managed conservatively; post procedural bleeding 10.3% (3/29) all managed endoscopically. 0/24 and 0/8 had a residual or recurrent disease at 3 and 12 months respectively.
SOD increase linearly during the 8 first procedures to reach a plateau between 15 and 20 mm^2/min.
The SOD of the first 8 rectal ESD was significantly lower than the 10 next and the ten last ESD: 7.48 vs 15.68-15.93 mm^2/min ($p = 0.0035$).
Conclusion: Our prospective study of rectal ESD of large spreading tumors is one of the largest in a monocentric european center. A local training program with pig model allows starting human dissection with high safety and efficiency close to results published by japanese experts. Initial training accelerates the learning curve and the continuous practice in pig model allows maintaining constant training until the recruitment of patients becomes sufficient. The collaboration of two physicians during the long dissections probably helps improving the results.

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Disclosure of Interest: None declared

OP300 SURGICAL MARGIN NEGATIVE ENDOSCOPIC MUCOSAL RESECTION (SN-EMR) FOR ENDOSCOPY TRAINEE: A RANDOMIZED MULTICENTER PROSPECTIVE STUDY

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Introduction: As endoscopic mucosal resection (EMR) is an established colorectal polyp treatment, local recurrence occurs in 13% of cases due to inadequate snaring by endoscopy trainees.
Aims & Methods: A randomized multicenter prospective study was conducted whether surgical margin negative endoscopic mucosal resection (SN-EMR) with simple pre-clipping procedure enabled endoscopy trainees to perform complete resection. Of 159 polyps from 80 patients with colorectal polyps under 20 mm, we included 106 polyps from 51 patients. We randomly allocated polyps to the conventional injection group (CG) (55 polyps) or the pre-clipping injection group (PG) (51 polyps). The PG received three-point pre-clipping to ensure ample gripping to the muscle layer on the oral and both sides of the tumor with 4 mL local injection. Endoscopic ultrasonography was performed to measure the resulting bulge. Outcomes included the number of instances of thermal denaturation of the horizontal margin (HMX) or positive horizontal margins (HM+), the shortest distance from tumor margins to resected edges, and the maximum bulge distances from tumor surface to the muscularis propria.
Results: The numbers of HMX and HM+ in the CG and PG were 15 (27%) and 2 (3.6%) and 3 (5.8%) and 0 (0%), respectively ($P = 0.001$). The shortest distance from tumor margin to resected edge (±standard deviation, SD, mm) in polyps in the CG and PG were 0.673 ± 0.546 and 3.910 ± 1.271, respectively ($P = 0.017$). The maximum bulge distances were 4.740 ± 1.379 and 11.14 ± 2.924 ($P = 0.006$), respectively. In CG group, local saline injection extended horizontally to become larger and flatter, making the snare slippery resulting in HMX. In PG, pre-clipping from the mucosa to the muscularis propria allowed the snare to accurately strangulate the tumor without slippage by creating maximally vertical rather than horizontal bulges, resulting in resections with 3-4 mm of safety margin.
Conclusion: SN-EMR enabled endoscopy trainees to perform complete resection.

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Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 14:00–15:30

VISCERAL HYPERSENSITIVITY AND ALTERED GUT MOTILITY: MECHANISTIC INSIGHTS – ROOM E5

OP301 MODULATION OF MUCOSAL SENSITIVITY VIA THE EPITHELIAL GUANYLATE CYCLASE-C/CYCLIC GMP PATHWAY: LINACLOTIDE AS A REGULATOR OF VISCERAL SENSATION

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Introduction: Linaclotide, a guanylate cyclase-C (GC-C) agonist, effectively improves abdominal pain and constipation in patients with irritable bowel syndrome with constipation (IBS-C). Using a mouse model, we have previously shown that both linaclotide and exogenous extracellular cyclic guanosine monophosphate (cGMP) inhibit colonic nociceptor mechanosensitivity with greater efficacy during chronic visceral hypersensitivity (CVH) compared with healthy mice.[1]
Aims & Methods: To determine the effect of linaclotide and extracellular cGMP on other afferent classes, we investigated healthy C57BL/6 mice and mice with CVH (28 days after administration of 2,4,6-trinitrobenzenesulfonic acid).[1] Mechanosensory responses of colonic pelvic mucosal afferents were compared in the presence and absence of linaclotide (1–1000 nM) using *ex vivo* electrophysiological recordings. In addition, we assessed the ability of intracolonic linaclotide (1000 nM) to modulate mucosal signalling transmission *in vivo* by measuring the activation of dorsal horn neurons in the lumbosacral (LS:L6–S1) spinal cord in response to fine mechanical stimulation of the colorectal mucosa. Finally, we investigated the effects of exogenous extracellular cGMP (10–50 μM) on subpopulations of retrogradely traced colonic dorsal root ganglion

(DRG) neurons isolated from mice using whole-cell patch-clamp recordings in current clamp mode.
Results: Linaclotide caused a dose-dependent increase of low-threshold pelvic mucosal afferent mechanosensitivity in healthy mice ($P<0.001$; n = 7). This potentiating effect was completely lost in CVH mice ($P>0.05$; n = 7). *In vivo*, fine mechanical stimulation of the colorectal mucosa activated discrete populations of dorsal horn neurons within the LS spinal cord (n = 4). In healthy mice, intra-colonic administration of linaclotide increased the number of LS dorsal horn neurons activated by fine mucosal stimulation ($P<0.05$; n = 5), and the potentiating effect of linaclotide was lost in CVH mice ($P>0.05$; n = 5). In patch-clamp studies from healthy mice, application of cGMP, a known downstream mediator of GC-C activation, resulted in increased excitability of a subpopulation of colonic DRG neurons, as indicated by a reduced rheobase ($P<0.05$; n = 9) and increased firing frequency ($P<0.05$; n = 9). Notably, these potentiating effects of cGMP were not apparent in colonic DRG neurons from CVH mice.
Conclusion: Chronic oral administration of linaclotide reduces colonic nociceptor mechanosensitivity and reduces nociceptive signalling within the spinal cord in response to noxious CRD, with greater effect during CVH compared with healthy mice. Results complement our previous findings[1] and provide further mechanistic insight into how linaclotide, through GC-C agonism and the release of cGMP from mucosal epithelial cells, can reduce nociceptive signalling from the colon.

Reference

1. Castro J, Harrington AM and Hughes PA, et al. *Gastroenterology* 2013; 145: 1334–1346.

Disclosure of Interest: A. M. Harrington Financial support for research: Ironwood Pharmaceuticals, J. Castro Financial support for research: Ironwood Pharmaceuticals/Forest Laboratories, S. Garcia-Caraballo Financial support for research: Ironwood Pharmaceuticals, J. Maddern Financial support for research: Ironwood Pharmaceuticals/Forest Laboratories, T. O'Donnell Financial support for research: Ironwood Pharmaceuticals, L. Grundy Financial support for research: Ironwood Pharmaceuticals/Forest Laboratories, G. Rychkov: None declared, C. Kurtz Shareholder: Ironwood Pharmaceuticals, Conflict with: Employee of Ironwood Pharmaceuticals, I. Silos-Santiago Shareholder: Ironwood Pharmaceuticals, Conflict with: Employee of Ironwood Pharmaceuticals, S. M. Brierley Financial support for research: Ironwood Pharmaceuticals/Forest Laboratories/Takeda Pharmaceuticals/Key Pharmaceuticals, Consultancy: Takeda Pharmaceuticals/Key Pharmaceuticals

OP302 ALUMINUM INGESTION PROMOTES THE DEVELOPMENT OF COLORECTAL HYPERSENSITIVITY IN RODENTS

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Introduction: Irritable bowel syndrome is a common disease characterized by chronic abdominal pain. Involvement of environmental factors is suspected in the development of this syndrome, especially because of the high prevalence in Western countries.
Aims & Methods: Our aim was to analyze the effect of aluminium ingestion on visceral sensitivity in rodent models.
Visceral pain threshold was assessed by colorectal distension in rats intoxicated with Aluminium Citrate (AlCi) at the environmentally relevant dosage of 1.5 mg/kg bw/day. Different doses and timings, gender specificity were evaluated. Effect of the co-administration of a well-known inhibitor of mast cells degranulation, cromolyn sodium, was assessed on visceral sensibility. Expression levels of 23 selected genes known to be involved in visceral pain were quantified in colons of rats intoxicated or not with AlCi. Visceral sensitivity and intestinal permeability assessed by FITC-dextran method were compared between PAR2 WT and KO mice treated with AlCi.
Results: A significant increase of response to colorectal distension was observed in AlCi treated rats from the day 8 of intoxication, which lasted at day 15 and even worsened at day 30, compared to non-intoxicated rats. This effect was time and dose dependent, and persists other time. A new administration of AlCi after discontinuation of intoxication led to a higher decrease of pain threshold. Females were more susceptible than males to AlCi induced visceral hypersensitivity. Although mast cells numbers did not vary, the percentage of degranulated mast cells was increased in AlCi treated rats compared to controls rats. The co-administration of cromolyn sodium reversed the decrease of pain threshold induced by 8 days intoxication with AlCi. Cannabinoid receptor 1 (*Cnr1*), the transient receptor potential cation channel (*Trpa1*), the proteinase activated receptor 2 and 4 (*Par2* and *Par4*), the vanilloid receptor 1 and 4 (*Trpv1* and *Trpv4*) genes showed significant mRNA expression alterations in Al intoxicated rats. Consistently, we observed in WT mice a significant increase of visceral motor response induced by AlCi intoxication. Notably, AlCi ingestion failed to induce significant variation on visceral motor response in PAR2 KO mice. Finally, the significant increase of intestinal permeability observed in PAR2 WT mice treated with AlCi compared to untreated mice was not found in PAR2 KO mice.
Conclusion: We have demonstrated that currently ingested amounts of Al in humans induced in mice and rats a dose dependent increase of colorectal sensitivity. Al-induced hypersensitivity persists over time so that intoxication was arrested, and appears again when Al intoxication resumes, dismissing any tolerance phenomenon. As for irritable bowel syndrome frequency, female gender was more affected by Al-induced hypersensitivity than male gender. The mechanisms involved a degranulation of masts cells and an increased permeability. Finally, the Al-induced visceral pain increase is PAR2 dependent.
Disclosure of Interest: None declared

OP303 LINACLOTIDE-INDUCED CHRONIC ACTIVATION OF THE GUANYLATE CYCLASE-C/CYCLIC GMP PATHWAY INHIBITS ASCENDING NOCICEPTIVE PATHWAYS AND RESTORES ABERRANT SPINAL CORD SIGNALLING

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Introduction: Linaclotide, a guanylate cyclase-C (GC-C) agonist, effectively improves abdominal pain and constipation in patients with irritable bowel syndrome with constipation (IBS-C). Recently, we have shown that in a mouse model acute application of linaclotide inhibits colonic nociceptor mechanosensitivity with greater efficacy during chronic visceral hypersensitivity (CVH) compared with healthy mice.[1]
Aims & Methods: To determine the effects of chronic linaclotide administration on nociceptor function, we investigated healthy C57BL/6 mice and mice with CVH (28 days post-2,4,6-trinitrobenzenesulfonic acid administration, when inflammation had resolved and nociceptors were mechanically hypersensitive).[1,2] Mice from each group were randomly assigned to either chronic linaclotide (3 μg/kg/day) or placebo (water) administered as a once-daily oral gavage for 2 weeks prior to experimentation. The effects of chronic oral linaclotide administration on colonic nociceptor function (stimulus response functions and activation thresholds to mechanical stimuli) from healthy and CVH mice were determined using *ex vivo* electrophysiological recordings. In addition, we assessed the ability of chronic oral linaclotide to alter nociceptive signalling transmission *in vivo* by measuring the activation of dorsal horn neurons in the thoracolumbar (TL:T10–L1) and lumbosacral (LS:L6–S1) spinal cord in response to noxious colorectal distention (CRD).
Results: In healthy mice, chronic linaclotide administration significantly reduced nociceptor mechanosensitivity compared with placebo ($P<0.05$; n = 10–12). Colonic nociceptors from CVH mice displayed mechanical hypersensitivity ($P<0.001$; n = 13) and reduced mechanical activation thresholds ($P<0.05$; n = 13) compared with healthy mice. In CHV mice, chronic linaclotide administration significantly reduced colonic nociceptor mechanosensitivity compared with placebo ($P<0.001$; n = 10–13). Furthermore, chronic linaclotide administration reversed the reduced mechanical activation thresholds of nociceptors from CVH mice compared with placebo. In separate *in vivo* experiments, chronic linaclotide administration to CVH mice significantly reduced the signalling of noxious CRD to the TL spinal cord ($P<0.01$; n = 4) compared with CVH mice administered placebo.
Conclusion: Chronic oral administration of linaclotide reduces colonic nociceptor mechanosensitivity and reduces nociceptive signalling within the spinal cord in response to noxious CRD, with greater effect during CVH compared with healthy mice. Results complement our previous findings[1] and provide further mechanistic insight into how linaclotide, through GC-C agonism and the release of cGMP from mucosal epithelial cells, can reduce nociceptive signalling from the colon.

References

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Disclosure of Interest: J. Castro Financial support for research: Ironwood Pharmaceuticals/Forest Laboratories, A. M. Harrington Financial support for research: Ironwood Pharmaceuticals, S. Garcia-Caraballo Financial support for research: Ironwood Pharmaceuticals, J. Maddern Financial support for research: Ironwood Pharmaceuticals/Forest Laboratories, T. O'Donnell Financial support for research: Ironwood Pharmaceuticals, L. Grundy Financial support for research: Ironwood Pharmaceuticals/Forest Laboratories, C. Kurtz Shareholder: Ironwood Pharmaceuticals, Conflict with: Employee of Ironwood Pharmaceuticals, I. Silos-Santiago Shareholder: Ironwood Pharmaceuticals, Conflict with: Employee of Ironwood Pharmaceuticals, S. M. Brierley Financial support for research: Ironwood Pharmaceuticals/Forest Laboratories/Takeda Pharmaceuticals/Key Pharmaceuticals, Consultancy: Takeda Pharmaceuticals/Key Pharmaceuticals

Abstract number: OP304

	WT + DSS	WT + DSS + Nicotine	TLR2KO + DSS	TLR2KO + DSS + Nicotine
Body weight loss %	12	8*	16	14
IL-1β pg/ml	33 ± 6	12 ± 8*	93 ± 12	78 ± 10
MPO activity U/mg tissue	0.05 ± 0.1	0.02 ± 0.05*	0.08 ± 0.15	0.07 ± 0.2

*$p < 0.01$ vs WT + DSS

OP304 ENTERIC NEUROPATHY IMPAIRS EXPRESSION OF ALPHA7 NICOTINIC RECEPTOR IN INTESTINAL MUCOSAL MACROPHAGES: EVIDENCE FOR A NEURON-MACROPHAGE INTERPLAY TO MODULATE GUT INFLAMMATION

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Introduction: In inflammatory bowel diseases nicotine exhibits opposing effects on intestinal inflammation: it's beneficial in ulcerative colitis (UC) while it is detrimental in Crohn's disease (CD). We recently reported that expression of alpha7 nicotinic acetylcholine receptor (α7nAChR) is significantly lower in colonic macrophages (MΦc) of CD compared to UC and healthy subjects.

Aims & Methods: Since anomalies of the enteric nervous system (ENS) have been described mainly in CD patients we postulated that a diffuse gut neuropathy could influence the cholinergic counter-inflammatory mechanism in MΦc. To this goal we investigated the phenotype of MΦc in TLR2 knockout (KO) mice, a well described animal model of ENS dysfunction resulting in severe colitis[1]. Mild colitis was induced in C57Bl/6J (WT) and TLR2KO mice by 3% dextran sulphate sodium (DSS) for 3 days. CD11$^+$ MΦc were isolated by magnetic beads separation and α7nAChR expression was evaluated by FACS analysis using α-Bungarotoxin (αBgt)-FITC. Otherwise, CD11$^+$ MΦc were cultured with ATP (1 mM)/LPS (100 ng/ml) with or without nicotine (10 mM) for 16 hrs. The inflammatory phenotype was evaluated investigating the activation of caspase-1 by FACS analysis. To assess the influence of enteric neuropathy on MΦc phenotype, anomalies of the ENS in TLR2KO mice were cured with recombinant murine (rm)GDNF (2 µg/g body weight) for 10 days. Colitis was induced by 3% DSS for 5 days with or without nicotine supplementation in drinking water (25 µg/ml). Colitis severity was assessed by evaluating body weight loss, IL-1β level and MPO activity.

Results: In basal conditions, α7nAchR expression and caspase-1 activity were comparable in MΦc from WT and TLR2KO mice. Following induction of mild colitis, expression of α7nAchR and activation of caspase-1 significantly increased in MΦc from WT but not from TLR2KO mice ($P<0.01$). Moreover, exposure of activated WT MΦc to nicotine significantly reduced LPS/ATP-induced caspase-1 activity (by 28%, $P<0.05$). Furthermore, *in vivo* nicotine administration significantly reduced the severity of DSS colitis in WT but not in TLR2KO mice (see table).

In TLR2KO mice pre-treatment with rmGDNF, able to rectify the anomalies of the ENS, corrected the inflammatory phenotype of MΦc. Indeed, in rmGDNF-treated TLR2KO mice the α7nAchR expression and caspase-1 activation levels following 3 days DSS exposure were comparable to WT mice.

Conclusion: In the gut, the integrity of the ENS is required to up-regulate α7nAchR expression and activate caspase-1 in MΦc, events mandatory in modulating mucosal inflammation. We speculate that in CD patients the severe and diffuse neuropathy of the ENS contributes to the inadequate expression of α7nAChR in MΦc thus accounting for the lack of the cholinergic counter-inflammatory mechanism during colitis.

Reference

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Disclosure of Interest: None declared

OP305 GUT MICROBIOTA DEPLETION ALTERS THE STRUCTURE AND FUNCTION OF THE ENTERIC NERVOUS SYSTEM IN ADOLESCENT MICE

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Introduction: Gut microbiota colonisation has a key role during the development of enteric nervous system (ENS) circuitries. Any change of its composition triggered by environmental factors or drugs could impact ENS homeostasis and determine the onset of functional bowel disorders.

Aims & Methods: The aim of the present study was to evaluate the effect of gut microbiota depletion on ENS integrity and intestinal motility during mouse adolescence. Depletion of gut microbiota was performed on male C57Bl/6 mice (age = 21 ± 5 days) by administering for 14 days an antibiotic cocktail (50 mg/kg vancomycin, 100 mg/kg neomycin, 100 mg/kg metronidazol and 100 mg/kg ampicillin) by oral gavage every 12 hours. In antibiotic–treated (ABX) and control (CNTR) animals we assessed: i) gastrointestinal transit 30 minutes after intragastric administration of nonabsorbable fluorescein isothiocyanate labeled dextran; ii) pellet frequency, measured as changes in stool output during a 60 minutes collection period; iii) stool water content; iv) contractile activity of isolated ileum segments, vertically mounted in organ baths, measured as changes in isometric muscle tension following carbachol (0.001-100 μM), KCl (60 mM), electric field stimulation (EFS, 1-40 Hz) or inhibition in non-adrenergic, non-cholinergic (NANC) conditions (EFS = 10 Hz, 1 μM atropine, 1 μM guanethidine, in the absence or presence of 0.1 mM L-NAME); v) distribution of the neuronal HuC/D and glial fibrillary acidic protein (GFAP) by double labelling confocal immunofluorescence in longitudinal muscle myenteric plexus preparations (LMMPs); vi) neurochemical coding integrity, evaluated by acetylcholinesterase biochemical staining, neuronal nitric oxide synthase (nNOS) immunohistochemistry and GluN1 mRNA levels in LMMPs.

Results: Antibiotic depletion determined a marked enlargement (+92 ± 0.1% $p < 0.01$) in cecum, associated with a three-fold increase in organ weight. ABX mice showed a significant reduction in the number/hour output of fecal pellets (-29.5 ± 0.5% $p < 0.01$) and increased stool water content (+35 ± 7% $p < 0.01$). Gastrointestinal transit was delayed in ABX mice compared to CNTR mice (GC 3.5 ± 0.2 vs 7.3 ± 0.2, $p < 0.01$, respectively). In vitro contractility studies showed altered receptor- and KCl-mediated responses and an overall modified neuronal excitability. NANC-mediated relaxations were significantly increased (+144 ± 30% at 10 Hz $p < 0.05$) in ileum segments from ABX mice. In the ENS of ABX mice HuC/D immunoreactivity decreased while acetylcholine-esterase$^+$ stained fibres increased (+37 ± 3%; $p < 0.01$). GFAP immunostaining showed distorted cellular processes as well as the distribution of nNOS$^+$ neurons was altered following gut microbiota depletion. A two-fold increase of GluN1 mRNA levels was also found in LMMPs of ABX mice.

Conclusion: Gut microbiota depletion determines complex anomalies in ENS architecture, neurochemical coding and function leading to intestinal dysmotility. On the whole such changes are highly indicative of the primary role played by the enteric microbiota in ensuring ENS integrity, consequently contributing to maintain the gut in a long-term healthy state.

Disclosure of Interest: None declared

OP306 IMPACT OF ADHERENT-INVASIVE E.COLI AND FAECALIBACTERIUM PRAUSNITZII ON COLONIC HYPERSENSITIVITY

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Introduction:
Irritable Bowel Syndrome (IBS) and Inflammatory Bowel Diseases (IBD) are believed to result in part from breakdown of homeostasis between intestinal microbiota and the mucosal immune system and which may be associated with visceral pain.

Aims & Methods: The aim of this work was to study the impact of an intestinal dysbiosis on mouse model of colonic hypersensitivity (CHS) by determining if, (1) intestinal Crohn's disease-associated Adherent-Invasive *E.coli* (AIEC) colonization could spontaneously induce a CHS in mice, and (2) if *F. prausnitzii*, whose abundance is decreased in these gastrointestinal disorders, could have an impact on CHS, in a non-inflammatory CHS mouse model induced by Neonatal Maternal Separation (NMS). Visceral hypersensitivity was assessed using a technique based on measuring electromyographic abdominal contractions induced by colorectal distension for each models and inflammation and intestinal permeability was evaluated.

Results: Crohn's disease-associated AIEC (reference strain LF82) infection of transgenic mice overexpressing the human form of CEACAM6 protein dramatically and quickly (D4) increased levels of CHS, associated with a low-grade inflammation and increased intestinal permeability. In addition, such CHS persists in mice, even after AIEC clearance and a restoration of the colon homeostasis (inflammation and permeability) to a normal level.

NMS treatment induced an increased visceromotor response (VMR) in the absence of alteration in gut wall macroscopic integrity or colonic mucosa inflammation status. However, a slight increase of intestinal permeability has been measured. *F. prausnitzii* treatment (reference strain A2-165) significantly decreased VMR and restored intestinal permeability in NMS model.

Conclusion: These results suggested a direct involvement of CD-associated AIEC LF82 infection in CHS and a protective role of *F. prausnitzii* A2-165 on CHS in a non-inflammatory model. Thus, intestinal dysbiosis could impact on CHS, suggesting that targeting intestinal microbiota could be a new therapeutic approach to modulate CHS and associated abdominal pain in patients.

Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 14:00–15:30
MOLECULAR MECHANISMS OF PROGRESSION AND THERAPY RESISTANCE IN PANCREATIC CANCER – ROOM E6

OP307 LYMPHOTOXIN ACCELERATES PRE-NEOPLASTIC CONVERSION IN PANCREATIC TUMORIGENESIS BY PROMOTING ACINAR CELL REPROGRAMMING

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Introduction: Despite the availability of multimodal therapies, patients with pancreatic cancer have less than 5% 5-year survival rate after diagnosis. For developing early detection methods and treatments, it is essential to understand the primary events leading to tumor initiation. The most common oncogenic mutations associated with all stages of pancreatic cancer (PDAC) are found in the *KRAS* gene; however signaling pathways that drive progression of pre-neoplastic PanIN lesions need to be investigated. Recent studies using genetically engineered mice propose a stepwise process starting from acinar cells undergoing ductal reprogramming (acinar-to-ductal metaplasia, ADM) throughout premalignant PanIN (pancreatic intraepithelial neoplasia) lesions leading to tumor formation in mice harboring a mutated Kras allele. Inflammation has been described as a risk factor for PDAC development. Still, little is known about the cellular and molecular mechanisms how inflammation promotes ADM and PanIN progression. The pro-inflammatory cytokines TNFa, Lymphotoxin (LT) and Light and their downstream master transcription factor NF-κB emerged as critical regulators linking inflammation to cancer.
Aims & Methods: The aim of the study is to explore the inflammatory mechanisms promoting ADM and PanIN development. Therefore, we established a new genetic model (LTKC) by crossing $p48^{+/Cre};Kras^{+/G12D}$ (KC) model for pancreatic tumorigenesis, with a transgenic mouse developing spontaneous pancreatitis, due to Lymphotoxin (LT) overexpression. Immunohistochemistry and qPCR were used to obtain an inflammatory signature. Ras activity and activation of pathways downstream of EGFR and LTbR were compared in LT, LTKC and KC models. *In-vitro* experiments were performed to investigate the direct role of LT in ADM development.
Results: Overexpression of Lymphotoxin in mice harbouring an activating Kras mutation in the pancreas (LTKC) dramatically accelerates the development of premalignant PanIN lesions compared to KC animals. Already after 8 weeks extensive ADMs and PanIN lesions up to PanIN3 are observed in LTKC mice. This coincides with significant upregulation of inflammatory genes and increased Ras activity. Similar molecular and phenotypic changes were observed around 16 weeks in Kras animals. LT overexpression alone could transiently increase Ras activity and phosphorylation of EGFR in early time points. *In vitro* experiments show that LT overexpression in wt acinar cells is sufficient to initiate spontaneous transdifferentiation. Furthermore, acinar cells derived from LTKC animals form ADMs significantly faster than acini from KC animals. Pharmacological inhibition of LTbR signalling mitigated inflammatory environment but could not significantly moderate PanIN development in both KC and LTKC models.
Conclusion: We conclude that Lymphotoxin may contribute to the initiation of PDAC precursor formation: By (1) inducing inflammatory environment and by (2) regulating cell autonomous acinar transdifferentiation, leading to accelerated PanIN development. LTbR inhibition was not sufficient to influence PanIN formation which could imply that LTbR activation results in a secondary activation of EGFR and Ras.
Disclosure of Interest: None declared

OP308 THE INNER PLASMA MEMBRANE PROTEIN PLAC8 REGULATES CELL CYCLE PROGRESSION IN PANCREATIC DUCTAL ADENOCARCINOMA (PDAC)

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Introduction: Pancreatic ductal adenocarcinoma (PDA) is the most aggressive pancreatic cancer with an overall 5-year survival rate of $<5\%$. Despite significant advances in treatment of the disease, the median survival rate ($\sim$6 months) remains unchanged, warranting the need to identify new targets for therapeutic approaches. Our previous transcriptomic analyses as well as parallelised cell-based assays indicated a previously unknown role for Plac8 in pancreatic cancer. Plac8 is a small protein whose physiological functions remain largely unclear. The main aim of this project is to characterise the cellular localisation as well as the molecular function of Plac8 PDAC cells.
Aims & Methods: Tissue microarrays, RNAi, FLIP-, FRAP-, and TIRF microscopy, cell proliferation and viability assays, FACS analysis, Western blot, transgenic mouse models.
Results: qRT-PCR as well as tissue microarray data confirmed strong ectopic expression of Plac8 in pancreatic cancer tissues. High Plac8 expression is also retained in the majority of pancreatic tumour cell lines *in vitro*, with negligible expression in non-transformed cell lines. Using TIRF microscopy and FLIP/FRAP experiments, we show for the first time that Plac8 locates to the inner face of the plasma membrane and stably interacts with distinct membrane structures. Functionally, proliferation and viability were strongly impaired by Plac8 down-regulation, achieved by transient RNAi-mediated knockdown. Western blot and flow cytometry did not show any involvement of classical apoptosis pathways (Caspase-3 and PARP cleavage). Flow cytometry analyses and time course experiments with cell cycle inhibitors demonstrated strong attenuation of cell cycle progression after loss of Plac8 expression. *In vivo*, genetic Plac8 deficiency selectively prolonged survival in *Kras*-driven, but not *Kras*/*p53*-driven PDAC mouse models.
Conclusion: Our experimental data show that ectopic expression of Plac8 is indispensable for proliferation, viability and cell cycle progression in pancreatic cancer cells and suggests Plac8 as a potential new therapeutic target in pancreatic ductal adenocarcinoma.
Disclosure of Interest: None declared

OP309 TRAIL-INDUCED NF-KB/RELA ACTIVATION TARGETS A CCL20-DEPENDENT PATHWAY MEDIATING IMMUNE CELL RECRUITMENT CONFERRING APOPTOSIS RESISTANCE OF PANCREATIC CANCER CELLS

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Introduction: Pancreatic ductal adenocarcinoma (PDAC) represents one of the deadliest malignancies with an overall life expectancy of up to one year despite palliative chemotherapy. The transcription factor NF-κB has been shown to be a critical component of molecular mechanism conferring profound apoptosis resistance in PDAC. Despite extensive data on the role of the most abundant NF-κB subunit p65/RelA in PDAC apoptosis control, there is only little knowledge of the downstream targets and their functional relevance in PDAC.
Aims & Methods: In the present study, a panel of pancreatic carcinoma cell lines (Panc1, PancTu1, Capan-1, Patu8988t, MiaPaca2) were analyzed for the role of RelA target genes in the resistance against TRAIL induced apoptosis.
Results: Resistant PDAC cell lines exhibit a high basal NF-κB activity that was further strongly induced by TRAIL. In contrast, sensitive MiaPaca2 cells displayed only little basal NF-κB activity and only weak induction of the transcription factor by TRAIL. Transfection with siRNA against the RelA subunit of NF-κB sensitized the TRAIL-resistant PDAC cells. Gel shift analysis revealed that the p65/RelA subunit is critical component of the TRAIL-inducible and the basal expressed NF-κB complex in PDAC. By analysis of genome-wide expression patterns of RelA dependent gene expression we were able to show that CCL20 represents the strongest TRAIL-inducible RelA target gene in resistant PDAC cells. Using Chip and luciferase assay we were able to describe the RelA responsive element in the CCl20 promoter. ELISA confirmed that RelA dependent upregulation of CCL20 mRNA after TRAIL treatment leads to a strongly increased secretion of CCL20. Surprisingly targeting CCL20 by siRNA, blocking antibodies or by downregulation of the CCL20 receptor CCR6 had no effect on PDAC cell death or cancer cell migration. However by using an *ex vivo* coculture system with PBMC of healthy donors we were able to show that CCL20 secreted by the TRAIL-treated resistant PDAC cells strongly induces migration of PBMC. Furthermore these PBMC showed a CCL20/RelA-dependent TH17-like differentiation. Finally these cocultured PBMC conferred apoptotic protection of PDAC cells against TRAIL-induced apoptosis.
Conclusion: In conclusion we were able to establish a RelA-CCL20 pathway in TRAIL-resistant PDAC cells which does not confer direct apoptotic protection or migration of the tumor cells but instead leads to the recruitment and TH17-like differentiation of immune cells which in turn mediate apoptosis resistance of PDAC cells.
Disclosure of Interest: None declared

OP310 CANCER-CELL-DERIVED CXCL12 ACTIVATES SCHWANN CELLS AND SUPPRESSES PAIN SENSATION IN PANCREATIC CANCER

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Introduction: Neural invasion (NI) is an independent prognostic factor for overall and progression-free survival in pancreatic cancer (PCa). Recently, we showed that peripheral glia, i.e. Schwann cells (SC), specifically migrate toward PanIN lesions and initiate NI in PCa, but the mediators of this glia-cancer crosstalk are unknown. Here, we aimed to analyze the role of the CXCL12-CXCR4-CXCR7 chemokine-receptor axis in the glial attraction to pancreatic cancer.
Aims & Methods: Here, we aimed to analyze the role of the CXCL12-CXCR4-CXCR7 chemokine-receptor axis in the glial attraction to pancreatic cancer. Expression of CXCL12, CXCR4 and CXCR7 was analyzed in human SC, in SC-PCa-cell-co-cultures, in human PCa tissues and correlated to pain sensation of PCa patients. In novel 3D-SC-migration/outgrowth-assays, native SC and SC derived from glia-specific CXCR4-knockout mice ($GFAP\text{-}Cre^{ERT2};CXCR4^{lox/lox}$) were tracked for their migration to PCa cells via digital-time-lapse-microscopy. Mice with PCa and simultaneous pancreas-specific depletion of CXCL12 ($Ptf1a\text{-}Cre;LSL\text{-}Kras^{G12D};CXCL12^{lox/lox}$, termed "KC12") were generated and analyzed for the frequency of SC around PanINs, and for their abdominal mechanosensitivity via von-Frey-filaments.
Results: PCa cells were major producers of CXCL12, which strongly chemoattracted human SC via CXCR4 and CXCR7. SC constitutively expressed CXCR4 and CXCR7 which they upregulated in co-culture with PCa cells. Glia-specific depletion of CXCR4 in mice abrogated the glial chemoattraction to tumor cells in the 3D-SC-migration-/outgrowth-assays. In KC12 mice, SC-chemoattraction

to PanINs was suppressed, and KC12 mice had increased abdominal hypersensitivity, which was in accordance with the reduced intrapancreatic expression of CXCR4 and CXCR7 among PCa-patients with pain.
Conclusion: Cancer-cell-derived CXCL12 chemoattracts CXCR4- and CXCR7-expressing SC and results in analgesia. These findings propose a novel explanation for the lack of symptoms like pain in early stages of PCa.
Disclosure of Interest: None declared

OP311 IEX-1 KNOCKOUT IN AN EX VIVO MOUSE MODEL OF PANCREATIC CANCER INHIBITS DNA DAMAGE INDUCED NF-KAPPAB ACTIVITY AND MCL-1 NUCLEAR TRANSLOCATION LEADING TO ENHANCED APOPTOSIS

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Introduction: Pancreatic ductal adenocarcinoma (PDAC) represents one of the deadliest malignancies with an overall life expectancy of up to one year despite palliative chemotherapy. The transcription factor NF-κB has been shown to be a critical component of apoptosis and therapeutic resistance in PDAC. Recently we showed in an in vitro model that the immediate early response NF-kB target gene regulates apoptosis of PDAC cells by interfering with NF-kB activation.
Aims & Methods: In the present study, we investigated the role of IEX-1 in murine $Kras^{G12D}$-driven models of PDAC. We isolated primary cancer cell lines from murine PDACs, IEX-1 proficient or deficient. These cell lines were treated with chemotherapeutics and analyzed for responsiveness, NF-kB acitivity and expression of death limiting BCL2 family members.
Results: IEX-1 deficiency is associated with decreased gemcitabine and etoposid responsiveness. Apoptosis, measured by sub-G1 analysis and caspase-3/-7 assay upon treatment with either etoposid or gemcitabine was significantly reduced in IEX-1-deficient murine PDAC cells. Mechanistically, both drugs induce NF-kB and activation of this signaling pathway was enhanced in IEX-1-deficient cells. In addition, DNA damage induced nuclear translocation of Mcl1, was reduced in IEX-1 knock out cell lines. Finally, a genetic rescue experiment, by stably transfection of IEX-1, proved IEX-1 specificity.
Conclusion: In conclusion we were able to confirm a central role of IEX-1 in regulation of apoptosis, NF-kB activity and MCL1 localization in novel PDAC models. Furthermore, such data point to an IEX-1 specific stratification strategy to select for patients benefit from DNA-damage inducing therapies
Disclosure of Interest: None declared

OP312 ACTIVATED GLIA IN PANCREATIC CANCER DECREASES PAIN VIA INHIBITION OF SPINAL ASTROCYTIC ACTIVITY

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Introduction: Pancreatic cancer (PCa) is characterized by a pronounced neuropathy and neuropathic pain, but the role of glia cells in PCa-associated neuropathy and pain is unknown.
Aims & Methods: In the present study, we aimed to analyze the impact of PCa-associated activated Schwann cells (SC) on pain sensation and spinal activity in vivo. Human SC were cultured under hypoxia, or in co-culture with PCa cells or T-lymphocytes and assessed for glial-fibrillary-acidic-protein (GFAP) expression, viability and cell size. Expression of glial-activation-markers and of hypoxia-inducible-factor-1alpha in human PCa nerves was correlated to pain severity. In conditional PCa mouse models, SC activation, abdominal mechanosensitivity, pain-related behavior, astroglial, microglial and neuronal activity in the spinal cord were assessed after *in vivo* blockade of interleukin-6/IL-6 signaling.
Results: SC upregulated GFAP expression and became "stellated "under hypoxia, or in co-culture with PCa cells and T-lymphocytes, and this SC activation was reversible upon inhibition of IL-6 *in vitro*. Correspondingly, inhibition of the classical IL-6-signaling suppressed SC activation around the PanIN lesions in Ptf1a-Cre;$Kras^{G12D}$;$IL6^{-/-}$ mice. Activated, GFAP- and p75NTR-upregulating SC were associated with diminished pain in human PCa and with decreased abdominal mechanosensitivity and increased locomotor activity in mice with PCa. In the spinal cord, the proportion of activated astrocytes was significantly less among mice with increased pancreatic SC activation during PCa.
Conclusion: Activated SC in PCa undergo "reactive gliosis" and attenuate pain sensation via suppression of spinal astroglia. These findings point out a novel mechanism for how and why cancer may not evoke pain during cancer progression.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 15:45–17:15
ENDOSCOPY MEETS PATHOLOGY: ADENOCARCINOMA OF THE OESOPHAGOGASTRIC JUNCTION – ROOM A3

OP313 EXPLORING DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS OF ENDOSCOPIC MUCOSAL RESECTION IN EUS-STAGED T2 OESOPHAGEAL ADENOCARCINOMA

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Introduction: Most oesophageal cancers are assessed by endoscopic ultrasound (EUS). EUS is accurate in staging clinical (c)T3-4 tumours and loco-regional lymph node metastases but the accuracy is lower when it comes to differentiating cT1 from cT2 tumours with a tendency to 'overstage'. Endoscopic mucosal resection (EMR) allows for a histological diagnosis and staging and is emerging as a treatment option for early oesophageal adenocarcinoma (EAC). Because of the possible overstaged cT2 tumours, in recent years we have adopted the policy to be suspicious of cT2 tumours with a low threshold tendency to endoscopic reassessment. The aim of this study is to evaluate the final histological diagnosis in patients with a cT2 EAC as determined by EUS and also to assess the value of endoscopic reassessment followed by EMR if deemed possible.
Aims & Methods: Patients with cT2 EAC were identified from 2 institutional databases: a surgical cohort of patients who underwent oesophagectomy between January 1990 and October 2014, and a gastroenterological cohort where endoscopic reassessment was done between November 2010 and April 2014. Main outcome measures were final pathological (p) T-stage after oesophageal resection without preoperative therapy, and the final pT-stage of patients that underwent endoscopic reassessment with or without subsequent EMR.
Results: A total of 158 patients with T2-staged EAC by EUS were identified retrospectively. 87 Patients underwent oesophagectomy without neoadjuvant therapy for a cT2-tumor. In 46 patients (53%) the pT-stage was less than T2. In 21 (24%) of these patients the resection specimen showed tumour characteristics that fulfil current criteria for endoscopic resection.
In 11 prospectively identified patients with cT2 EAC and no evidence of lymph node or distant metastasis, an endoscopic reassessment was done to evaluate endoscopic resectability. In 10 patients (91%) a complete EMR was successfully performed by multiband mucosectomy and histological evaluation demonstrated a pT1 tumour in all 10 patients. In 3 patients (30%), the resection specimen showed tumour characteristics that fulfil current criteria for endoscopic resection and were successfully treated with EMR. Poor tumour characteristics were present in 7 patients (70%); 3 patients were referred for oesophagectomy, 1 for definitive chemoradiotherapy, and 3 patients receive ongoing endoscopic surveillance.
Conclusion: This study demonstrates that 53% of cT2 EAC are pT1 tumours after histological examination of the oesophagectomy specimen. Curative treatment by EMR is possible in 24-30% of these patients avoiding the need for oesophagectomy. Endoscopic reassessment seems to be justified for all cT2 staged oesophageal adenocarcinomas followed by EMR if deemed possible.
Disclosure of Interest: None declared

OP314 BURIED BARRETT'S DYSPLASIA: RFA IS NOT THE ONLY CULPRIT

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Introduction: Buried Barrett's' or Subsquamous Intestinal Metaplasia (SSIM) refers to glands which are 'buried' underneath the squamous epithelium. Buried Barrett's can pose significant diagnostic and surveillance challenges. Buried Barrett's has mainly been reported in the post ablation context (APC, RFA, PDT).
Aims & Methods: We aim to evaluate its prevalence in patients who are ablation naïve, and understand the reasons behind it. This is a prospective cohort study. We investigated our Barrett's database for patients who were referred for endoscopic treatment (EMR) of Barrett's neoplasia between June 2006 to June 2014. We assessed histology reports before and after endoscopic therapy (EMR), specifically looking for evidence of buried Barrett's.
Biopsy: Biopsies were first obtained from any suspicious-looking area. Following this, biopsies were then obtained from the neosquamous area. Finally, random biopsies were obtained. These were sent in separate cassettes. Histopathology was reported by two independent GI pathologists and was prospectively recorded on a central pathology database.
Buried Barrett's was defined as any metaplastic or glandular tissue beneath the squamous epithelium. Pathology specimens were reported by 2 independent, accredited GI pathologists.
Results: Our study shows that in the pre-EMR cohort, there was an overall prevalence of 12.2% of buried Barrett's and a 9.1% prevalence of buried Barrett's with high grade neoplasia (HGD or IMC) (see Table 1). Our results in the post-EMR cohort shows an overall prevalence of 16.8% of buried

Barrett's with 6.1% prevalence of buried high-grade neoplasia (HGD or IMC). This has significant implications for post EMR endoscopic assessment and surveillance.

Table 1: Buried Barrett's with and without dysplasia

	Buried Barrett's diagnosed in endoscopic therapy naïve patients	Buried Barrett's diagnosed in patients post EMR procedure
Total	16/131 (12.2%)	22/131 (16.8%)
Buried Barrett's with no dysplasia	2/131 (1.5%)	10/131 (7.6%)
Buried Barrett's dysplasia	14/131 (10.7%)	13/131 (9.9%)
HGD	9/131 (6.9%)	4/131 (3.0%)
IMC	3/131 (2.3%)	4/131 (3.0%)
HGD + IMC	12/131 (9.1%)	8/131 (6.1%)
LGD	2/131 (1.5%)	5/131 (3.8%)

Conclusion: 1) Buried Barrett's and Barrett's cancer are seen in endotherapy naïve patients. This is likely to be related to intensive biopsies.
2) EMR, despite being a non ablation technique, still results in buried Barrett's and Barrett's cancer.
3) The overall prevalence of buried Barrett's is higher than previously reported. We need to be aware of this while assessing Barrett's patients.
Buried Barrett's glands after ablation (APC/RFA/PDT) are well reported.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 15:45–17:15

WHAT'S NEW IN BARRETT'S OESOPHAGUS? – ROOM 7.1

OP315 THE IMPACT OF ENDOSCOPIC ERADICATION FOR BARRETT'S ESOPHAGUS ON ESOPHAGEAL ADENOCARCINOMA INCIDENCE AND MORTALITY: A COMPARATIVE MODELING ANALYSIS

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Introduction: Esophageal adenocarcinoma (EAC) incidence increased dramatically over the past 40 years in Western countries and neither EAC incidence nor mortality has plateaued. New techniques for endoscopic eradication of the EAC precursor Barrett's esophagus (BE) such as radiofrequency ablation (RFA) are utilized to prevent progression to EAC. The efficacy and durability of endoscopic eradication are reported, but the long-term impact of eradicative treatment and recurrent disease on EAC incidence and overall mortality reduction has not been analyzed with comprehensive and robust simulation models using this recently updated clinical data. In this study we analyzed the impact of RFA for endoscopic eradication of BE with or without dysplasia on EAC incidence and mortality using a comparative simulation modeling approach.
Aims & Methods: This study includes the predictive modeling of endoscopic eradicative treatment (EET) using three previously established population-based EAC models calibrated to NCI-SEER data. The modeling of clinical aspects of EET was based on available clinical data for RFA and endoscopic mucosal resection (EMR). We simulated a hypothetical cohort of 60 year old patients with BE for whom multiple management strategies were tested, selected on initial dysplasia status and evaluated the simulation outcomes for EAC incidence and mortality reduction; required surveillance endoscopies and treatments including RFA and EMR and numbers of treatments needed to avert one EAC death (NNT/death).
Results: A strategy to endoscopically eradicate BE with high-grade dysplasia will decrease EAC incidence by 50% (range 44% > 58%) and EAC mortality by 46% (41% > 53%) with NNT/death of 30 (26-34). If all BE (dysplastic and non-dysplastic) were eradicated, EAC incidence would incrementally decrease by 83% (81% > 86%) and mortality by 80% (75% > 85%). However, this reduction in EAC was associated with a four-fold increase in the number of treatments with an incremental NNT/death of 209 (132-316). Halting post-treatment surveillance after a recurrence-free period of 5-10 years has a negligible influence on NNT/death when eradicating only patients with HGD.
Conclusion: The resources needed to achieve EAC mortality reduction increase substantially as patients with lower severity of disease are selected for treatment. From a resource efficiency perspective, the large NNT/death suggests that treatment benefits justify endoscopic eradication only among BE patients with HGD.
Disclosure of Interest: None declared

OP316 ACETIC ACID GUIDED FOCAL ENDOSCOPIC RESECTION WITHOUT RFA REMAINS AN EFFECTIVE TREATMENT FOR BARRETT'S NEOPLASIA: TIME TO REASSESS THE ROLE OF RFA?

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Introduction: Endoscopic resection (ER) is an established effective treatment for Barrett's neoplasia. ER can lead to recurrence due to residual neoplasia left behind, so it is suggested that all patients should undergo radiofrequency ablation (RFA) after ER. Acetic acid chromoendoscopy has been shown to be an effective method of localising and delineating dysplastic areas of Barrett's oesophagus.
Aims & Methods: We aim to review the outcome of Acetic Acid-guided focal ER without RFA in our patients. All ER procedures between January 2005 and November 2014 were recorded in a prospective database which was analysed. Acetic acid guided focal ER was the treatment strategy with the aim of removing all neoplasia visible with acetic acid chromoendoscopy. RFA was not used in this group.
Results: 112 patients were treated for dysplastic Barrett's oesophagus or early Barrett's cancer by ER. The mean age at first procedure was 68 years and 82% of the patients were male. Mean initial Barrett's length was 5.1cm. 35 of 112 patients had advanced histological features on the initial ER specimen and were referred for radical cure. The remaining 77 cases showed; intramucosal cancer (IMC) in 46, high-grade dysplasia (HGD) in 28 and low-grade dysplasia in 3. All 77 cases have follow-up data with a mean duration of 5.4 years. 67 of 77 cases (87%) have sustained eradication of HGIN/IMC after focal ER. 10 patients (13%) developed further neoplasia during follow up. 5/10 patients (6.5%) developed invasive cancer in the residual Barrett's, all were diagnosed endoscopically and successfully managed with radical curative treatment. Focal ER was successful in a mean of 1.3 procedures per patient (range 1-3). Complication rate was 4% (4 bleeds, 2 strictures). No additional RFA was performed in this patient group. Table 1 compares our outcomes with UK HALO registry outcomes where all patients receive RFA.

	AA guided EMR	UK RFA Data[1]
Clearance of neoplasia	87%	77%
Progression to Cancer	6.5%	6.7%
Mean Follow up	5.4 Years	2.6 Years
Stricturing	2.6%	9.4%
Mean number of therapeutic procedures	1.3	ER + 2.6 RFA

Conclusion: Acetic acid-guided ER is an effective and safe treatment for dysplastic Barrett's oesophagus. Progression to cancer after acetic acid guided ER is equivalent to the reported rate of progression after EMR + RFA[1]. Equal rates of sustained eradication of HGIN/IMC are achieved. An acetic acid + ER strategy is potentially much cheaper than an ER + RFA strategy. This data calls for a better stratification of patients who require RFA after ER.

Reference

1. Haidry et al *Gastroenterology* 2013; 145: 87–95.

Disclosure of Interest: None declared

OP317 INCREASED DETECTION OF BARRETT'S ESOPHAGUS AND ESOPHAGEAL DYSPLASIA USING TRANSEPITHELIAL BRUSH BIOPSY WITH THREE DIMENSIONAL COMPUTER-ASSISTED TISSUE ANALYSIS: A PROSPECTIVE MULTI-SITE COMMUNITY-BASED STUDY

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Introduction: Barrett's esophagus (BE) is a known precursor to esophageal adenocarcinoma. Endoscopic guidelines for BE and esophageal dysplasia (ED), rely on random four-quadrant forceps biopsies (FB) obtained every 1-2 cm in the BE segment, and are subject to sampling error. Wide area transepithelial brush biopsy combined with 3 dimensional computer image analysis of the sample (WATS^{3D}) previously has been shown to provide incremental value as an adjunct to FB in the detection of both BE and ED.
Aims & Methods: A prospective multi-center, community-based trial utilizing WATS^{3D} testing was conducted during the period 2012-2014. Patents with symptoms of reflux, suspected BE, and known BE undergoing surveillance for ED were enrolled. A specially designed transepithelial WATS^{3D} biopsy brushes for

tissue sampling in addition to forceps biopsies (FB) during the same endoscopy. WATS^{3D} and FB samples were sent to a central laboratory for analysis. In contrast to the standard 2 micron cut tissue slice, WATS^{3D} biopsy specimens also include an uncut direct smear of up to 150 microns in thickness to better capture the natural three dimensional appearance of the glandular tissue. Laboratory analysis of this uniquely thick tissue sample is aided by a computer based image processing system that integrates into a single three dimensional image information taken from up to 150 separate one micron focal planes. This information is then automatically reviewed by the systems image processing algorithms and neural networks which select and display to the pathologist the most suspicious cells that are found in every focal plane of the entire WATS^{3D} specimen.

Results: There were 4203 patients enrolled in the study with adequate FB and WATS^{3D} specimens. The medianage was 59 yr with 43% being males. BE was diagnosed in 594 patients by FB and in 799 patients byWATS^{3D}. Of these 799 patients, 493 had no BE seen on FB. Thus, the addition WATS^{3D} tothe standard forceps biopsy protocol increased the detection of BE by 83.0% (493/594; 95%confidence interval 74% > 93%), This added detection of BE in 12% (493/4203) of all patients testedwith WATS^{3D} results in a number of patients needed to test (NNT) to obtain one additional BEpatient of 8.53. Esophageal dysplasia was diagnosed in 26 patients by FB and in 33 patients byWATS^{3D}. Of these 33 patients, 23 had no ED on FB. Thus, the addition of WATS^{3D} to the standardforceps biopsy protocol increased ED detection by 88.5% (23/26; 95% confidenceinterval 48% > 160%). This augmented ED detection in 0.5% (23/4203) of all screening patients testedwith WATS^{3D}, results in an NNT to obtain one additional ED case of 182.7. There were no adverse events which resulted from use of WATS^{3D}.

Increased detection of BE Increased detection of ED

	WATS^{3D} Neg	WATS^{3D} BE		WATS^{3D} Neg	WATS^{3D} Dysplasia
FB Neg	3116	493	**FB Neg**	4154	23
FB BE	288	306	**FB Dysplasia**	16	10

Conclusion: This multi-center trial demonstrates the benefit of WATS^{3D} use in daily community-based endoscopic practice. These results underscore previous data demonstrating the adjunctive benefit of adding WATS^{3D} to FB for augmented detection of both Barrett's metaplasia and dysplasia.

Disclosure of Interest: S. Gross Consultancy: CDx Diagnostics, M. Smith: None declared, R. Ali: None declared, V. Kaul: None declared

OP318 PERSISTENT LOW-GRADE DYSPLASIA IN BARRETT'S ESOPHAGUS IDENTIFIES PATIENTS AT HIGHER RISK FOR ESOPHAGEAL ADENOCARCINOMA: A DUTCH NATIONWIDE COHORT STUDY

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Introduction: Confirmation of low-grade dysplasia (LGD) in Barrett's esophagus (BE) by an expert pathologist has been suggested to increase the risk of progression to esophageal adenocarcinoma (EAC). However, even after a confirmed LGD diagnosis, non-dysplastic (ND) BE is found in follow-up biopsies of 28-39% of patients. To avoid unnecessary risks and costs associated with ablative treatment, further risk stratification of patients with confirmed LGD is therefore required.

Aims & Methods: To determine whether persistence of LGD in BE could be used for risk stratification in identifying the subgroup of patients actually benefiting from ablative treatment.

Patients with a first diagnosis of LGD in BE were selected from PALGA, a registry of histopathology diagnoses in the Netherlands, in the period 2005-2010. Exclusion criteria were a diagnosis of high-grade dysplasia (HGD)/EAC prior to or simultaneously with the initial LGD diagnosis, or within 1 year after LGD diagnosis, a diagnosis of indefinite for dysplasia and patients with a follow-up less than 1 year. Persistent LGD was defined as LGD at the index and the first follow-up endoscopy.

Results: A total of 1582 LGD patients were identified, of whom 161(10%) had confirmed and 1351(85%) unconfirmed LGD at the index endoscopy. Patients were followed-up for a median of 4.2 years (IQR 2.76-5.96). The overall incidence rate of developing HGD/EAC and EAC in patients with LGD at the index endoscopy was 2.10(95% CI 1.78-2.46) and 1.19(95% CI 0.96-1.48) per 100 person years, respectively. In the subgroup of patients with confirmed LGD, the incidence rate significantly increased to 5.18(95% CI 4.32-8.10) and 2.51(95% CI 1.46-3.99) per 100 person years, respectively. Of patients with a confirmed LGD diagnosis, 51% (n = 82) regressed to ND and 30% (n = 49) had persistent LGD. For patients with confirmed and persistent LGD (median follow-up 3.72 years, IQR 1.78-5.38), the incidence rate of developing HGD/EAC and EAC was 7.65(95% CI 4.45-12.34) and 2.04 (95% CI 0.65-4.92) per 100 person years, respectively. The incidence rate for patients with ND at follow-up endoscopy after initial confirmed LGD was significantly lower, 2.32(95% CI 1.08-4.40) and 1.45(95% CI 0.53-3.21) per 100 person years, respectively. Patients with 2 consecutive endoscopies showing ND BE (29%, n = 46) after a confirmed LGD diagnosis developed no HGD/EAC during follow-up.

Conclusion: In this large population-based cohort of patients with LGD in BE, confirmed and persistent LGD identifies patients at an increased risk of developing of HGD/EAC. Ablative treatment should therefore be considered in patients with confirmed and persistent LGD in BE.

Disclosure of Interest: None declared

OP319 IDENTIFICATION OF METHYLATED TISSUE FACTOR PATHWAY INHIBITOR 2 (TFPI2) AS A DIAGNOSTIC BIOMARKER FOR BARRETT'S ESOPHAGUS USING THE CYTOSPONGE™

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Introduction: Barrett's Esophagus (BE), a known precursor to Esophageal Adenocarcinoma (EAC), commonly remains undiagnosed. Whilst routine endoscopic screening is not recommended, the advent of non-invasive techniques may allow for screening of individuals at risk for BE as a strategy to reduce the rising mortality from EAC. A minimally invasive cell sampling device, the Cytosponge™, coupled to an immunohistochemical marker, Trefoil Factor 3 (TFF3), has good sensitivity and specificity for diagnosing BE.[1] Aberrant DNA methylation of several genes has been shown to occur in BE and these genes have the potential to be utilised as biomarkers.

Aims & Methods: The aim of this study was to validate methylation of a tumour suppressor gene, Tissue Factor Pathway Inhibitor 2 (*TFPI2*), as a diagnostic biomarker for BE using Cytosponge™ samples and investigate whether it can further improve the accuracy of TFF3.

Previous methylation data from our laboratory was examined for differential methylation of *TFPI2* in BE (n = 22) and controls (n = 2). For validation, Cytosponge™ samples from a randomly selected cohort of 150 non-dysplastic Barrett's cases and 134 controls without BE from the Barrett's Esophagus Study Trial 2 (BEST2) were included. DNA was extracted, bisulphite converted and analysed for methylation from the samples. *TFPI2* methylation was compared between the two groups and sensitivity and specificity for diagnosing BE were determined using Receiver Operating Characteristic analysis. The accuracy of methylated *TFPI2* for diagnosing BE was compared to TFF3.

Results: We observed a significant difference in methylation of *TFPI2* CpG islands between BE and controls ($p = 0.03$) in the discovery cohort. We confirmed that the levels of *TFPI2* methylation are significantly different between the cases and controls ($p = < 0.0001$) in the validation cohort. The sensitivity of methylated *TFPI2* for diagnosing BE was 78.7% [95% CI, 71.4%–84.5%] and the specificity was 97.0% [95% CI, 92.2%–99.1%]. When the same cases were analysed for TFF3 the sensitivity was 94.0% [95% CI, 88.8%–96.9%] and the specificity was 99.3% [95% CI, 95.4%–100%], with more false positives with *TFP12* (4 versus 1) and more false negatives (32 versus 9).

Conclusion: We have identified that *TFPI2* in Cytosponge™ samples is significantly deferentially methylated in BE patients compared to healthy controls. Whilst the sensitivity and specificity data are encouraging, comparison with the sensitivity of the established TFF3 marker in the same cohort revealed that methylated *TFPI2* is not as accurate, putting its use as a potential diagnostic marker in question. Further work to determine the functional role of *TFP12* in this disease is warranted.

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Disclosure of Interest: N. Bezawada: None declared, H. Chettouh: None declared, N. Galeano-Dalmau: None declared, I. Debiram-Beecham: None declared, M. O'Donovan: None declared, P. Lao-Sirieix: None declared, R. Fitzgerald Conflict with: Rebecca Fitzgerald is named on patents related to the Cytosponge. The Cytosponge technology has been licensed by the Medical Research Council to Covidien (now Medtronic).

OP320 TAILORED PROTON PUMP INHIBITOR THERAPY, BASED ON ACID REFLUX PARAMETERS, IN LONG-SEGMENT BARRETT'S ESOPHAGUS PATIENTS: THE SIGNIFICANCE OF THE LEVEL OF SYMPTOM CONTROL

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Introduction: In clinical practice the management Barretts esophagus (BE), is based on a symptom control approach where the dose of proton pump inhibitors (PPI) is adjusted until symptoms are controlled. But few data are available

on the correlation between symptoms relieve, decrease in acidic reflux and PPI dosing, using taylored PPI dosing.
Aims & Methods: The objectives of the present study were threefold. First to determine whether the acid reflux variables co-varied with the symptom scores, throughout the upwards titration of the respective PPI doses. Second to ascertain whether it is possible to eradicate acid reflux in these patients. Finally to determine if tailored medical therapy can reach the same level of reflux and symptom control as a successful total fundoplication does. A consecutive series of patients with long-segment BE (LSBE) were invited. Esophageal manometry, ambulatory 24h pH recording, symptoms assessment and endoscopy were performed at baseline. Thereafter patients were given pantoprazole in a daily dose of 40mg for 8 weeks, and then re-evaluated with ambulatory 24h pH recording, endoscopy and symptoms assessment. Dose escalation then ensued and the respective investigations repeated after each 8 weeks until normalization of intraesophageal pH. The second study group (group 2), included patients with LSBE that had previously undergone ARS.
Results: Group 1 included 24 patients, 18 male, median age 64.7 years-old, with BE median length of 5 cm (range 3-15cm). In 14 of these, we were able to normalize acid reflux into the esophagus already by a daily dose of 40mg of pantoprazole. Doubling the dose for another 8 weeks left still 8 with abnormal acid reflux. Only one patient did not reach normalization of pH. The acid suppression was associated with a significant reduction in GERD/HRQL symptoms ($p = 0.001$). However, when considering individual steps of the PPI titration process, it was only possible to statistically confirm the connection between acid reflux and symptom relief during the initial 8 weeks of therapy with the lowest PPI dose ($p < 0.001$). When symptoms were objectively assessed in BE patients in clinical remission after ARS, using the same GERD-HRQL questionnaire, complete absence of acidic reflux was associated with somewhat but statistically lower symptoms scores ($p = 0.030$) than in those with remaining reflux. Globally, non-operated patients with reflux normalization under PPI treatment achieved the same GERD/HRQL scores as BE patients after successful ARS ($p = 0.51$).
Conclusion: Most BE patients can reach complete acid suppression under tailored PPI therapy. Acid reflux normalization is associated with a significant improvement in symptoms score similar to that seen after effective ARS. The symptom relief PPI dose response curve seemed to be extremely steep with a predominant and close association between the level of acid reflux control and symptom control only for the first dose of PPI. Patients with no acidic reflux under PPI treatment have the same level of symptoms control as patients after ARS with all reflux eradicated.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 15:45–17:15
IMPROVED CLASSIFICATION OF COLORECTAL LESIONS – ROOM E1

OP321 CLINICOPATHOLOGICAL STUDY OF LATERALLY SPREADING TUMORS OF THE COLORECTUM

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Introduction: Laterally spreading tumors (LSTs) of the colorectum are classified into the following four subtypes according to their morphology ; granular homogeneous type (LST-GH), granular nodular mixed type (LST-GM), non-granular flat-elevated type (LST-NGF), and non-granular pseudo-depressed type (LST-NGPD). Clinical features of each subtype of LSTs have not been fully evaluated.
Aims & Methods: The aims of this study was to clarify the clinicopathological features of colorectal LSTs focusing on their subtypes. We reviewed clinical charts and pathology files of 3591 endoscopically resected specimens during January 2007 and December 2014 at our institution. A total of 286 LSTs were detected. We examined the clinical features (mean age, male to female ratio, size, location, Incidence of concomitant carcinoma) according to their subtypes.
Results: Of these 286 lesions, a total of 95 (33.2%) were LST-GH, 24 (8.4%) LST-GM, 146 (51.1%) LST-NGF, and 21 (7.3%) LST-NGPD. Mean age of patients with each subtype was 69.0 years old for LST-GH, 65.9 for LST-GM, 68.4 for LST-NGF, and 69.3 for LST-NGPD. Male to female ratio (M/F) was 1.07 for LST-GH, 2.0 for LST-GM, 1.92 for LST-NF, and 1.33 for LST-NGPD. Mean size of LST-GM (21.9mm) was significantly larger than that of LST-NGF (15.2mm) and LST-NGPD (13.7mm). All subtypes were located predominantly in the proximal colon. Incidences of concomitant carcinomas in LST-GH, LST-GM, LST-NGF, and LST-NGPD were 20% (19 out of 95), 70.8% (17 out of 24), 15.8% (23 out of 146), and 61.9% (13 out of 21), respectively. Incidences of concomitant submucosal carcinomas in LST-GH, LST-GM, LST-NGF, and LST-NGPD were 0% (0 out of 95), 12.5% (3 out of 24), 1.4% (2 out of 146), and 23.8% (5 out of 21), respectively.
Conclusion: Each subtype of LSTs has distinct clinical features. LST-GM and LST-NGPD have higher malignant potentials than other subtypes. Especially LST-NGPD has the highest risk of invasive carcinoma regardless of its size. Therefore we should carefully detect these lesions and choose appropriate treatment according to the subtypes.
Disclosure of Interest: None declared

OP322 ENDOSCOPIC CHARACTERIZATION OF SESSILE SERRATED ADENOMAS/POLYPS; BOTTLENECK FOR THE IMPLEMENTATION OF A "RESECT AND DISCARD" POLICY?

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Introduction: Sessile serrated adenomas/polyps (SSA/P) are the main precursors in the serrated neoplasia pathway, responsible for up to 15-30% of colorectal cancer (CRC). Optical diagnosis of SSA/P is difficult and the common classification models do not enable the differentiation of SSA/P. Inaccurate characterization of SSA/P might have major implications for a ''Resect and Discard'' policy. To date, no studies have assessed this issue in a prospective cohort setting.
Aims & Methods: We aimed to assess the performance of optical diagnosis of SSA/P among endoscopists in routine practice and to evaluate its impact for the implementation of a ''Resect and Discard'' policy. Colonoscopy data were retrieved from a colonoscopy center, specialized in surveillance and screening, between 2011 and 2014 using a structured reporting system, enabling prospective data collection and automatic quality assessment.[1] Endoscopists were instructed to resect all lesions, irrespective of predicted polyp histology. Size, location, morphology and predicted histology were recorded for every polyp in a structured manner.[1] All endoscopists were familiar with the NICE- and KUDO-classification for optical diagnosis of polyps. All lesions were assessed by gastrointestinal pathologists in routine practice. Patients with a known hereditary CRC syndrome were excluded from analysis. Performance of optical diagnosis of SSA/P was analyzed, stratified for polyp size and morphology.
Results: In total 3360 colonoscopies were included for analysis in which 373 SSA/P were detected. The prevalence of at least one detected SSA/P was 8%. Of all detected lesions, 10% was a SSA/P (7% for lesions 1-5mm and 19% for lesions 6-9mm). In total 76% of SSA/P were located in the proximal colon. The median size of SSA/P was 5mm (IQR 3-8). Overall, 54% of SSA/P were sessile and 46% were flat or flat-elevated. Of all SSA/P with an optical diagnosis ($n = 360$), 36% were accurately characterized, while 37% were diagnosed as hyperplastic polyps and 27% as adenomas (Table). The optical diagnosis was accurate for 25% of diminutive SSA/P, 51% of small SSA/P and 53% of large SSA/P ($p < 0.001$). The optical diagnosis was accurate for 56% of flat SSA/P and 21% of sessile SSA/P ($p < 0.001$).

Optical diagnosis of SSA/P

Predicted histology	Overall (n = 360); n (%)	SSA/P 1-5mm (n = 200); n (%)	SSA/P 6-9mm (n = 113); n (%)	SSA/P ≥10mm (n = 45); n (%)
Adenoma	97 (27)	70 (35)	20 (18)	7 (16)
Hyperplastic polyp	132 (37)	81 (41)	35 (31)	14 (31)
Sessile serrated adenoma/polyp	131 (36)	49 (25)	58 (51)	24 (53)

Conclusion: This study demonstrates the performance of optical diagnosis of SSA/P in routine practice. Our results show that overall only 36% of SSA/P were accurately characterized, decreasing to 25% for polyps 1-5mm in size. These results may impede the implementation of a ''Resect and Discard'' policy, since the proportion of both diminutive as well as small SSA/P seems to be larger than assumed in literature. To increase the performance of optical diagnosis and enable a safe implementation of a ''Resect and Discard'' policy, classification systems that facilitate the endoscopic differentiation of adenomas, hyperplastic polyps and SSA/P should be introduced and validated in clinical practice.

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Disclosure of Interest: None declared

OP323 APPLICATION OF KUDO PIT PATTERN CLASSIFICATION IN ENDOMICROSCOPIC DESCRIPTION OF COLONIC NEOPLASTIC CHANGES

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Introduction: Confocal laser endomicroscopy is a novel and "high-tech'' imagistic approach of colonic neoplastic lesion. Comparing the images with a normal control image of colonic mucosa and accordingly to endomicroscopic Mainz and Sanduleanu classification there are glandular opening characteristics that are specific to neoplastic changes. This can be improved by using as a tool Kudo pit-pattern clasiffication in establishing the morphological criteria.
Aims & Methods: In this study were examined more than 4200 endomicroscopic images from 40 colonic neoplastic lesions. Were included 29 patients patients aged > 18,mean age 63.7, with colonic polyps. The lesions were examined with Pentax integrated endomicroscope after injection of Fluoresceince as a contrast agent, and described characteristics of colonic glandular openings, using the following features: regularity, shape (round, star shaped, elongated with or witout branching, distorted), and sizes raported to a normal endomiscroscopic

image of normal colonic mucosa and compared with histological findings and diagnostic. The histological diagnostic was made by to experienced pathologists and the neoplasia grading was made accordingly to Vienna classification.
Results: We found that the shape of glandular opening as seen in endomicroscopic examination is statistical significant associated with the grade of neoplasia (Cramer's V = 0.666, $p < 0.0001$). According to the results the star shape is associated with absence of neoplasia (PPV = 83.33% for absence of neoplasia) and low-grade dysplasia, and the distorted-anarchic appereance is associated with adenocarcinoma with PPV = 85%.
The size and regularity of the crypts openings also had a high corellation with neoplasia grade: the increased size had VPP = 84% for high grade dysplasia and adenocarcinoma ($p < 0.0001$ Cramer'sV = 0.672) and the regular preserved aspect is strongly associated ($p < 0.0001$ Cramer's V = 0.784) with the absence of neoplasia and low-grade dysplasia, while irregularity and lost of pattern is correlated with high-grade dysplasia and adenocarcinoma.
Conclusion: Since 1994 Kudo has described the 5 types of cryptal opening patterns that suggest the neoplasic characteristic of a colon polyp. This classification has still a place in high performance endoscopy and it can be well adapted to the newest elaborated classification to describe endomicroscopic features of colonic neoplastic lesions, alongside to description of vascular changes and the nuclear ones that should be achieved.

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Disclosure of Interest: None declared

OP324 DISTINCT CLINICOPATHOLOGICAL AND MOLECULAR FEATURES BETWEEN LATERALLY SPREADING TUMORS AND POLYPOID NEOPLASMS IN THE COLORECTUM

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Introduction: Laterally spreading tumors (LSTs) were defined as large flat tumors of the colorectum. LSTs are subcategorized into granular-type LST (LST-G) and nongranular-type LST (LST-NG). LSTs tend to extend laterally and circumferentially rather than vertically along the colonic wall and seem be found at an early stage tumor such as adenoma. These characteristics suggest that there may be biological differences between LSTs and polypoid neoplasms (PNs).
Aims & Methods: We examined the clinicopathological and molecular features of 156 colorectal neoplasms including 54 LST-Gs, 52 LST-NGs and 50 PNs that were endoscopically resected at Showa University Hospital from July 2007 through December 2014. We evaluated the frequency of *KRAS* and *BRAF* mutations by pyrosequencing and DNA methylation of nine genes or sequences (*MINT1, MINT2, MINT31, CDKN2A, MLH1, SFRP1, HPP1, ESR1* and *LINE1*) by bisulfite-pyrosequencing. We also investigated the methylation level of *SFRP1, HPP1, ESR1* and *LINE1* in adjacent normal mucosa. A tumor was considered to be CpG island methylator phenotype (CIMP) -positive if 2 or more CIMP markers (*MINT1*, *MINT2*, *MINT31*, *CDKN2A* and *MLH1*) were methylated.
Results: We observed significant differences in age (71 yrs. vs. 62 yrs.), and tumor size (27 mm vs. 14 mm) between LSTs and PNs ($P < 0.001$). The frequency of *KRAS* mutation of LST-Gs was significantly higher than the other groups (LST-Gs, 65%; LST-NGs, 12%; PNs, 23%, $P < 0.001$). The frequency of CIMP tended to be higher in LST-Gs than LST-NGs or PNs (16% vs. 9% or 0%, respectively). No *BRAF* mutation was detected in any tumor samples. On the other hands, we observed methylation densities of *SFRP1, HPP1* and *ESR1* in adjacent normal mucosae as well as tumor tissues of LST-Gs, LST-NGs and PNs (*SFRP1*, 20%, 21% and 22%; *ESR1*, 18%, 17% and 19%; *HPP1*, 10%, 11% and 11%, respectively). There were no significant differences in the methylation densities of *SFRP1, HPP1* and *ESR1* between any groups. For elderly patients who were more than 70 years old, however, *SFRP1, HPP1* and *ESR1* methylation densities of adjacent normal mucosae were significantly higher in PNs than LSTs ($P < 0.05$). Furthermore, the methylation level of *LINE1* was significantly lower in LST-Gs than LST-NGs or PNs (67% vs. 70% or 69%, respectively; $P < 0.01$).
Conclusion: Our results suggest that different molecular mechanisms may exist in these subtypes of colorectal tumors and that DNA methylation of adjacent normal mucosa might be associated with field effects defined by epigenetic changes.
Disclosure of Interest: None declared

OP325 KID: A CAPSULE ENDOSCOPY DATABASE FOR MEDICAL DECISION SUPPORT

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Introduction: Computer-based systems support medical decision-making by integrating expert knowledge with machine learning algorithms. The use of such systems in capsule endoscopy (CE) is limited[1]. Therefore, a database to be used as source of data for the development of automated medical-decision support, as well as educational resource for physicians, was created[2].
Aims & Methods: The database, named KID, is publicly available at **http://is-innovation.eu/kid/**. It accommodates anonymized CE images & video files. Lesion categorisation follows the Capsule Endoscopy Structured Terminology (CEST)[3]. Contributions should be of high quality (original resolution) & not distorted by compression. For image contributions, the recommended standard is ISO/IEC 15948 PNG (Portable Network Graphics); popular, platform-independent & with lossless compression. However, acceptable standards include popular near-lossless coding; ISO/IEC 14496-10 MPEG-4 AVC (Advanced Video Coding) H.264. Supported container formats for synchronized videostreams through the web include F4V & FLV (Flash video). Furthermore, KID delivers knowledge through image annotations. Semantic & graphic annotations are supported by an open access & platform-independent annotation tool (**Ratsnake**)[4]. Semantic annotation is based on standard web ontology language description logics (OWL DL). The quality of data & annotations submitted to KID is scrutinized by an international scientific committee; contributions not conforming with the afore-mentioned standards & objectives are rejected.
Results: More than 1,500 annotated CE images, 47 videoclips & full videos have been registered in KID during its first 6 months of operation (Sept. 2014-Feb. 2015). These include normal images & images of the following lesion categories: a) vascular: angiectasias and/or intraluminal bleeding; b) inflammatory: mucosal aphthae & ulcers, erythema, cobblestone, and luminal stenosis; c) lymphangiectasias: chylous cysts, nodular lymphangiectasias, punctuate lymphangiectasias, and d) polypoid lesions. Datasets submitted to KID have already been used for lesion detection by machine learning algorithms[4]. Direct comparisons with results of developing automated lesion detection/recognition algorithms can be made. In this context, we applied a novel algorithm for blood detection in KID (*dataset 1*). The algorithm is capable of identifying salient image regions[2], from which color features are extracted & classified by a support vector machine[4]. The average sensitivity & specificity obtained are 96% & 91%, respectively.
Conclusion: KID provides a platform for data & knowledge exchange between medical & IT researchers. It enables direct comparisons between methods for medical-decision support in CE, thus leading to essential progress in the field.

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Disclosure of Interest: None declared

OP326 AUTOMATED DIAGNOSIS SYSTEM USING ENDOCYTOSCOPY CAN BE A POWERFUL TOOL FOR ON-SITE CHARACTERIZATION OF COLORECTAL POLYPS: A PILOT STUDY EVALUATING A "SECOND-GENERATION" MODEL

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Introduction: Endocytoscopy (EC) enables *in vivo* observation of nuclei at 380-fold magnification during gastrointestinal endoscopy, thus allowing precise prediction of lesion pathology; however, it requires training and experience.[1] Therefore, for untrained endoscopists, we have developed a computer-aided diagnosis system for EC imaging (EC-CAD) that provides fully-automated classification of colorectal polyps.[2]
Aims & Methods: The aim of the present study was to evaluate the efficacy of a second-generation model of EC-CAD. The EC-CAD comprises image acquisition, nuclear segmentation, feature extraction, and classification into three pathological groups (neoplastic, adenoma, and invasive cancer). The classification algorithm was programmed based on 350 features of each image (e.g., area, circularity, diameter, and perimeter of nuclei, and over 300 variables calculated by texture analysis of a whole image). We used a support vector machine to help classify these many features; 4880 EC images were used for machine

learning in the process of construction of the model. As a pilot study to validate the EC-CAD, we evaluated its diagnostic ability, speed, and reproducibility for prediction of neoplastic change on a test set of 476 randomly selected EC images (234 neoplastic and 242 non-neoplastic lesions that had not been used for machine learning).
Results: The EC-CAD automatically output pathological predictions with "high confidence" (over 90% probability calculated by support vector machine) in 63% (302/476) of the subject images, providing sensitivity of 98%, specificity of 96%, and accuracy of 97%. On the other hand, the overall diagnostic abilities for the total of 476 subjects were sensitivity of 92%, specificity of 87%, and accuracy of 89%. The EC-CAD also enabled instant diagnosis, taking only 0.2 seconds for each lesion with perfect reproducibility (Kappa = 1).
Conclusion: The EC-CAD achieved almost perfect diagnostic performance in classification of colorectal polyps with "high confidence" mode. It can be a powerful tool for supporting endoscopists' decisions during colonoscopy.
Acknowledgement: We express great gratitude to Prof. Kensaku Mori and Yukitaka Nimura (Nagoya University, Information and Communications Headquarters) for their invaluable support as co-researchers.

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Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 15:45–17:15
IMPACT OF ENDOSCOPIC OESOPHAGEAL INTERVENTIONS ON CLINICAL OUTCOME – ROOM E3

OP327 PERSISTENT OR RECURRENT INTESTINAL METAPLASIA IN PATIENTS WITH NORMAL NEO-Z-LINE AFTER RFA IS NOT A RISK FACTOR FOR RECURRENCE OF NEOPLASIA

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Introduction: It is not known whether persistent or recurrent intestinal metaplasia (IM) within a normal neo-Z-line represent a risk factor for recurrence of Barrett's esophagus related neoplasia (BORN) in patients undergoing radiofrequency ablation (RFA).
Aims & Methods: Aims of this study were: 1. To assess the long-term efficacy of endoscopic treatment (RFA with or without endoscopic resection - ER) for BORN; 2. To assess the clinical relevance of persistent or recurrent IM in patients with macroscopically normal neo-Z-line after RFA; 3. To investigate the origin of persistent/recurrent IM at the level of neo-Z-line.
A single center, prospective cohort study with consecutive patients undergoing RFA for BORN. After treatment, the patients undergo regular endoscopic surveillance with multiple biopsies (neo-Z-line and esophagus). The median follow-up was 36 months (range 3-74). Conover one-way analysis was used to calculate the risk factors for recurrence of IM and neoplasia. All specimens obtained from patients with persistent/recurrent IM were examined with regard to expression of cytokeratins 7 and 20 (CK7, CK20).
Results: The study involved 76 consecutive patients (mean age 62, range 20-86) undergoing endoscopic treatment for BORN (early adenocarcinoma: 30 (40%), high-grade dysplasia (HGD): 23 (30%), low-grade dysplasia (LGD): 23 (30%); during 2009-3/2015. In 24 patients (32%), RFA was a single treatment modality while in 56 patients (68%) RFA was combined with ER or ESD. At present, 62 patients completed the treatment.
Complete remission of IM (CR-IM) and complete remission of neoplasia (CR-N) were achieved in 71% (95% CI 69-81%) and 98% (95% CI 95-99%), respectively. Among 18 patients without CR-IM (29%), 17 (94%) had macroscopically normal neo-Z-line.
During the follow-up, there were 18 recurrences (41%) of IM and all occurred at the level of neo-Z-line. In 14 of these patients (78%), the neo-Z-line was macroscopically normal. There were 3 patients (5%) with recurrent neoplasia (2x LGD, 1x HGD), 1 of them occurred at the macroscopically normal neo-Z-line but this patient has had no CR-N (persistent LGD). The risk factors for recurrence of IM were male sex, younger age and diagnosis of cancer. The presence of IM at the level of macroscopically normal neo-Z-line has not been found as a risk factor for BORN recurrence.
Among 31 patients with persistent/recurrent IM with normal neo-Z-line, 90% had typical Barrett's esophagus expression pattern (CK7+, CK20+).
Conclusion: A majority of patients without CR-IM or with a recurrence of IM have macroscopically normal neo-Z-line. Persistent or recurrent IM in patients with normal neo-Z-line is mostly of Barrett's esophagus origin but is not a risk factor for BORN recurrence.
Disclosure of Interest: None declared

OP328 ENDOSCOPIC RESECTION AND RADIOFREQUENCY IN MANAGEMENT OF BARRETT'S ESOPHAGUS WITH HIGH-GRADE DYSPLASIA

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Introduction: High-grade dysplasia (HGD) and intramucosal carcinoma (IMC) developed on Barrett's esophagus (BE) are now well-established indications for endoscopic resection (ER) as first line treatment. Radiofrequency (RF) is also a recognized treatment for BE with dysplasia and is actually associated with ER for complicated BE ablation.
Aims & Methods: Aim of this study was to evaluate the efficiency of combined ER and RF compare to ER alone for management of BE with HGD. We retrospectively reviewed computerized data from 89 patients who had endotherapy for HGD on BE, between 2006 and 2013. 2 subgroups were created corresponding to patients treated by ER alone (group 1) or by combination of ER and RF (group 2).
Results: 55 patients were included in group 1 (7F/48M, mean age 68). 53/55 (96%) had HGD on preoperative sample histological analysis. Surgical specimen confirm HGD in 30/53 (57%), low-grade dysplasia (LGD) in 16/53 (30%) and metaplasia in 7/53 (13%). 2/55 (4%) patients had HGD on surgical specimen and LGD on preoperative sample. With an average of 1.8 sessions of ER per patient, the respective complete eradication rate of HGD, DBG and metaplasia was 100% (32/32), 94% (15/16) and 16% (9/55). Median Prague classification of BE was C3M5. HGD recurrence rate was 9% within an average of 22 months.
34 patients were included in group 2 (3F/31M, mean age 67). 32/34 (96%) had HGD on preoperative sample histological analysis. Surgical specimen confirm HGD in 25/32 (78%), low-grade dysplasia (LGD) in 5/32 (16%), metaplasia in 1/32 (3%) and normal stratified squamous epithelium in 1/32 (3%). 2/34 (6%) patients had HGD on surgical specimen and metaplasia on preoperative sample. With an average of 2 sessions of ER and 1.6 sessions of RF per patient, the respective complete eradication rate of HGD, DBG and metaplasia was 93% (25/27), 100% (5/5) and 59% (20/34). Median Prague classification of BE was C4M7. HGD recurrence rate was 15% within an average of 18 months.
HDG or LGD relapse rates were not significantly different between the 2 groups ($P = 0.13$ for group 1 and 0.42 for group 2). Initial length of BE was significantly superior for group 2 ($P < 0.015$). Complication rate in group 1 was 16% (9/55) with perforation in 1/55 (1.8%) and stenosis in 8/55 (15%), always treated endoscopically. Complication rate in group 2 was 24% (8/34) with haematemesis in 1/34 (3%), intraperitoneal hemorrhage without perforation in 1/34 (3%) and stenosis in 6/34 (18%), always treated conservatively or endoscopically. No death has been observed during all the follow-up.
Conclusion: Combined treatment of ER and RF can treat significantly longer BE with HGD than ER alone, with the same efficiency and safety. The long-term recurrence has not been studied.
Disclosure of Interest: None declared

OP329 EFFECTS OF RADIAL AND AXIAL FORCE OF ESOPHAGEAL STENTS ON OCCURRENCE OF SEVERE ADVERSE EVENTS AND RECURRENT DYSPHAGIA IN PATIENTS WITH MALIGNANT DYSPHAGIA

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Introduction: Self-expanding stent placement is an effective palliative treatment for malignant dysphagia. However, serious adverse events (SAEs) and recurrent dysphagia are frequently encountered. Stent-related forces, i.e. radial force (RF) and axial force (AF), are thought to play a causative role in these events, with a high RF being associated with migration risk and pain, and AF with stent-induced complications to the esophageal wall, such as perforation, hemorrhage and fistula formation. Furthermore, knitted esophageal stents elongate when compressed, depending on the braiding angle, which may also be of clinical relevance.
Aims & Methods: The aim of this study was to evaluate whether RF, AF and the degree of elongation of esophageal stents is associated with the occurrence of SAEs and recurrent dysphagia in clinical practice. Follow-up data of seven types of esophageal stents, placed for malignant dysphagia between January 2006 and December 2013, were collected in two academic centers. Stent types included the Ultraflex (n = 50, 20%, high RF, low AF), fully covered (FC) Wallflex (n = 32, 13%, low RF, high AF), partially covered (PC) Wallflex (n = 45, 18%, low RF, high AF), PC Evolution (n = 40, 16%, low RF, moderate AF), Hanaro (n = 40, 16%, moderate RF, moderate AF), Polyflex (n = 11, 5%, high RF, high AF) and SX-Ella (n = 27, 11%, low RF, moderate AF). Multivariate Cox regression analysis was performed to assess the effect of RF, AF and elongation on SAEs.
Results: In total, 245 patients (178 male [73%], mean age 67 ± 11 years) were included. SAE's were observed in 59 patients (24%, after a median of 14 days, IQR 2-45) and included hemorrhage (n = 14, 24%), fistula formation (n = 14, 24%), pneumonia (n = 11, 19%), severe pain (n = 11, 19%), perforation (n = 3, 5%) and other (n = 6, 10%). Recurrent dysphagia was seen in 74 patients (30%, after a median of 52 days, IQR 18-122), mainly due to migration (n = 20, 27%) and tumor in-/overgrowth (n = 31, 42%). After correction for patient, tumor, treatment and stent characteristics, multivariable analysis showed no association between RF, AF or elongation and SAEs ($P = 0.23$, $P = 0.30$, $P = 0.32$, respectively), recurrent dysphagia ($P = 0.07$, $P = 0.39$, $P = 0.18$, respectively) and stent migration in particular ($P = 0.22$, $P = 0.48$, $P = 0.40$, respectively). Furthermore,

no association was found between stent forces and the occurrence of pain, perforation, hemorrhage or fistula formation.
Conclusion: Both SAEs and recurrence of dysphagia following esophageal stent placement were not associated with RF, AF or degree of elongation. It can be speculated that their occurrence is a multifactorial process determined by a combination of stent-, tumor- and patient-related characteristics.
Disclosure of Interest: None declared

OP330 CLINICAL OUTCOMES FOLLOWING STENT PLACEMENT IN REFRACTORY BENIGN ESOPHAGEAL STRICTURE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: The management of benign esophageal strictures is challenging. Common causes are represented by peptic injury, caustic ingestion, radiation treatment and anastomotic ischemia after esophageal resection. The first management strategy includes endoscopic dilation using bougies or balloons. Although the immediate success rate is up to 90%, about 30% to 40% of patients experience recurrent dysphagia within the first year of follow-up. The management of such relapsing refractory cases consists of repeat dilations. To provide alternative and more definitive treatment option, self-expandable stents have been proposed. Three different types of stents have been used: metallic (SEMS), plastic (SEPS) and biodegradable stents (BD).
Aims & Methods: We performed a systematic review and meta-analysis to examine the efficacy of stent placement in the long-term resolution of dysphagia in patients with refractory benign esophageal stricture (RBES). PubMed, SCOPUS, Google Scholar were searched (up to January 2015). Studies recruiting adults with RBES treated with stent placement were eligible. The success, complication and migration rates were pooled by means of a random effect model to obtain an odds with a 95% confidence interval (CI).Statistical heterogeneity was tested using the Q^2 test (significance level: 0.05) and I^2 statistic. If high levels of heterogeneity among the trials occurred ($I^2 >= 50\%$ or $P < 0.05$), the sources of heterogeneity were explored by sensitivity analysis and meta-regression analysis.
Results: Eighteen studies (444 patients) were eligible for inclusion. The pooled clinical success rate was 40.5% (95%CI, 31.5%>49.5%), yielding an odds of 0.68 (95%CI 0.46-0.98) with high heterogeneity ($I^2 = 65.0\%$). The meta-regression analysis showed stricture etiology as the only influencing factor. Patients treated with plastic (SEPS) and metallic stents (SEMS) reported not significantly higher success rates than patients treated with biodegradable (BD) stent [SEPS > SEMS > BD: 46.2% (95%CI 27-66.3%) > 40.1% (95%CI 28.1-54.1%) > 32.9% (95%CI 23.1-44.1%)]. The migration rate was 28.6% (95%CI 21.9-37.1%) yielding an odds of 0.40 (95%CI 0.28-0.59), with SEPS and SEMS reporting not significantly higher migration rates than BD stent [SEPS > SEMS > BD: 33.3% (95%CI 19.4-51.5%) > 31.5% (95%CI 22.5-42.2%) > 15.3% (95%CI 8.3-25.4%)]. The complication rate was 20.6% (95%CI 15.3-28.1%) yielding an odds of 0.26 (95%CI 0.18-0.39) without significant difference between stents [SEMS = BD > SEPS: 21.9% (95%CI 11.5-37.5%) = 21.9% (95%CI 13.8-32.9%) > 19.4% (95%CI 12.3-30.1%)].
Conclusion: Stent placement for the treatment of RBES is effective in about 40% of cases. Since patients with RBES have only two possible treatment options, i.e. life-long dilations or surgery, the overall success rate reported by stent placement should not be considered negligible. Furthermore, the success rates might be even higher in subgroups of patients, according to the stricture etiology (i.e. post-surgery or post-radiotherapy strictures). Further studies should investigate whether the clinical success rate varies according to the stricture etiology.
Disclosure of Interest: None declared

OP331 PREDICTORS OF PARTIAL VS. COMPLETE SYMPTOMATIC RESPONSE IN PATIENTS WITH ESOPHAGEAL ACHALASIA TREATED BY PER ORAL ENDOSCOPIC MYOTOMY (POEM)

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Introduction: POEM results in treatment success in more than 90% of operated patients. Treatment success is usually defined as an Eckardt score (ES) 0-2 (or 0-3). The aim of our study was to assess whether there are any predictive factors for only partial symptomatic improvement with residual symptoms (ES 1 or 2) vs. complete symptomatic response (ES = 0).
Aims & Methods: Since 2012, we performed 87 POEM procedures in 86 patients with achalasia. The overall treatment success at 12 months was 98%. We analyzed clinical outcomes of 59 patients who have had a treatment success (ES= 0, 1 or 2) and completed at least 6 months follow up (27 female, 32 male, mean age 48 years). We performed multivariate logistic regression with stepwise selection of predictors and tested equality of means for continuous variables for the two target levels and Fisher's exact test for independence of the target level and factor variables.
Results: Among 59 analyzed patients, 36 (61%) had a complete symptomatic response (post-POEM ES = 0) while 23 patients (39%) had partial symptomatic response (post-POEM ES 1 or 2). The mean age of patients with a complete response was lower(51 vs. 42 years) as well as the frequency of pre-POEM treatments (botulinum toxin injection or pneumatic dilatation; 11% vs. 35%). The patients with a complete symptomatic response had higher both the pre-POEM IRP (mean 30.1 vs. 23 mmHg) and the mean basal LES tonus (44 vs. 32 mmHg). The frequency of type II achalasia was higher in patients with a complete symptomatic response (83% vs. 61%). Both groups did not differ with regard to the procedure related data (length of the procedure, length of myotomy, etc.). The stage of the disease (duration of symptoms, esophageal width) and the frequency of partial recovery of esophageal peristalsis after POEM (33% vs. 30%) were similar in both groups. Post-POEM esophagitis was more frequent in patients with a complete symptomatic response (36% vs. 26%). In multivariate logistic regression analysis, only age (under 40, p = 0.03), pre-POEM basal LES-tonus (under 40 mmHg, p = 0.04) and any prior treatment for achalasia (p = 0.04) have been found as independent predictors of partial symptomatic response.
Conclusion: Among the patients with treatment success, approx. 40% do not have a complete symptomatic response. Younger age, lower pre-POEM basal LES tonus and previous treatment attempts with botulinum toxin or balloon dilatation are independently associated, despite the overall treatment success, with an incomplete symptomatic response.
Disclosure of Interest: None declared

OP332 PERORAL ENDOSCOPIC REMYOTOMY (RE-POEM): A SALVAGE OPTION FOR PERSISTENT/RECURRENT SYMPTOMS AFTER PREVIOUS POEM

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Introduction: Peroral endoscopic myotomy (POEM) has been described with high success rates for the treatment of achalasia. However, persistence/recurrence of symptoms can occasionally occur after POEM.
Aims & Methods: Our purpose was to evaluate the feasibility, safety and efficacy of salvage peroral endoscopic remyotomy (Re-POEM) for patients after failed POEM. Fifteen patients with persistence/recurrence of symptoms (Eckardt symptom score ≥4) after previous POEM were identified from a prospectively maintained database that included a total of 1454 consecutive achalasia patients. The primary outcome was symptom relief during follow-up, defined as an Eckardt score of ≤3. Secondary outcomes were procedure-related adverse events, lower esophageal sphincter (LES) pressure on manometry, and reflux symptoms before and after Re-POEM.
Results: All patients underwent successful Re-POEM after a mean of 13.5 months (range 4–37 months) from the time of the primary POEM. The mean operation time was 41.5 minutes (range 28–62 minutes). Submucosal tunnel infection occurred in one case and was successfully managed with conservative treatments. During a mean follow-up period of 11.3 months (range 3–18 months), treatment success was achieved in all patients. The mean symptom score pre-treatment was 5.6 (range 4–8) compared with a mean post-treatment score of 1.2 (range 0–3; $P < 0.001$). Mean LES pressure also decreased from a mean of 25.0 mmHg to 9.5 mmHg after Re-POEM ($P < 0.001$). The overall clinical reflux complication rate of Re-POEM was 33.3%.
Conclusion: Re-POEM seems to be a safe and effective salvage option for failed POEM, resulting in short-term symptom relief in all patients and without serious complications.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 15:45–17:15
BASIC ASPECTS OF HEPATOCARCINOGENESIS AND REGENERATION – ROOM E5

OP333 CONTRIBUTION OF NATIVE AND ACTIVATED HEPATIC STELLATE CELLS IN LIVER REGENERATION AFTER PARTIAL HEPATECTOMY AND 2-ACETYLAMINOFLUOREN INJECTION

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Introduction: Actual problem of modern hepatology is to find new and athogenetic treatment of liver diseases. One of these methods could be cell therapy with using hepatic stellate cells (HSC), that are thought to be regional stem cell of the liver. Experiments on freshly isolated rat HSC transplantation confirmed their participation in liver regeneration after partial hepatectomy (PH). However, the role of freshly isolated and activated in vivo HSC transplantation to rats undergoing PH and the injection of 2-acetylaminofluoren (AAF) is still unknown.
Aims & Methods: To study the influence of transplanted HSC on activity of liver regeneration after PH and AAF injection.
Before transplantation HSC were labeled by the gene of Enhanced Green Fluorescent Protein (GFP). We selected the classical model of acute liver damage – partial hepatectomy. In one case, we transplanted native HSC, in the other – in vivo activated HSC. Activation was carried out by lead nitrate injection into the tail vein of rats donor, HSC were isolated 2 days thereafter.

To inhibit hepatocyte proliferation in the recipient rats, animals were administered intraperitoneally AAF 5 days before and after surgery. The animals were sacrificed after 1, 2, 3, 5, 7 and 14 days after the transplantation of HSC. Paraffin slices were stained by immunohistochemistry with antibodies to desmin – marker of HSC and è-SMA - myofibroblast marker.
Results: GFP + hepatocytes were detected (found, stained) in liver parenchyma even at the first days after transplantation. All groups showed an increase in the number of desmin - positive cells in the parenchyma. After transplantation of freshly isolated and activated HSC to rats after PH and AAF administration, the maximum number of such cells was found 2 days after surgery, then their number gradually decreased. Desmin-positive HSC in animals after PH without AAF injection retained in the liver longer: in case of freshly isolated HSC transplantation – till the 5th day, after in vivo activated HSC transplantation - till the 7th day. In all the groups è-SMA positive myofibroblasts were not detected.
Conclusion: Transplantation of native and activated HSC stimulates liver regeneration and contributes to hepatocytes repopulation without the risk of liver fibrosis.
Disclosure of Interest: None declared

OP334 O-GLCNAC TRANSFERASE PROMOTES FATTY LIVER-ASSOCIATED LIVER CANCER THROUGH ACTIVATING JNK AND NF-KB PATHWAYS

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Introduction: O-GlcNAc transferase (OGT), a unique glycosyltransferase, is involved in metabolic reprogramming. Using transcriptome sequencing, OGT was identified to be highly expressed in non-alcoholic steatohepatitis (NASH)-associated hepatocellular carcinoma (NASH-HCC) compared to their adjacent non-tumor tissues of 18 patients. However, the role of OGT in NASH-HCC is still unclear.
Aims & Methods: We aim to investigate the functional role of OGT in NASH-HCC and its potential clinical implication. The biological function of OGT was determined by proliferation, clonogenicity, migration and invasion experiments through gain- or loss- of OGT functional assays *in vitro* and in nude mice. OGT target factors and pathways were identified by promoter luciferase assay, DNA binding activity assay and Western blot. The effects of OGT on oxidative stress, reactive oxygen species (ROS), lipid peroxide and endoplasmic reticulum (ER) stress and ER stress-related cascades were also investigated. The clinical impact of OGT was evaluated in 209 serum samples of 137 NAFLD patients and 72 control subjects by ELISA.
Results: OGT was upregulated in 12 out of 18 (66.7%) NASH-HCC tumor tissues compared with their adjacent non-tumor tissues by transcriptome sequencing. Enhanced OGT expression was further confirmed in an independent set of 9 pairs of human NASH-HCC tissues (66.7%) by Western blot and in six HCC cell lines and two NASH-HCC cell lines, but silenced in normal livers and weak in immortalized normal hepatocyte cell lines MIHA and LO2. OGT production was significantly induced in MIHA cells treated with insulin ($P<0.01$) or cholesterol ($P<0.01$). Ectopic expression of OGT in MIHA and LO2 cells promoted cell growth, clonogenicity, migration and invasion ability; whereas stable knockdown of endogenous OGT in two NASH-HCC cell lines had opposite effects. Moreover, subcutaneous tumor xenografts of LO2 cells with stable OGT expression in nude mice exhibited an increased tumor growth compared with the control cells ($P<0.01$). Mechanistically, OGT induced ROS production, increased lipid peroxide levels and enhanced the protein expression of ER stress markers GRP78 and IRE1α in LO2 and MIHA cells. In this connection, OGT significantly activated JNK cascade as evidenced by increased protein expression of p-JNK, p-c-Jun and activation of AP-1; induced NF-κB pathway through enhancing the protein levels of p-IKKα/ p-IKKβ, p-p65, p-p50 and the NF-κB DNA binding activity in OGT-transfected LO2 cells compared to the control cells. Moreover, the serum levels of OGT were significantly higher in patients with steatosis (3.30 ng/ml vs 1.83 ng/ml, $P<0.0001$) or NASH (3.49 ng/ml vs 1.83 ng/ml, $P<0.001$) compared with control subjects. The AUROC of diagnosing NAFLD was 0.741 (95% CI: 0.671-0.812) and diagnosing NASH was 0.749 (95% CI: 0.681-0.816). Multivariate analysis showed that OGT was an independent risk factor for NASH patients.
Conclusion: OGT plays an oncogenic role in NASH-associated HCC through inducing ER stress and ROS production and consequently activating oncogenic JNK and NF-κB pathways. Serum detection of OGT may serve as a potential diagnostic marker for NASH patient.
Disclosure of Interest: None declared

OP335 ANTI-ANGIOGENIC TREATMENT WITH OCTREOTIDE ATTENUATES PORTAL HYPERTENSION OF THE CIRRHOTIC RATS THROUGH SOMATOSTATIN RECEPTOR 2

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Introduction: Angiogenesis is pivotal for the devolvement of portal hypertension in cirrhosis. Somatostatin (SST) and its analogue octreotide are widely used for the management of gastroesophageal varices bleeding. However, the molecular and cellular mechanism of SST and octreotide on portal hypertension remains unclear.
Aims & Methods
Aims: To investigate the mechanism of octreotide on regulation of portal hypertension.
Methods: Peritoneal injection of thiacetamide (TAA) was employed to induce liver cirrhosis (200 mg/kg every 3 days for 16 weeks). 36 male Sprague-Dawley rats were randomized into control, TAA and TAA + octreotide with 12 animals in each group. TAA + octreotide group received TAA plus octreotide (50 mg/kg/day) from the initiation of TAA administration. TAA group received TAA plus placebo and control group received injections of normal saline. Scanning electron microscope of vascular casting, hematoxylin-eosin staining (HE), Masson trichrome staining (MT) were applied to evaluation of cirrhosis and angiogenesis. Portal pressure was also measured. Immunohistochemistry (IHC), quantitative real-time PCR (qRT-PCR) and Western blot for alpha-smooth muscle actin (a-SMA), collagen III, CD31, vascular endothelial growth factor (VEGF), phosphorylated extracellular signal-regulated kinase (p-ERK) and somatostatin receptors (SSTRs) were determined. *In vitro*, human umbilical vein endothelial cell line (HUVEC) was treatment with vehicle, octreotide, octreotide plus SSTR-2 antagonist (CYN154806) or octreotide plus SSTR-5 antagonist (BIM23056) for 24 hours. Afterwards, wound-healing assay for cell migration, tube formation assay for angiogenesis, immunocytofluorescence and Western blot for VEGF and p-ERK were carried out.
Results: *In vivo*, compared with TAA group, liver fibrosis and portal pressure in TAA + octreotide group were remarkably decreased by 40.4% and 17.1%, respectively. And the mRNA levels of a-SMA and collagen III in TAA + octreotide group were also reduced. Histological sections, vascular casts of hepatic portal vein, IHC and qRT-PCR for CD31 showed that angiogenesis in TAA + octreotide group were dramatically reduced when compared with TAA group. The up-regulation of VEGF, p-ERK and SSTR-2, SSTR-5 induced by TAA administration were significantly inhibited after treatment with octreotide. *In vitro*, compared with vehicle treated cells, the migration rate, tube length, VEGF and p-ERK protein were obviously substantially decreased in octreotide treated cells. However, these inhibitory effects afford by octreotide were remarkably restored by SSTR-2 antagonist but not SSTR-5 antagonist.
Conclusion: Octreotide could ameliorate portal hypertension in cirrhotic rat through inhibition of intrahepatic angiogenesis. The anti-angiogenesis effect afford by octreotide may attribute to regulation of integrated signal pathways involving SSTR-2 - p-ERK – VEGF.
Disclosure of Interest: None declared

OP336 GENOMIC MUTATIONS AND PATHWAYS IDENTIFIED BY WHOLE-EXOME SEQUENCING IN NAFLD-ASSOCIATED HEPATOCELLULAR CARCINOMA

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Introduction: Epidemiological studies have shown that obesity and its related non-alcoholic fatty liver disease (NAFLD) promotes the development of hepatocellular carcinoma (HCC). However, the underlying genetic mechanism of obese-related HCC is still largely unknown.
Aims & Methods: We aimed to uncover the genetic alterations of obesity-associated HCC using cross-species oncogenomics and whole-exome sequencing. HCC development in genetic obese (*db*/*db*) mice and dietary obese mice kept on high-fat diet was monitored in comparison with wild-type lean mice kept on normal diet treated with diethylnitrosamine (DEN). Paired HCC tumor and adjacent normal samples from obese mice and lean mice were subjected to whole-exome sequencing and cross-species oncogenomics to reveal genetic alteration landscapes. Candidate mutation genes were further validated in HCC tumor and adjacent normal samples from 16 genetic and 13 dietary obese mice and 16 control lean mice by PCR Sanger sequencing. The bio-functional significance and molecular pathways of the candidate mutation genes was evaluated.
Results: Significantly higher tumor incidence, multiplicity and larger tumor size of NAFLD-HCCs were found in both genetic and dietary obese mice compared with those of lean HCCs in wild-type mice. Totally 277 and 268 genes were found to be mutated in liver tumors from obese mice and control lean mice, respectively, with only 8 genes overlapped by whole-exome sequencing. Eight important metabolic or cancer-related pathways were significantly enriched in mutated genes found in obese HCC, whereas only two pathways were enriched in mutated genes found in lean HCC. Mutation frequency of *Cel* was significantly higher in obese HCC than in lean HCC (34.5% *vs.* 6.3%, $P < 0.05$). Mutations in *hRas* were detected in 10.3% of obese HCCs, all located at codon 61, but not in lean HCCs. *CEL* inactivating mutation and *hras* activating mutation promote liver cell growth. Inactivating mutation in CEL (D454E and D555N) led to the accumulation of cholesteryl ester, which activated ER stress and consequent IRE1α/JNK/c-Jun/AP-1 signalling cascade; whist activating mutations in hRas (Q61R and Q61K) activated MAPK and PI3K/PDK1/Akt signaling cascades to promote cell growth.
Conclusion: The genetic alterations of NAFLD-associated HCC are distinguished from that of lean HCC. Mutations in *CEL* and *hRas* play important roles in NAFLD-associated hepatocellular carcinogenesis.
Disclosure of Interest: None declared

OP337 EX VIVO-EXPANSION OF CD34+ CELLS FROM PATIENTS WITH LIVER CIRRHOSIS UP-REGULATES THERAPEUTIC EFFICACY OF CELL TRANSPLANTATION FOR LIVER CIRRHOSIS RAT

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Introduction: We demonstrated that the transplantation of human peripheral blood-$CD34^+$ cells into an immunodeficient rat liver fibrosis model reduced liver fibrosis by suppressing activated hepatic stellate cells and increasing matrix metalloproteinase (MMP) activity, and led to hepatic regeneration[1]. Recently, we reported that autologous granulocyte-colony stimulating factor (G-CSF)-mobilized peripheral blood-$CD34^+$ cell transplantation for patients with decompensated liver cirrhosis (LC) had therapeutic potential, but the colony-forming ability of $CD34^+$ cells from patients with decompensated LC was reduced[2]. So, recovery of $CD34^+$ cell function is indispensable for cell transplantation therapy of patients with decompensated LC.

Aims & Methods: The aim of this study was to investigate the efficacy of cell transplantation therapy with ex vivo-expanded human $CD34^+$ cells for carbon tetrachloride (CCl_4)-induced liver fibrosis model. Human G-CSF-mobilized peripheral $CD34^+$ cells of patients with LC were isolated by magnetic cell sorting system. Recipient nude rats were injected intraperitoneally with CCl_4 twice weekly for 3 weeks before initial treatment. Then, saline, 5×10^4, 2×10^5, or 1×10^6 non-expanded and expanded $CD34^+$ cells/kg body weight were transplanted via spleen, respectively. The administration of CCl_4 was continued for three more weeks until the rats were sacrificed. Examination items were as follows. 1) FACS and RT-PCR analysis of freshly isolated and expanded $CD34^+$ cells, 2) morphometry of fibrotic areas of Azan-Mallory stained liver, and 3) immunohistochemistry using anti-CD31, smooth muscle myosin heavy chain-1 (SM1), αSMA, Ki67, and PCNA antibodies.

Results: Seven days in culture, G-CSF-mobilized $CD34^+$ cells were effectively expanded in the serum-free culture medium. Expanded $CD34^+$ cells were also increasingly characterized as positive for cell surface markers of VE-cadherin, KDR and Tie-2, whereas they were down-regulated for CD34, CD133 and CD117. The expression of pro-angiogenic growth factors in expanded $CD34^+$ cells increased compared with non-expanded $CD34^+$ cells. The transplanted cells differentiated into $CD31^+$ and $SM1^+$ cells. Expanded $CD34^+$ cell transplantation had dose-dependently reduced liver fibrosis, with the decrease of collagen type-I and αSMA positive cells. Assessments of hepatocytes and sinusoidal endothelial cells proliferative activity indicated the superior potency of expanded $CD34^+$ cells over non-expanded $CD34^+$ cells.

Conclusion: These findings strongly suggest that expanded $CD34^+$ cell transplantation induces better therapeutic effects for LC.

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Disclosure of Interest: None declared

OP338 TRANSPLANTATION OF HEMATOPOIETIC STEM CELLS CAN CHANGE THE INTENSITY OF LIVER CELLS' APOPTOSIS IN PATIENTS WITH ALCOHOLIC LIVER CIRRHOSIS

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Introduction: Stem cell therapy is a promising technology for treating liver cirrhosis. Main source of these cells is bone marrow. The current method of aspiration of bone marrow under general anesthesia is inadvisable in patients with liver failure. Hematopoietic stem cells (HSCs) can be collected from blood stream with a non-invasive harvesting technique.

Aims & Methods: In this clinical trial we checked safety and efficacy of autologous HSCs from peripheral blood in patients with alcoholic liver cirrhosis and their influence to apoptosis intensity of liver cells. We examined liver biopsy specimens of 11 alcoholic cirrhosis patients (Child-Pugh class A and B). Biopsies were taken before the injection of autologous HSCs mobilized by granulocyte-colony-stimulating factor (G-CSF) into celiac trunk, 3 and 12 months after the procedure. Formalin-fixed, paraffin-embedded liver biopsy preparations were stained immunohistochemically with antibodies against Bcl-2, the anti-apoptotic protein.

Results: In the biopsies that were taken before the transplantation of HSCs we have seen many Bcl-2 positive cells in portal tracts. They were localized in liver parenchyma and in inflammatory infiltrates around the portal tracts. Positive cells could be divided into 3 types of cells: inflammatory cells with round or oval nucleus, cells with processes (sinusoidal cells) and single hepatocytes. We also observed weak expression of Bcl-2 in cholangiocytes. Three months after transplantation the number of positively stained cells significantly decreased. Nevertheless, twelve months after transplantation the amount of cells expressing anti-apoptotic protein grew up again, but didn't reach the level of first biopsies.

Conclusion: The analysis showed that the HSC treatment had no side effects. These results might indicate an intensification of inflammatory cells' apoptosis as a result of HSCs therapy. However, the effect of treatment remains only a few months and it is necessary to repeat the procedure.

Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 15:45–17:15

HOT TOPICS IN THE MANAGEMENT OF COLORECTAL PATHOLOGY – ROOM E6

OP339 LAPAROSCOPIC COLON RESECTION: TO PREP OR NOT TO PREP? ANALYSIS OF 1,535 PATIENTS

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Introduction: Recent systematic reviews and metanalyses of randomized controlled trials have shown that mechanical bowel preparation (MBP) should be omitted before elective open colon resection. However, there are very few data regarding the utility of preoperative MBP in patients undergoing laparoscopic colon resection (LCR).

Aims & Methods: The aim of this study was to challenge the use of MPB before elective LCR. It is a retrospective analysis of a prospectively collected database. All patients undergoing elective LCR with primary anastomosis were included. Preoperative MBP with polyethylene glycol solution was used routinely between April 1992 and December 2004, then it was abandoned. The early postoperative outcomes in patients who had preoperative MBP (MBP group) and in patients who underwent LCR without preoperative MBP (No-MBP group) were compared.

Results: From April 1992 to December 2014, 1,535 patients underwent LCR: 706 MBP patients and 829 No-MBP patients. There were no differences in demographic data, indication for surgery and type of procedure performed between MBP and No-MBP group patients. The incidence of anastomotic leakage was similar between the two groups (3.4% vs. 3.6%, $P = 0.925$). No differences were observed in intra-abdominal abscesses (0.6% vs. 0.8%, $P = 0.734$), wound infections (0.6% vs. 1.4%, $P = 0.149$), infectious extra-abdominal complications (1.8% vs. 3%, $P = 0.190$), and non-infectious complications (6.1% vs. 6.8%, $P = 0.672$). The overall reoperation rate was 4.6% for MBP patients and 5% for No-MBP patients ($P = 0.813$).

Conclusion: The use of preoperative MBP does not lead to lower incidence of intra-abdominal septic complications after LCR and therefore it should be abandoned.

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Disclosure of Interest: None declared

OP340 NORMAL MUCUS COMPOSITION IS ESSENTIAL IN COLONIC ANASTOMOTIC HEALING IN MICE

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Introduction: Anastomotic leakage (AL) is one of the most dreaded complications after colorectal surgery causing high morbidity and mortality. Despite extensive research, it is unclear why the incidence of AL remains approximately 10%. We hypothesize that mucus plays a pivotal role in the healing of colorectal anastomoses, since the mucus layer forms the first line of defense in the gastrointestinal tract. Previous research showed that Prostaglandin E2 (PGE2) supplementation in $COX2^{-/-}$ mice reduced the anastomotic leakage rate and ex vivo stimulation of the colon with PGE2 showed significant increase in mucus thickness. Therefore, we investigated if MUC2 (mucin 2, main component of mucus) depletion is associated with AL.
Aims & Methods: Twenty-two male and 22 female mice of different Muc2 genotypes were subjected to a model of colonic AL. Mice were matched for age, gender and when possible littermates were used as controls. Half of the mice received daily administration of dmPGE2 to potentially stimulate mucus secretion, starting a day prior to surgery and follow-up was 3 days. Mucus thickness measurements were performed ex vivo by measuring the distance between the epithelial surface and the mucus surface by a micropipette to ascertain presence of mucus at the anastomosis. Bacterial translocation into mesenterial lymph node (MLN) and spleen was determined by qPCR of bacterial 16S rDNA. Histological scoring of anastomosis, control proximal and distal colon was performed according to van der Ham et al. Intestinal Fatty Acid Binding Protein (I-FABP) levels were determined by ELISA as a marker of enterocyte damage.
Results: Of $Muc2^{-/-}$ mice, 91% developed AL, compared to 32% of control animals ($p < 0.001$). An evident mucus layer could be found at the anastomotic site of control animals, but not in colon of $Muc2^{-/-}$ mice. DmPGE2 did not reduce the anastomotic leakage rate, neither in $Muc2^{-/-}$ nor in control mice. Histologically, normal healing could be found in control animals, while $Muc2^{-/-}$ showed more inflammation with granulocyte influx and less fibroblast activity and neoangiogenesis at the anastomotic site, although not significant. Of $Muc2^{-/-}$ 90% had bacterial 16S rDNA in their MLN and 27% in their spleen at day 3 after surgery, while only 61% of the control animals had bacterial 16S rDNA in their MLN and no bacterial 16S rDNA could be found in spleens of these animals. I-FABP levels were significantly higher in $Muc2^{-/-}$ mice (3.89 ± 0.6ng/mL) compared to control mice (1.82 ± 0.4ng/mL, $p < 0.01$).
Conclusion: Normal mucus composition is essential in the healing process of colonic anastomosis in mice. DmPGE2 cannot stimulate mucus secretion in vivo in order to promote anastomotic healing, at least not in this model. Further research on anastomotic healing should focus on ways to positively influence the mucus layer as a way to promote better postoperative recovery.
Disclosure of Interest: None declared

OP341 LONG-TERM RESULTS OF INTERSPHINCTERIC RESECTION FOR VERY LOW RECTAL CANCER WITHOUT PREOPERATIVE CHEMORADIOTHERAPY

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Introduction: In Japan, the standard treatment of advanced rectal carcinoma is surgery with adjuvant chemotherapy. Intersphincteric resection has recently been considered as an alternative option to avoid permanent colostomy for selected patients with very low rectal carcinoma. However, with intersphincteric resection, there is a potential risk of increasing short- and long-term morbidity and mortality.
Aims & Methods: To evaluate the morbidity, mortality, and short-term, long-term results of intersphincteric resection for patients with very low rectal cancer, retrospective clinicopathologic analysis of prospective data registry was done. Between 1997 and 2012, 181 patients with cT1-to-cT3 rectal cancer below 5 cm from the anal verge underwent total mesorectal excision with intersphincteric resection. All patients did not receive preoperative chemotherapy and chemoradiotherapy.
Results: There were 134 men and 47 women with a median age of 58 (range 22-79) years. Median distance between tumor and the anal verge was 3 (range 1-5) cm. There were 50 pT1, 64 pT2, and 67 pT3 tumors. Eighty-four patients had disease categorized as stage I, 31 as stage II, 61 as stage III, and 5 as stage IV. Radial and distal margins were negative for 178 patients, but 3 patients had positive margins. Short-term morbidity and mortality were 26% and 0.6%, respectively. 11 patients underwent emergency operation and 5 patients had permanent stoma due to complication. Fifteen patients (8%) developed anastomotic leakage.Median follow-up was 61 months. Five-year overall and relapse-free survival rates of the 181 patients were 91% and 77%, respectively. The rates of local and distant recurrence of the 181 patients were 6% and 17%, respectively. One patient with T1 and 10 patients with T3 tumor developed local recurrence. Positive surgical resection margin and T3 tumor were significantly associated with local recurrence.
Conclusion: This study suggested that intersphincteric resection without neoadjuvant therapy is safe procedure for selected patients with cT1-to-cT3 rectal cancer below 5 cm from the anal verge in terms of short- and long-term morbidity and mortality.
Disclosure of Interest: None declared

OP342 WAITING TIME TO TREATMENT FOR PATIENTS WITH COLORECTAL CANCER IN FRANCE FROM MEDICO-ADMINISTRATIVE DATABASES

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Introduction: Time to treatment of cancer is becoming a social and political issue. In France one of the objectives of cancer plan is to "better understand the timing of cancers" care in order to reduce inequalities on access to care due to any delays"
Aims & Methods: We aim to study time elapsed from the colonoscopy to various first treatments such as surgery, and adjuvant treatments before and after surgery.
Based on International classification on diseases 10th revision and French medical procedures codes, we selected patients newly diagnosed for colorectal cancer in 2009 or 2010, who underwent to surgery or adjuvant treatment, from national hospital discharge and long term illness databases. We analyzed time to first treatment after colonoscopy according to the patient's pathway, the therapy's combination and the region of the patient's residence.
Results: We included in our study 15 694 and 6 623 patients suffering from colon and rectum cancers respectively. The median waiting time from colonoscopy to surgery was 22 (Q1: 14; Q3: 34) and 97 (Q1: 34; Q3: 141) days for colon and rectum cancers respectively. It was 36 (Q1: 21; Q3: 59) and 40 (Q1: 27; Q3: 59) days from colonoscopy to first chemotherapy, for colon and rectum cancers respectively and 53 (Q1: 39; Q3: 78) days from colonoscopy to first radiation for rectum cancer.
Median waiting times were longer in most of north regions (Picardie, Basse-Normandie) and overseas departments (Guadeloupe, Martinique, La Réunion, Guyane), and shorter in south regions (Languedoc-Roussillon, Limousin, Provence-Alpes-Côte-d'Azur) in France for both Colon and rectum cancer.
Conclusion: This original study is the first performed at national and regional level including overseas departments in France. Waiting times to treatment were longer for rectum cancer compared to colon cancer. There was heterogeneity on waiting times between regions of patient's residence.
Disclosure of Interest: None declared

OP343 CONSIDERATIONS FROM THE FIRST DELAYED BLEEDING RISK SCORE FOR ENDOSCOPIC MUCOSAL RESECTION OF LARGE COLORECTAL LESIONS: TO CLIP OR NOT TO CLIP?

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Introduction: Delayed bleeding (DB) is the main complication after endoscopic mucosal resection (EMR) of large colorectal lesions. Many of the risk factors of DB described remain controversial.
Aims & Methods: The aims of this study were to create a DB risk score for EMR of large colorectal lesions (≥2 cm) and to consider the cost-effectiveness of prophylactic clipping in the high-risk group.
EMR of non-pedunculated large colorectal lesions were prospectively registered in an ongoing Spanish multicenter study from February 2013 to February 2015. A score for DB was developed by assigning a weight from 0 to 3 to each risk factor category found based on the β parameter from the multivariate logistic regression. We evaluated the cost-effectiveness of the prophylactic complete closure of the mucosal gaps in the high-risk group.
Results: A total of 1255 EMR were performed. There were 46 (3.7%, 95%CI: 2.7%>4.9%) cases of DB.
Factors associated to DB in the multivariate analysis ($p \leq 0.05$) were age ≥75 years, ASA classification III-IV, lesion size ≥40 mm, location proximal to transverse colon, aspirin use during EMR and not fully clipped mucosal gaps after EMR. Taking the continuous score (ROC=0.79, 0.72-0.85), we classified patients into three DB risk categories: low (score 0-3, risk 0.6% [CI 0.2%>1.8%]), average (score 4-7, risk 5.5% [CI3.8%>7.9%]) and high (score 8-10, risk 40% [CI 21.8%, 61.1%]).

In the high-risk group (n = 25, 2%) DB occured in 40%. None of the mucosal gaps were clipped. The patients with DB needed 33 hospitalization days (medium 3.3 days/patient) and 5 (20%) required transfusion. This implies a hospitalization cost of 19800 €whereas the cost of the complete closure of these 25 mucosal defects (medium size 40.8 mm) would be around 7500 €.
Conclusion: DB rate after EMR of large colorectal lesions was 3.7% (95%CI: 2.7% > 4.9%).
Six easily available predictors can be used to calculate a simple and novel DB risk score that allows endoscopists to stratify patients and colonic lesions.
In the high-risk group DB rate reaches 40%. Complete clip closure of the mucosal gap after EMR appears to be a cost-effective preventive method when used in high-risk patients.
Disclosure of Interest: None declared

OP344 AN AUDIT OF COLONIC STENTING IN ACUTE LARGE BOWEL OBSTRUCTION IN A UK GENERAL HOSPITAL

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Introduction: The objective of this study was to audit practice in colonic stenting in acute presentations of malignant bowel obstruction in a London Hospital (UK) against the UK's National Institute of Health and Care Excellence (NICE) recommendations.
Aims & Methods: Patients were retrospectively identified using the hospital's endoscopy database ('Scorpio') and by using the hospital's data warehouse to identify all patients who presented with acute large bowel obstruction. Data were captured between May 2009 and December 2012 by two independent doctors. A notes check was performed 6 months after the data capture period closed to check for: stent complications; progression to colorectal surgery; length of time to colorectal surgery where applicable; and stoma rate where applicable. The following endpoints were used to determine the gold standard: 1) The use of CT chest, abdomen and pelvis prior to stent deployment 2) The exclusion of self-expanding metallic stents in low rectal lesions or to relieve right-sided colonic obstruction or if clinical or radiological evidence of colonic perforation or peritonitis 3) Deployment of self expanding stents within 24 hours of presentation 4) Enrolment into an RCT.
Results: During the audit period 363 patients presented with acute large bowel obstruction. Of these 36 patients (9.9%) had stents deployed within the audit period. Median age of those who had stents was 77 years (range 50-98 years) and 55.5% were male. The stent was intended as a palliative measure in 53% and as bridge to colorectal surgery in 47% of cases. In 2 instances the stent could not be deployed for technical reasons: in one instance due to patient hypoxia, and in a second due to an impassable stricture. 100% of patients had a CT abdomen and pelvis and 83% also had a CT chest. No stents were placed where there was evidence of perforation or peritonism. One right sided stent and one rectal stent were placed. Only 44% of stent procedures were carried out within 24 hours of hospital admission for obstruction. Patients were not offered the opportunity to take part in an RCT as none was available. The stent failure rate was 8.8% at 6 weeks. In two cases the stent became blocked with faecal matter and in one case the stent was occluded by tumour growth. There were no cases of stent migration or perforation. 15 patients (41.2%) went on to have colorectal surgery. Mean time to surgery after stenting was 51 days (range 1-256 days). The primary anastomosis rate was 66.6%; 33.3% had a stoma. Of these 15 patients there were two surgical deaths, both of whom died in ITU on the third post-operative day; one following a cardiac arrest, the second in which ITU withdrew care as multi-organ failure led to an unsustainable inotrope requirement.
Conclusion: Colonic stenting can be deployed safely in a district general hospital and it is effective. However a stent was placed in fewer than 10% of admissions for acute large bowel obstruction and of those who had a colonic stent insertion fewer than half had the procedure within 24 hours of hospital admission. This suggests that greater awareness is still required amongst clinicians.

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Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 15:45–17:15
MOTILITY, MECHANISMS AND THE UPPER GI TRACT – ROOM B3

OP345 INCREASED RISK OF OVERWEIGHT, OBESITY AND MOOD DISORDERS IN PATIENTS WITH FUNCTIONAL GASTROINTESTINAL DISORDERS (FGID)

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Introduction: Functional gastrointestinal disorders (FGIDs) are common clinical conditions of unknown etiology. Around 30% of North American adults are obese, and the prevalence of obesity is increasing. Although some reports have suggested that obesity may be more prevalent in FGIDs, the data on adult patients are scarce and contradictory.
Aims & Methods: Thus our objective was to evaluate the association between obesity and FGIDs and to determine the factors contributing to this association.
This is an observational study conducted between January 2008 and January 2015. New patients referred to the Gastroenterology outpatient clinic at McMaster University completed questionnaires evaluating FGIDs (Rome III), anxiety and depression (HAD score) and basic demographic data. A chart review was then performed in a random sample of the total population to collect further clinical and demographic data, and to rule out organic diseases. Continuous variables were expressed as mean ± SD and categorical variables as percentages. $\chi 2$, and logistic regression analyses were performed and adjusted by age, gender, lifestyle habits, psychiatric medication and mood.
Results: Three thousand and thirty four patients out of 4965 were included in the analysis. From them, 71% of patients fulfilled the Rome III criteria for FGIDs but only 53% were confirmed as FGIDs after organic diseases were ruled out. 53% of all the patients were overweight or obese (BMI ≥ 25 and ≥ 30, respectively). An increased risk for overweight and obesity was observed in patients with FGIDs compared to those who did not meet the Rome III criteria for FGIDs (aOR1.2, 95% CI 1.01-1.42). The highest risk for overweight/obesity was observed in patients with functional dyspepsia (FD; aOR 2.55, 95% CI 1.70-3.80) followed by irritable bowel syndrome (IBS; aOR 1.67, 95% CI 1.62-2.20). The use of antidepressants contributed to the association between FGIDs and overweight/obesity (OR 1.46, 95% CI 1.17-1.82). An increased risk for depression (OR 1.28, 95% CI 1.10-1.46) but not for anxiety was found in the overall overweight/obesity population. However, both anxiety and depression were significantly increased in population with both overweight/obesity and FGIDs (OR 1.33, 95% CI 1.14-1.56 and OR 1.51, 95% CI 1.26-1.80 for anxiety and depression, respectively).
Conclusion: Overweight and obesity are frequently found in patients with FGIDS, mainly in patients with IBS and FD, and in those patients using antidepressants. The patients with concomitant obesity/overweight and FGIDs have increased risk for anxiety and depression.

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Disclosure of Interest: None declared

OP346 GAS SWALLOW DURING MEALS IN PATIENTS WITH UPPER ABDOMINAL SYMPTOMS

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Introduction: Previous studies using ultrafast CT-scans have shown that in each swallow of a 10 ml liquid bolus, 8-32 ml of gas can be ingested. In patients with aerophagia, the association between swallowed gas and belching have been addressed under laboratory conditions. However, and despite gas-related digestive symptoms are common, our knowledge of volume and number of meal-related gas swallows in humans performed during a normal day is unknown.
Aims & Methods
Aim: To characterize the number of meal-related swallows and the proportion of gas containing swallows during a 24-h period in a group of patients with excessive belching and a group of patients without abdominal symptoms.
Methods: A 24-h pH-impedance monitoring was performed in 6 patients complaining of excessive belching. As control group, 11 patients studied for chronic cough and without digestive symptoms or reflux in the pH-impedance study were included. In each patient we counted the number of liquid swallows, gas swallows and mixed gas/liquid swallows during meals, as oro-caudal drops and increments of impedance over 50% from baseline, respectively. During the study, patients were asked to follow with their daily routine and customary meals, without any specific limitation. Data is expressed as mean ± standard desviation.
Results: Control patients expended 75 ± 26 min to eat along the 24-h study period, distributed in 4 ± 1 meals. During this time, a total of 74 ± 28 swallows were detected by impedance, with the majority of them being mixed gas/liquid swallows (94 ± 10%). Pure liquid swallows or pure gaseous swallows were rarely detected (2 ± 1% and 4 ± 5%, respectively). Patients with frequent belching expended a similar length of the day to eat (83 ± 24 min; p = 0.514 vs. controls), distributed in a somewhat greater number of meals (5 ± 1 meals; p = 0.038 vs. controls). In contrast to controls, and despite a similar length of time expended to eat, patients with frequent belching performed a significantly greater number of swallows during meals along the day (124 ± 37 swallows; p = 0.004 vs controls), due to a greater frequency of swallows while eating (15 ± 4 swallows vs 10 ± 3 swallows/10 min, belchers vs controls, respectively; p = 0.006). Similar to the control group, most swallows were mixed gas/liquid swallows (89 ± 6%), with only a minority of pure liquid or gaseous swallows (5 ± 4% and 6 ± 2% swallows, respectively). Consequently, patients with frequent belching performed during meals a significantly greater number of gas-containing swallows during 24 h (116 ± 34 swallows) than the control group (69 ± 26 gaseous swallows; p = 0.003 vs controls).
Conclusion: Under normal customary conditions, relevant volumes of gas can be ingested during meals along the day. In patients complaining of excessive belching, gas ingestion is greater, due to a different pattern of food swallow,

with a greater rate of swallows per time. This specific eating behaviour could play a pathophysiological role in gas-related symptoms, and opens the possibility to new therapeutic approaches in patients with gas-related symptoms.
Disclosure of Interest: E. N. Caballero: None declared, C. Julia: None declared, J. Serra Financial support for research: ALMIRALL, Lecture fee(s): NORGINE, Consultancy: RECKITT BENCKISER

OP347 DISTENSIBILITY OF THE ESOPHAGO-GASTRIC JUNCTION IN PATIENTS WITH SYSTEMIC SCLEROSIS: A STUDY WITH THE FUNCTIONAL LUMEN IMAGING PROBE

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Introduction: Manometry is widely used for evaluating the function of the esophagus, including the esophago-gastric junction (EGJ). However, studies suggest that distensibility is a better parameter than pressure for assessment of EGJ function. The functional lumen imaging probe (FLIP) is a novel method that provides detailed information on geometric properties of the gastrointestinal sphincter function during distension. Systemic sclerosis (SSc) is a connective tissue disease which causes fibrosis and atrophy of smooth muscle cells. In 90% of patients with SSc the esophagus is affected often resulting in severe gastro-esophageal reflux and dysphagia.
Aims & Methods
Aim: To provide comprehensive evaluation of EGJ function by means of FLIP in a well characterized group of patients with smooth muscle dysfunction caused by SSc.
Method: We included 11 patients with SSc (10 women, median age 58, [range 35-72], duration of disease 1- 20 years) referred because of upper GI symptoms. After doing upper endoscopy the EGJ was distended with FLIP. Standard esophageal manometry had been performed in all patients. Patients were compared to 9 healthy volunteers (HVs) with no gastrointestinal symptoms. The FLIP recorded pressure and minimum diameter along the EGJ, which were used for the distensibility analysis.
Results: The FLIP procedure was successful in all patients. The pressure and diameter increased during the inflation in both groups. At the maximum distension volume 50ml, the pressure in the HVs was higher than in the SSc (49.5 ± 18.8 mmHg for HVs and 38.2 ± 16.1 mmHg for SSc, $p = 0.02$) whereas the diameter was largest in the SSc group (14.8 ± 4.5 mm for HVs and 21.9 ± 4.8 mm for SSc, $p = 0.004$) (Figure 1). The pressure strain elastic modulus (*Ep = (Pressure at volume 50ml - Pressure at volume 0ml)/ (Diameter at volume 50ml -Diameter at volume 0ml) * Diameter at volume 50ml*) was significantly reduced in SSc (3.4 ± 1.7 kPa in HVs and 1.7 ± 1.1 kPa, $p = 0.006$), indicating a more distensible EGJ in SSc patients. There was no correlation between duration of disease and Ep (rho = 0.32 and $p = 0.33$).
Conclusion: FLIP is an easy-to-perform method for assessment of EGJ function. Patients with SSc and dysphagia or reflux have significantly higher distensibility of the EGJ than healthy volunteers. Distensible of the EGJ is, however, not associated with duration of the disease.
Disclosure of Interest: L. Fynne: None declared, D. Liao: None declared, C. Lottrup: None declared, K. Aksglaede: None declared, H. Gregersen Consultancy: Consultancy with the manufacture of FLIP, Crospon, N. C. Bjerregaard: None declared, A. Drewes: None declared, K. Krogh: None declared

OP348 VELUSETRAG IMPROVES GASTRIC EMPTYING TIME IN SUBJECTS WITH DIABETIC OR IDIOPATHIC GASTROPARESIS

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Introduction: Patients with diabetic or idiopathic gastroparesis have delayed gastric emptying (GE) time. Velusetrag (VEL) is an oral, once-daily, investigational, highly-selective 5-HT4 agonist that has demonstrated prokinetic effects in the lower gastrointestinal tract in subjects with chronic idiopathic constipation. The current study evaluated VEL prokinetic effects in the upper gastrointestinal tract by assessing GE time in both diabetic and idiopathic gastroparesis subjects.
Aims & Methods: Subjects with gastroparesis were screened for increased GE time ($t_{1/2} > 160$ mins), symptoms consistent with gastroparesis for ≥ 3 months, Gastroparesis Cardinal Symptom Index score between 2 and 4 inclusive, and HbA1c $< 10\%$ (diabetics). Subjects were randomised in an incomplete block, 3-period, cross-over design to 3 of 4 treatments, VEL 5-, 15- and 30-mg and placebo stratified for diabetic or idiopathic gastroparesis. In all 3 treatment periods, subjects performed a 6-hr ^{13}C-octanoate breath test of GE time on Day -1 (baseline) and after the 7th dose. Efficacy was assessed by the change from baseline in GE $t_{1/2}$. All efficacy endpoints were evaluated using mixed-effect models with a covariate for baseline GE.
Results: 34 subjects were randomised; n = 26 (placebo), 26 (VEL 5-mg), 25 (VEL 15-mg), and 25 (VEL 30-mg). The study population was 68% female, 82% Caucasian, and 53% diabetic, with mean (SD) age of 46 (10.3) yrs and baseline GE $t_{1/2}$ mean (SD) [range]: 206 min (91.1) [107-640]. The proportion of subjects with at least a 20% reduction in GE $t_{1/2}$ was 5% for placebo and 26%, 20%, 52% for VEL 5-, 15-, and 30-mg, respectively. Statistical significance was observed in the 30-mg dose group ($p = 0.002$). The mean (SD) change from baseline of GE $t_{1/2}$ was -13 (14.9) mins for placebo and -35 (14.6), -34 (15.5), and -52 (15.2) mins for VEL 5-, 15-, and 30-mg, respectively. Similar treatment effects were observed with VEL in both diabetic and idiopathic subjects. A pre-specified analysis of subjects with delayed GE time at baseline (GE between 180-350 mins excluding relatively normal and extremely abnormal GE times) revealed a placebo-adjusted mean (SD) reduction [% improvement] from baseline in VEL-treated subjects of -76 (41.9) [-33%], -73 (50.4) [-28%] and -85 (40.9) [-37%] mins for VEL 5-, 15- and 30-mg, respectively. All doses of VEL were generally well tolerated. The most common adverse events were diarrhoea (n = 16) and headache (n = 6). No on-treatment serious adverse events were observed.
Conclusion: Velusetrag treatment was generally well tolerated and resulted in a statistically significant improvement in GE time at the 30mg dose in subjects with diabetic or idiopathic gastroparesis. Future studies will assess the translation of these pharmacodynamics effects into symptomatic improvement.
Disclosure of Interest: A. Ahn Shareholder: Stocks received, Conflict with: Employee, C. Barnes: None declared, D. Shaywitz Shareholder: Received stock, Conflict with: Employee at time of conduct, M. Grimaldi Conflict with: Employee, D. Canafax Shareholder: Received stocks, Conflict with: Employee

OP349 COMPARATIVE QUANTITATIVE ASSESSMENT OF GLOBAL SMALL BOWEL MOTILITY USING MAGNETIC RESONANCE IMAGING IN CHRONIC INTESTINAL PSEUDO-OBSTRUCTION AND HEALTHY CONTROLS

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Introduction: Chronic Intestinal Pseudo-Obstruction (CIPO) is a rare but life-threatening disorder characterised by failure of the intestinal tract to propel its contents. In this study, we compare resting and stimulated global small bowel motility in Chronic Intestinal Pseudo-Obstruction (CIPO) patients and normal controls using software quantification of cine MRI.
Aims & Methods: Twenty healthy volunteers (mean age 28, range 22-48, 14 Male) and 11 CIPO patients (7 male, mean age 47, range 19-90) were recruited prospectively and underwent 3T MRI enterography including a dedicated motility sequence (3D Balanced Turbo Field Echo, 2.5x2.5x10mm voxel size, FA 20, TE = 1.7ms, TR = 3.5ms) to capture global small bowel motility over a 20 second breath-hold. All CIPO patients stopped taking motility influencing medication (laxatives, antiemetics, opioids etc.) for 5 days prior to their scan.
11 controls and 7 CIPO patients in addition underwent a randomized placebo-controlled crossover study of either IV 0.5 mg neostigmine (Mercury Pharma, UK) or saline with motility MR imaging repeated at a mean of 3 weeks. Motility was quantified in regions of interest (placed by an experienced radiologist blind to the motility data) to encompass the whole small bowel volume using a validated, post-processing technique to give a global motility index in arbitrary units (AU)[1,2]. Baseline and stimulated motility was compared using Wilcoxon rank sum paired T-tests.
Results: Baseline small bowel motility was significantly lower in CIPO patients (0.25AU) compared to controls (0.35AU), $p < 0.001$. Motility in both groups significantly increased after neostigmine against placebo although compared to baseline, response was greater in the CIPO group (mean 38%) than controls (mean 13.5%) $p = 0.0015$.
Conclusion: Global small bowel motility in CIPO patients is significantly lower than in controls and the relative response to the pro-kinetic agent neostigmine appears exaggerated. Software quantified bowel motility using cine MRI appears to be a useful tool and, in combination with a pharmacological probe, could represent a safe and cost-effective approach for the investigation of enteric dysmotility.

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Disclosure of Interest: A. Menys Shareholder: Motilent Ltd, Directorship(s): Motilent Ltd, S. Butt: None declared, A. Emmanuel : None declared, A. Plumb : None declared, A. Fikree: None declared, C. Knowles: None declared, D. Atkinson: None declared, N. Zarate: None declared, S. Taylor: None declared

OP350 EFFECT OF AMINO ACIDS ON GASTRIC EMPTYING AND SATIATION HORMONES IN LEAN AND OBESE SUBJECTS

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Introduction: Changes in gut motor and hormonal function contribute to the eating-inhibitory and glucose-lowering effects of protein. The effect of amino acids, the digestive products of protein, on gastrointestinal function, hormone

release, and glycemia has not been investigated comprehensively. The aim of this study was to investigate the effect of L-tryptophan (L-trp) and L-leucine (L-leu) on gastric emptying, gastrointestinal satiation hormones and appetite perceptions in lean and obese subjects.
Aims & Methods: The study was conducted as a randomized, placebo-controlled, parallel-group trial. A total of 10 lean (5 men and 5 women) and 10 obese (BMI > 30), non-diabetic participants (5 men and 5 women) took part in the study. Subjects received intragastric infusions of different physiological concentrations of L-trp (0.52 g and 1.56 g) and L-leu (1.56 g). Control treatment was tap water infusion. The test solutions were labelled with ^{13}C-sodium acetate for determination of gastric emptying rates. To investigate a second gut motor function in response to the amino acids, gallbladder contraction was measured by ultrasound. Plasma samples were collected for glucagon-like peptide-1 (GLP-1), peptide tyrosine tyrosine (PYY) and cholecystokinin (CCK), insulin and glucose analysis. Visual analogue scales (VAS) were used for appetite measurements.
Results: L-trp dose-dependently stimulated gallbladder contraction and CCK release ($p < 0.01$). L-leu did neither stimulate CCK release nor gallbladder contraction. Of note, the high dose of L-trp slowed gastric emptying ($p < 0.05$) in lean subjects. In obese subjects, gastric emptying rates were significantly ($p < 0.01$) delayed compared to lean controls. Both amino acids stimulated insulin release ($p < 0.01$, respectively) in obese, but not in lean subjects; fasting insulin was increased in obese documenting insulin resistance. Appetite ratings were not changed by the amino acid infusions in both subject groups. GLP-1 and PYY measurements are in process.
Conclusion: Low caloric intragastric loads of L-trp affect gastric emptying and CCK release. The increase in CCK may play a role in the observed delay of gastric emptying rates, but was not sufficient to modulate appetite sensations. Both L-trp and L-leu didn't stimulate insulin release in lean subjects confirming that amino acids can only stimulate insulin secretion in the presence of glucose. In contrast, in obese both L-trp and L-leu induced insulin secretion suggesting a disturbed metabolic pathway.
Disclosure of Interest: None declared

TUESDAY, OCTOBER 27, 2015 15:45–17:15
ABSTRACTS ON FIRE: ESD IN 2015 – EAST-WEST PERSPECTIVES – HOTSPOT

OP351 TECHNICAL FEASIBILITY AND SAFETY OF ENDOSCOPIC SUBMUCOSAL DISSECTION FOR RECTAL TUMOR WITH INVOLVEMENT TO THE ANORECTAL JUNCTION, COMPARE WITH THE RECTAL TUMOR WITHOUT INVOLVEMENT TO THE ANORECTAL JUNCTION

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Introduction: Endoscopic submucosal dissection (ESD) has been developed for en-bloc resection of mucosal gastric neoplasms. ESD for colorectal lesions is more difficult than for the gastric lesions because of anatomical feature of the colon and rectum. Especially, ESD for rectal lesions with involvement to the anorectal junction is more difficult than rectal lesion without involvement to the anorectal junction because of narrower lumen, comorbidity of hemorrhoid, fibrosis of submucosal layer, longer procedure time, and increased risk of bleeding. The curability by ESD brings large benefit because preservation of an anal function is closely related to quality of life.
Aims & Methods: The aim of this retrospective study was to investigate the clinical outcome and feasibility of ESD with involvement to the anorectal junction compare with ESD without involvement to the anorectal junction. ESD of 153 lower rectal lesion were performed under conscious sedation in our institute from January 2004 to December 2014. A total 37 lesions with involvement to the anorectal junction (with ARJ) and 116 lesions without involvement to the anorectal junction (without ARJ) treated with ESD. ESD procedure for rectal lesions with involvement to the anorectal junction: at first we inject lidocaine to squamous epithelium of anorectal junction for local anesthesia, next inject sodium hyarulonate acid to the submucosal layer of rectun. Circumferential incision and submucosal dissection was performed by Dual knife with CO2 insufflation.
Results: No statistically significant differences were noted between with ARJ and without ARJ for median age (70years old with ARJ, 67years old without ARJ), male/female ratio (19/18 with ARJ, 60/56 without ARJ), en-block resection rate (100% with ARJ, 98% witout ARJ), median hospital days (4days with ARJ, 4days without ARJ), perforation (0%with ARJ, 0% without ARJ) and local recurrence and residual tumor (0% with ARJ, 0% without ARJ). Statistically significant differences between the two groups were observed for mean tumor size (45.8mm with ARJ versus 28.7mm without ARJ; $p < 0.05$), mean time of procedure (86.5minutes with ARJ versus 33.8minutes without ARJ; $p < 0.05$), postoperative bleeding (27% with ARJ versus 8% without ARJ; $p < 0.05$) and postoperative pain (27% with ARJ versus 0% without ARJ; $p < 0.01$). The pain could be controled with NSAIDS or acetaminophen administration. We suppose that reasons for difficulty of ESD with ARJ are past history of treatment for hemorrhoid, fibrosis of submucosal layer due to prolapse of tumors and others. In both group, anal function of patients is preserved.
Conclusion: ESD of rectal lesions with ARJ appears to be a feasible and curative treatment, even though it is associated with a higher adverse event rate, higher degree of technical difficulty, and longer procedure time. Considering the potential poor quality-of-life after anorectal surgery, ESD for anorectal lesions becomes an attractive alternative.
Disclosure of Interest: None declared

OP353 LONG-TERM OUTCOMES OF ENDOSCOPIC SUBMUCOSAL DISSECTION (ESD) FOR EARLY GASTRIC CANCE(EGC): A PROSPECTIVE STUDY OF ITS EXPANDED INDICATION

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Introduction: ESD has been widely used as a minimally invasive treatment for EGC. Long-term outcomes such as survival rate would be the final endpoints, however it is not fully reported prospectively. The aim of this study was to investigate long-term outcomes of ESD for EGC in a study of its expanded criteria.
Aims & Methods: We designed a prospective study in which ESD was applied in patients with differentiated-type EGC up to 30 mm in diameter regardless of ulceration or above 30 mm without ulceration, but definite signs of submucosal invasion. According to final diagnosis after ESD, EGC below considered to have hardly metastasis, were enrolled and follow up and otherwise were advised to be operated on additionally; differentiated-type mucosal EGC above 30 mm in diameter without ulceration, and EGC up to 30 mm with ulceration and/or minute submucosal invasion. The protocol was approved by the ethics committee of our hospital. Followed-up endoscopic examinations are performed 6 months later, and then every six months.
Results: From April 2006 to March 2013, ESD was performed in 1070 lesions. En bloc resection was achieved in 1060 lesions (99%). Among them 950 were enrolled (guideline (less than 2cm without ulceration) group; 642, expanded criteria group; 308) and were followed up (median 45months (range 15 to 96)). R0 (margin-free) resection was achieved in 629 (98%), and 287 (93%) cases, respectively. Perforation and bleeding were encountered in 59 (5.6%) and 40 (3.8%) lesions, but there was no ESD-related death. During the follow-up, one patient (0.13%) in the expanded criteria group died from distant metastasis of the EGC and 55 patients (7%) died of some causes unrelated to EGC. Five-year overall survival rates were 97.9% and 94.7%, respectively. Metachronous multiple cancers were detected in 126 (16%) patients. Among the 120 patients with lesions not fulfilled the expanded criteria, 65 were underwent additional surgery, and 7 (11%) had LN metastasis and 7 residual lesions were found. The remaining 55 patients refused additional surgery and were followed up; 9 (16%) had local recurrence and 2 (4%) died from gastric cancer.
Conclusion: This study indicates favorable long-term outcomes of ESD for patients of not only guideline group but also of expanded group. The expanded criteria would be useful in clinical settings.
Disclosure of Interest: None declared

OP354 LONG-TERM OUTCOME AFTER ENDOSCOPIC SUBMUCOSAL DISSECTION FOR EARLY GASTRIC CANCER: ACCORDING TO FINAL PATHOLOGICAL RESULTS

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Introduction: Endoscopic submucosal dissection (ESD) is an effective treatment for selected patients with early gastric cancer (EGC). The purpose of this study was to examine the short-term and long-term outcomes after ESD in patients EGC according to the pathological extent.
Aims & Methods: ESD were performed in 599 patients with 611 EGC from January 2005 to January 2015. We performed a retrospective analysis of the medical records of these patients. The tumors were classified by pathological severity based on absolute indication (AI), expanded indication (EI), expanded indication with undifferentiated histology (EI(U), mucosal cancer, ulcer(-), 20mm) or beyond expanded indication (BEI). The therapeutic outcomes among the four groups were analyzed. After ESD, 40 patients underwent surgery immediately and 135 patients followed up less than 6 months. These 175 patients were excluded for the long-term outcome study.
Results: Number of patients was 447, 91, 19 and 54 in the AI-EGC, EI-EGC, EI(U)-EGC and BEI-EGC groups. The complete resection rates of EGC were 97.8%, 86.4%, 89.5% and 46.3% in the AI-EGC, EI-EGC, EI(U)-EGC and BEI-EGC groups, respectively ($P = 0.000$). *En bloc* resection rates were 99.1%, 98.9%, 100% and 98.1% in the AI-EGC, EI-EGC, EI(U)-EGC and BEI-EGC groups ($P = 0.833$). The 5-year tumor recurrence rates were 4%, 8.1%, 28.6% and 6.7% in the AI-EGC, EI-EGC, EI(U)-EGC and BEI-EGC groups ($P = 0.000$). The 5-year disease-free survival rates were 93.2%, 87.0%, 53.3% and 88.9% in the AI-EGC, EI-EGC, EI(U)-EGC and BEI-EGC groups ($P =$

Abstract number: OP354

Characteristics, n (%)	Total(n = 611)	AI-EGC(n = 447)	EI(n = 91)	BEI(n = 54)	EI(U)(n = 19)	p
Age (year)	67.9 9.6	67.5	69.7	69.3	68.6	0.146
Male	432 (75.7%)	326 (77.4%)	60 (73.2%)	35 (68.6%)	11 (64.7%)	0.325
Location						0.001
Upper	17 (2.8%)	10 (2.2%)	1 (1.2%)	6 (11.1%)	0	
Middle	176 (28.8%)	119 (26.6%)	29 (31.9%)	22 (40.7%)	6 (31.6%)	
Lower	418 (68.2%)	318 (71.1%)	61 (67%)	26 (48.1%)	13 (68.4%)	
Tumor size > 30mm	12 (2.0%)	0	8 (8.8%)	4 (7.4%)	0	0.000
ulcer	35 (5.7%)	0	26 (28.6%)	9 (16.6%)	0	0.000
Pathologic type						0.000
WD	402 (65.8%)	326 (78.9%)	54 (59.3%)	22 (40.7%)	0	
MD	178 (29.1%)	121 (27.1%)	37 (40.7%)	20 (37.0%)	0	
PD	25 (4.1%)	0	0	8 (14.8%)	17 (89.5%)	
SRC	5 (0.8%)	0	0	3 (5.6%)	2 (10.5%)	
Lymphovascular invastion	24 (3.9%)	0	6 (6.6%)	17 (31.5%)	1 (5.3%)	0.000
Depth of invasion						0.000
SM1	33 (5.4%)	0	28 (30.8%)	5 (9.3%)	0	
SM2	40 (6.5%)	0	0	40 (74.1%)	0	
Cancer recurrence in 5yrears	22 (5.0%)	14(63.6%)	5 (22.7%)	1 (4.5%)	2 (9.0%)	

0.082). The risk factors related to recurrence were undifferentiated histology (p = 0.048) and tumor size (> 3cm, p = 0.01).
Conclusion: ESD was effective and safe in treating AI-EGC and EI-EGC. But, EI(U)-ECG after ESD should be considered surgical treatment because of high recurrence rate.
Disclosure of Interest: None declared

OP355 HIGH-PRESSURE INJECTION OF GLYCEROL WITH HYBRIDKNIFE FOR ESD INCREASES THE EASE AND SPEED OF THE PROCEDURE: A RANDOMIZED STUDY IN PIGS AND FIRST USE IN HUMAN

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Introduction: The HybridKnife water-jet system (ERBE, Germany) has shown to increase dissection speed and decrease the risk of perforation during endoscopic submucosal dissection (ESD). Glycerol is a viscous, long-lasting solution preferentially used by Japanese experts and has shown an increase of the speed of dissection in a non-randomized control trial in pigs. We report here the results of a randomized control trial of ESD with HybridKnife injecting of either a glycerol mixture or normal saline and the first results of human use.
Aims & Methods: 20 gastric dissections of a virtual lesion (10 per group) with hybridknife were performed by 2 operators blinded of the injected solution (Glycerol or NaCl 0.9%) on 7 anaesthetised domestic mini-pigs. Dissection speed (mm^2/min), size of the specimen (mm^2), duration (min), en bloc resection rate, bleeding and perforation rates were prospectively recorded. An evaluation of operator comfort and perception of safety (dissection score) was performed using a visual analogue scale (0 = the worst, 10 = the best). In parallel; we performed a total of 36 ESD for precancerous or superficial cancerous lesions in humans. The setting of the Erbejet 2 varied from 12 to 15 bars in humans and between 30 to 35 bars in pigs due to the thickness of the pig gastric mucosae. In our experience we always chose the minimum pressure that allowed a good lifting of the lesion to avoid bleeding during the injection phase.
Results: In the randomized study in pigs, high-pressure injection of the glycerol mixture and dissection with the HybridKnife was feasible without complication. Dissection was significantly more rapid (1,38-fold) with glycerol injection than normal saline injection (28.94 vs. 20.91 mm^2/min; p = 0.035). The dissection score was significantly higher in the glycerol group than in the normal saline group (7.3 vs. 4.7; p = 0.006). No difference was observed in the rates of en bloc resection (100%), bleeding (20%) and perforation (0%); in the size of specimen (1166 vs 1080 mm^2 p = 0.55) and the duration of the procedure (42.6 vs 53.6 min p = 0.07). The injection system has failed several times due to the carbonization of the knife but with the same frequency in the 2 groups.
In parallel between September 2013 and March 2015 we performed 36 ESD for precancerous or superficial cancerous lesions: 8 oesophageal, 5 gastric and 23 rectal lesions. The en bloc resection rate, R0 resection rate and curative resection rate were respectively 100% (36/36) and 91.7% (33/36) and 86.1% (31/36). High-pressure injection of glycerol with hybridknife was always feasible with a pression between 12 and 15 bars. The injection system failed several times due to the carbonization and close regular cleaning of the knife allowed a longer life of the device. No complication or pathological damage occurred with high-pressure glycerol injection.
Conclusion: High-pressure jet injection of glycerol with HybridKnife for ESD is feasible and increases the speed and ease of the procedure compared with use of normal saline. This is the first study confirming the feasibility of injecting a viscous solution (glycerol) using the ERBE HybridKnife system in human ESD.

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Disclosure of Interest: None declared

OP356 ESD VERSUS EMR IN ESOPHAGEAL ADENOCARCINOMA (EAC) - REPORT OF A GERMAN CENTER

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Introduction: Endoscopic mucosal resection (EMR) is the standard treatment for superficial esophageal cancer but in larger lesions it may lead to piecemeal or incomplete resection. Endoscopic submucosal dissection (ESD) allows the en-bloc resection of a lesion regardless of its size, which enables histopathological assessment of R0 resection and may reduce the risk of recurrence. Studies from Asia have demonstrated the superiority of ESD in ESCC but in EAC data on ESD is rare.
Aims & Methods
Aim: To evaluate ESD and EMR in EAC.
Methods: Between 02/2003 and 12/2014 162 early esophageal adenocarcinomas were treated with EMR or ESD in a German tertiary referral center. ESD data was recorded prospectively, EMR results were analysed retrospectively.
Results: EMR: 54 resections in 37 patients, en-bloc-resections 16/54 (29.6%), R0 resections 13/54 (24.1%), R1 resections 30/54 (55.5%; R1 horizontal margin = 24, R1vertical margin = 2, R1 horizontal and vertical margin = 4), Rx 11/54 (20.4%). Residual or recurrent tumor in 17/54 (31.5%). Subgroup Barrett esophagus > M3: 35 EMRs in 23 patients, en-bloc-resections 9/35 (25.7%), R0 resections 9/35 (25.7%). Subgroup Barrett esophagus ≤ M3: 19 EMRs in 14 patients, en-bloc-resections 7/19 (36.8%), R0 resections 4/19 (21.1%). Complications: Stenosis 5/54 (9.3%), bleeding 3/54 (5.5%).
ESD: 108 resections in 107 patients, en-bloc resections 104/108 (96.3%), R0 resections 90/108 (83.3%), R1 resections 18/108 (16.7%, horizontal margin = 11, vertical margin = 3, dissection stopped = 4). No recurrent disease after curative resection so far (in 2 patients with R1 resection at the horizontal margin operation was recommended but not performed and local recurrence occurred 3

Abstract number: OP356

	EMR			ESD		
	n	en-bloc-resections	R0-resections	n	en-bloc-resections	R0-resections
EAC total	54	16/54 (29,6%)	13/54 (24,1%)	108	104/108 (96,3%)	90/108 (83,3%)
EAC withinBarrett's > M3	35	9/35(25,7%)	9/35(25,7%)	31	28/31 (90.3%)	21/31 (67,7%)
EAC within Barrett's ≤ M3	19	7/19(36,8%)	4/19(21,1%)	77	76/77 (98,7%)	69/77(89,6%)

months after ESD). Subgroup Barrett esophagus > M3: n = 31, en-bloc-resections 28/31 (90.3%), R0 resections 21/31(67.7%). Subgroup Barrett esophagus ≤ M3: n = 77, en-bloc resections 76/77 (98.7%), R0-resections 69/77 (89.6%). Complications: Stenosis in 12/108 (11.1%) (patients with ESD > 75% circumference), bleeding 1/108 (0.9%).
Conclusion: Our results show the advantage of ESD in terms of en-bloc and R0-resection rate and risk of recurrence. ESD should be considered the treatment of choice in early EAC when en bloc resection seems impossible with other resection techniques.
Disclosure of Interest: None declared

OP357 ENDOSCOPIC SUBMUCOSAL DISSECTION VERSUS LAPAROSCOPIC COLECTOMY FOR EARLY COLONIC NEOPLASM: AN INTERIM ANALYSIS OF A RANDOMIZED CONTROLLED TRIAL

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Introduction: Laparoscopic colectomy (LC) is a widely accepted treatment option for early colorectal neoplasms that are not amenable to *en bloc* endoscopic resection with conventional polypectomy. Endoscopic submucosal dissection (ESD) has emerged as a novel endoscopic procedure that enables resection of large colorectal tumors *en bloc* with low reported complication rate. To date, no randomized controlled trial (RCT) can be found in the literature comparing LC and ESD for early colorectal neoplasms. We report interim analysis of a RCT comparing the short-term clinical outcomes of the two approaches.
Aims & Methods: Consecutive patients diagnosed with early colorectal neoplasms > 2 and < 5 cm in size in the colon without endoscopic signs of massive submucosal invasion were randomized to receive either ESD or LC. Patients in the LC arm were managed using an enhanced recovery protocol. The primary endpoint of this study was short-term morbidity within 30 days after ESD/LC. Secondary outcomes included procedure time, post-ESD/LC recovery, analgesic requirement, hospital stay, and serial C-reactive protein (CRP) levels. Data were analyzed according to the intention-to-treat principle. This study was registered with the ClinicalTrials.gov, number NCT01112046.
Results: Between June 2010 and May 2015, 40 patients were randomized (20 to ESD, 20 to LC). Baseline characteristics did not differ between the two groups. The mean size of the lesions was 3.0 ± 0.9 cm in the ESD group and 2.9 ± 1.0 cm in the LC group ($P = 0.545$). Two lesions in the ESD group and one lesion in the LC group were early T1 adenocarcinoma, while the rest were adenomas. Nineteen out of twenty patients (95%) in the ESD group could achieve an *en bloc* resection. The short-term morbidity was lower in the ESD group than in the LC group (5% *vs.* 20%), but the difference did not reach a statistical significance ($P = 0.342$). The only morbidity in the ESD group was an intraprocedural perforation, which was successfully managed with endoscopic clipping. Comparing with the LC group, the ESD group had significantly shorter procedure time (97.5 *vs.* 162.5 min; $P < 0.001$), earlier time to resume full diet (2 *vs.* 3 days; $P < 0.001$), earlier time to full ambulation (0 *vs.* 2 days; $P < 0.001$), and shorter median hospital stay (3 *vs.* 4 days; $P = 0.001$). No patient in the ESD group required any analgesia, while the LC group required a median dose of 200 mg (range, 0-750 mg) of tramadol as postoperative analgesia. Median CRP level was significantly lower in the ESD group than in the LC group at 2 hours (1.0 *vs.* 2.4 mg/L; $P = 0.040$), 8 hours (3.3 *vs.* 12.9 mg/L; $P = 0.006$), 24 hours (4.2 *vs.* 72.8 mg/L; $P < 0.001$), and 48 hours (5.1 *vs.* 73.9 mg/L; $P < 0.001$) after the procedure. The median follow-up duration in the ESD group was 10 months (range, 4-43 months), and no recurrence was detected on regular endoscopic surveillance.
Conclusion: This interim analysis suggested that ESD was associated with better short-term clinical outcomes in terms of earlier recovery, lower analgesic requirement, shorter hospital stay, and less stress response when compared with LC for early colorectal neoplasms. Short-term morbidity was lower in the ESD group than in the LC group, but the difference did not reach a statistical significance. A larger trial size is required.
Disclosure of Interest: None declared

OP358 COLORECTAL ENDOSCOPIC SUBMUCOSAL DISSECTION IN A EUROPEAN CENTER

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Introduction: Endoscopic submucosal dissection (ESD) is an effective method for en bloc removal of large colorectal tumors in Japan but this technique is not yet widely established in western countries.
Aims & Methods: The aim herein was to report the experience of implementing colorectal ESD in a European center.
Between January 2014 and April 2015 were 287 patients with colorectal lesions larger than 2 cm referred to our center. All patients underwent colonoscopy and 101 patients were judged to be suitable for ESD (colon 48 and rectum 53 cases). The ESD procedures were standardized including consistent use of hood and flush knife. 10 patients had advanced macroscopic cancer and five cases were considered too difficult for ESD and these 15 patients were sent for surgery. The remaining 171 patients underwent endoscopic mucosa resection. Four cases of invasive cancer underwent ESD due to high co-morbidity excluding surgical intervention or as an unexpected finding. 53% of all ESD cases of which 83% and 17% were located in the rectum and sigmoid colon, respectively, were performed as outpatient procedures without hospitalization.
Results: The median age of patients undergoing ESD was 72 years (range 20-95). The median tumor size was 40 mm (range 21-105 mm). En bloc resection rate was 73% and a snare was used after starting the ESD procedure due difficulties or to time-limitation in 23%. In only four cases were the ESD resections incomplete. R0 resection rate was 61% and in 33% was it difficult for the pathologist to judge the resection margins and the remaining 6% were determined R1 resections. All four invasive carcinomas were R0 resections. Five perforations occurred amounting to a perforation rate of 6.1%. Two patients with perforation could be managed conservatively. Three patients with perforation underwent emergency surgery followed by an uneventful recovery. No peroperativ bleeding occurred having any impact on the treatment. Two cases (2%) of postoperative bleeding were managed conservatively but prolonged hospital stay.
Conclusion: This study represents the largest material on colorectal ESD in western countries in the literature and our results confirm that ESD is an effective method for en bloc resection of large colorectal adenomas and early cancers. This study demonstrates that implementation of colorectal ESD is feasible in Europe after proper training, careful patient selection and standardization of the ESD procedure.
Disclosure of Interest: None declared

OP359 ENDOSCOPIC SUBMUCOSAL DISSECTION OF COLORECTAL EPITHELIAL NEOPLASMS USING THE CLUTCH CUTTER IN 220 CONSECUTIVE CASES

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Introduction: The Clutch Cutter (CC) was developed to reduce the risk of complications related to endoscopic submucosal dissection (ESD) using conventional knives. The CC is able to grasp and coagulate and/or incise the targeted tissue using electrosurgical current, like a biopsy technique.
Aims & Methods: The aim of this study was to evaluate the efficacy and safety of ESD using the CC for colorectal epithelial neoplasms. From June 2007 to April 2015, 220 consecutive patients (121 men, 99 women; mean age 69 years, range 42-89) with a diagnosis of adenoma or intramucosal or superficial submucosal cancer without lymph node involvement, that had been confirmed by preliminary endoscopy, EUS, and endoscopic biopsies, were enrolled in this prospective study. The CC was used for all steps of ESD (mucosal incision, submucosal dissection, and hemostatic treatment). The therapeutic efficacy and safety were assessed.
Results: The mean size of the colorectal epithelial neoplasms and resected specimens was 26.7 ± 12.8 mm and 36.1 ± 13.3 mm, respectively. The mean operating time was 89.4 ± 68.9 minutes. The rate of en-bloc resection was 99.1% (218/220), and en-bloc resection with tumor-free lateral/basal margins (R0 resection) was 86.8% (191/220), respectively. The R0 resection rates according to histologic type, tumor size and location were 90.6% (87/96) in adenocarcinoma, 83.9% (104/124) in adenoma; 89.7% (70/78) in 0-20 mm, 86.4% (102/118) in 21-40 mm, 79.2% (19/24) in 41- mm ; 85.5% (53/62) in the rectum, 89.4% (42/47) in the sigmoid colon, 93.3% (14/15) in the descending colon, 90.5% (19/21) in the transverse colon, 78.3% (36/46) in the ascending colon and 93.1% (27/29) in the cecum. The mean operating time according to histologic type, tumor size and location were 85.3 ± 68.6 minutes in adenocarcinoma, 92.5 ± 69.4 minutes in adenoma; 64.9 ± 44.8 minutes in 0-20 mm, 90.3 ± 62.8 minutes in 21-40 mm, 164.1 ± 103.3 minutes in 41- mm ; 76.1 ± 67.7 minutes in the rectum, 80.5 ± 69.4 minutes in the sigmoid colon, 102.8 ± 74.5 minutes in the descending colon, 105.8 ± 71.8 minutes in the transverse colon, 94.8 ± 63.8 minutes in the ascending colon and 104.6 ± 72.1 minutes in the cecum. Perforation occurred in four cases (1.8%), which were managed with conservative treatment including endoscopic closure of the perforation. Post ESD bleeding occurred in 5 cases (2.3%), which were successfully treated by endoscopic hemostatic treatment.
Conclusion: ESD using CC is a safe and technically efficient method for resecting colorectal epithelial neoplasms.

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Disclosure of Interest: K. Akahoshi Conflict with: Patent, Y. Motomura: None declared, M. Kubokawa: None declared, J. Gibo: None declared, N. Kinoshita: None declared, S. Osada: None declared, K. Tokumaru: None declared, T. Hosokawa: None declared, R. Utsunomiya: None declared, A. Miyagaki: None declared, T. Sato: None declared, K. Miyamoto: None declared

WEDNESDAY, OCTOBER 28, 2015 08:30–10:30
MANAGEMENT OF NON-OBSTRUCTIVE DYSPHAGIA – ROOM 7.1

OP360 PERORAL ENDOSCOPIC MYOTOMY FOR ESOPHAGEAL ACHALASIA: OUTCOMES OF THE FIRST 37 PATIENTS IN TURKEY

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Introduction: Per oral endoscopic myotomy (POEM) is a minimally invasive endoscopic treatment option for achalasia patients that has been performed since 2009 and is spreading rapidly around the World. POEM is a less invasive endoscopic approach than Heller myotomy, and the short-term data demonstrate that it offers excellent outcomes that appear to rival those of the laparoscopic Heller myotomy. We present our results of POEM which are the first experiences of Turkey.

Aims & Methods: Between May 2014 and March 2015, 37 patients with achalasia whose complaints recurred after pneumatic balloon dilatation underwent POEM. The procedure was performed at the endoscopy unit in the gastroenterology clinic under general anesthesia by an endoscopist who was experienced at endoscopic submucosal dissection (ESD) and was educated for POEM. Demographic data was recorded before the procedure and results of the procedure were recorded prospectively.

Results: The median age of the patients was 42 (16-72) years. Preoperative and postoperative median Eckardt scores were 10 (6-12) and 0 (0-2) respectively. The median total length of the procedure was 74 (39-158) minutes, tunnel length 17 (13-26) cm and the myotomy length was 14 (10-16) cm. Postoperative oral intake started at median 1 (1-2) day and length of stay was 5 (3-7) days. Capnoperiteneum developed during the procedure in 9 patients and was treated with veress needle. Mucosal injury developed in 2 patients and was carried out endoscopic hemoclips successfully. Four patients had grade A esophagitis at control endoscopy in third month after procedure.

Table: Demographic features and results of POEM procedures

	N = 37
Sex (Male/Female), n	20/17
Age mean (SD) (median; range) year	41.43 ± 14.19 (42;16-71)
Prior achalasia treatment,n (yes/no)	13/24
Achalasia sub-type; Unknown I/ II/ III, n	3/5/27/2
Tunnel length, mean (SD) (median; range) cm	17.81 ± 2.66 (17;13-26)
Myotomy length, mean (SD) (median; range)cm	13.59 ± 2.30 (14;10-19)
Procedure Time, mean (SD) (median; range) min	77.86 ± 22.99 (74; 39-153)
Adverse events, n-Capnoperitoneum-Mucosal injury	92
Veress needle decompression, n(%)	9 (24.3)
Time of oral intake, (median; range) days	1;1-2
Length of hospitalization, (median; range) days	5;3-7
Dysphagia Score, (median; range)PreoperativePostoperative	3;3-40;0-2
Eckardt Score, (median; range)PreoperativePostoperative	10;6-120;0-2

Conclusion: POEM for esophageal achalasia is a novel, safe and effective endoscopic treatment modality in centers that are experienced in advanced endoscopic techniques such as ESD.

Disclosure of Interest: None declared

OP361 INTRAOPERATIVE MEASUREMENT OF ESOPHAGOGASTRIC JUNCTION CROSS-SECTIONAL AREA BY IMPEDANCE PLANIMETRY PREDICTS CLINICAL OUTCOMES OF PEROREAL ENDOSCOPIC MYOTOMY FOR ACHALASIA: A MULTICENTER STUDY

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Introduction: Peroral endoscopic myotomy (POEM) has been introduced as an endoscopic alternative to surgical myotomy. The endoluminal functional lumen imaging probe (endoFLIP) evaluates esophagogastric junction (EGJ) geometry and pressure in response to volume distension in real time via impedance planimetry. It can be used to monitor physiologic changes that occur at EGJ during POEM.

Aims & Methods: The aim of this study was to evaluate whether endoFLIP measurements during POEM can predict postoperative clinical outcomes in terms of symptom relief and development of post procedure reflux. We conducted a retrospective review of achalasia patients who underwent POEM and intraoperative endoFLIP at three tertiary centers. Patients were divided into 2 groups based on clinical response measured by Eckardt Score (ES): good response (ES < 3) or poor response (ES ≥ 3). Post procedure reflux was defined as the presence of esophagitis and/or abnormal pH study. EGJ diameter, cross-sectional area (CSA) and distensibility measured by endoFLIP were compared. The optimal cut-off level of FLIP measurements in predicting clinical response was calculated from receiver operator characteristic (ROC) analysis.

Results: A total of 63 patients (32 male, mean age 48yr) underwent POEM and intraoperative endoFLIP. Of these, 50 (79%) patients had ES < 3 (response group) and 13 patients (21%) had ES ≥ 3 (non-response group) after POEM. There was no significant difference in age, gender, race, BMI, history of previous treatment, preoperative LES relaxation pressure, baseline ES, achalasia subtype and baseline endoFLIP measurements between the two groups. Overall, ES decreased from 7.33 to 1.11 post POEM ($p < 0.001$). Mean LES relaxation pressure (mmHg) decreased from 30.78 to 13.46 ($p < 0.001$). The mean diameter and EGJ CSA significantly increased from 6.57 mm to 10.49 mm ($p < 0.001$) and 36.40 mm^2 to 88.5 mm^2 ($p < 0.001$), respectively. The EGJ distensibility was significantly improved from 1.53 mm^2 /mmHg before myotomy to 4.75 mm^2 / mmHg after myotomy ($p < 0.001$). Comparing the two groups, post operative LES relaxation pressure was significantly lower in the response group (11.79 vs 18.33 mmHg, p 0.03). Post-myotomy CSA was significantly higher in the response group vs non-response group (90.63 vs 70.91 mm^2, p = 0.001). Using ROC curve, the cutoff value of intraoperative EGJ CSA of 80.0 mm^2 yielded sensitivity of 83.3% and specificity of 71% in predicting postoperative response (ES of < 3) with an area under the curve of 0.74. The final EGJ CSA was also significantly higher in patients who had reflux esophagitis after POEM; 99.5 (91.2 – 103.7) mm2 vs 79.3 (57.1 - 94.2) mm^2 ($p = 0.02$).

Conclusion: Intraoperative endoFLIP during POEM for treatment of achalasia is useful in predicting clinical response and post procedure reflux. Impedance planimetry is a potentially important tool to guide the extent and adequacy of myotomy during POEM.

Disclosure of Interest: S. Ngamruengphong: None declared, B. H. A. von Rahden Conflict with: Travel grant, support equipment for POEM procedrure from Karl Storz GmbH Tuttlingen, J. Filser: None declared, A. Tyberg: None declared, A. Desai: None declared, R. Sharaiha: None declared, A. Lambroza: None declared, V. Kumbhari: None declared, M. El Zein: None declared, A. Abdelgelil: None declared, S. Besharati: None declared, J. Clarke: None declared, E. Stein: None declared, A. Kalloo Shareholder: Apollo Endosurgery, M. Kahaleh Financial support for research: Gore, MI Tech, and Pinnacle and Mauna Kea Technologies., Consultancy:, Consultancy: Boston Scientific and Xlumena, M. Khashab Consultancy: Boston Scientific, Xlumena, and Olympus

WEDNESDAY, OCTOBER 28, 2015 08:30–10:30
UPDATE ON NON-ALCOHOLIC STEATOHEPATITIS (NASH) – ROOM E1

OP362 VISCERAL AND PANCREATIC FAT ARE ASSOCIATED WITH LIVER DAMAGE AND ADVERSE METABOLIC PROFILE IN SUBJECTS WITH NON ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

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Introduction: Abdominal adiposity is involved in the hallmark of metabolic syndrome and might be implicated in the onset and development of non alcoholic fatty liver disease (NAFLD). Ectopic fat accumulation in liver, but also in other organs like pancreas, has been indicated as a major risk factor for adverse lipid profile, hyperglycemia and insulin resistance. The aim of this work was to evaluate the impact of visceral, hepatic and pancreatic fat on metabolic alterations, lipid and inflammatory profile and histological liver damage, in patients with proven NAFLD.

Aims & Methods: In 34 non diabetic subjects with biopsy proven NAFLD, and 8 controls, we measured visceral (VF), subcutaneous, pancreatic and hepatic fat by magnetic resonance imaging. Gas chromatography mass spectrometry was used to assess FFAs composition, de novo lipogenesis index (DNL = palmitic/linoleic acid) and unsaturated to saturated fat ratio (PUFA/SFA). By use of tracers we evaluated lipolysis and endogenous glucose production (EGP) and calculated adipose tissue insulin resistance (Adipo-IR = Lipolysis x Insulin) and hepatic insulin resistance (Hep-IR = EGP x Insulin). Histology was scored according to Kleiner.

Results: VF correlated with both hepatic and pancreatic fat ($r = 0.47$ and $r = 32$, $p < 0.05$). Hepatic and pancreatic fat also correlated with each other ($r = 0.41$ $p < 0.05$). in subjects with NAFLD and fibrosis we observed an increase in VF (F1-4 = 2.9 ± 0.2 kg; F0 = 2.0 ± 0.1 kg; CT = 0.7 ± 0.1 kg, $p < 0.03$), hepatic fat (F1-4 = 0.45 ± 0.05; F0 = vs 0.32 ± 0.08; CT = 0.1 ± 0.1) and pancreatic fat (F1-4 = 0.40 ± 0.07; F0 = 0.22 ± 0.07; CT = 0.19 ± 0.03; $p < 0.05$) compared to CT and patients with steatosis but no fibrosis. In general, patients with fibrosis had a worse metabolic profile, with increased Adipo-IR (F1-4 = 8.7 ± 1.0; F0 = 7.4 ± 1.9; CT = 3.6 ± 0.5), Hep-IR (F1-4 = 126 ± 14; F0 = 102 ± 14; CT = 52 ± 6), and HOMA index (F1-4 = 3.4 ± 0.4; F0 = 2.6 ± 0.4; CT = 1.3 ± 0.2, all $p < 0.05$).

Visceral, hepatic and pancreatic fat correlated with metabolic parameters, e.g. 1) hyperinsulinemia, 2) hepatic, adipose tissue and peripheral (i.e., HOMA) insulin resistance and 3) parameters of lipotoxicity, such as increased DNL index and decreased PUFA/SFA ratio. Moreover, patients with higher visceral and hepatic fat showed a pro-inflammatory profile as shown by positive correlation with MCP-1 ($r = 0.51$ and $r = 0.56$; $p < 0.01$) and negative correlation with adiponectin ($r = -0.49$ and $r = -0.53$; $p < 0.001$).

Conclusion: In patients with NAFLD, beside hepatic fat also visceral and pancreatic fat are major risk factors for metabolic derangement. In addition, they are associated with an adverse lipid and inflammatory profile that might contribute to progression of liver disease and increased liver damage.

Reference

1. Funding from the FP7/2007-2013 under grant agreement n°Health-F2-2009- 241762, for the FLIP project, CNR-Interomics.

Disclosure of Interest: None declared

OP363 PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE HAVE HIGH EXPRESSION AND ALTERED DISTRIBUTION OF CAVEOLIN-1 IN HEPATOCYTES

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Introduction: Nonalcoholic fatty liver disease (NAFLD) as the most common chronic liver disease represents an emerging health problem characterized with unresolved pathogenesis. Experimental models implied a possible role of caveolin-1 (cav1) in lipolysis, lipogenesis and pathogenesis of NAFLD.
Aims & Methods: The aim of this prospective study was to determine expression and distribution of cav1 in hepatocytes of NAFLD patients, as well as their relations to pathohistological changes, presence of metabolic syndrome, levels of liver enzymes and ultrasound characteristics. We included 66 biopsy-proven NAFLD patients and 15 controls that underwent liver resection due to non-diffuse liver disease. Pathohistological analysis of collected liver specimens was performed as well as additional immunohistochemical analysis of cav1 expression and distribution in hepatocytes. Low expression of cav1 was addressed for immunoreactivity seen only on basal membrane and high expression if immunoreactivity was seen additionally in cytoplasm of hepatocytes. Cav1 distribution was determinated according to natural course of progression of liver steatosis; immunoreactivity only in zone 3 was marked as unaltered, while periportal or translobular as altered distribution.
Results: In NAFLD patients, cav1 expression was positive in 59 (89.4%) cases while all controls (15 patients) had negative expression of cav1 in cytoplasm of hepatocytes (X^2, $p < 0.001$). Patients with high cav1 expression were younger (Mann-Withney U test, $p = 0.010$) and more often male (X^2, $p = 0.024$) when compared to NAFLD patients with low cav1 expression. Almost 70% (46 patients) of NAFLD patients had altered cav1 distribution and only 6.7% (1 patient) in control group, what was statistically significant (X^2, $p < 0.001$). NASH and NAFL/borderline groups, determinated according to NAFLD Activity score, had similar expression ($p = 0.199$) and distribution ($p = 0.709$) of cav1 in hepatocytes. Patients that had low cav1 expression had more often MS ($p = 0.041$) and detected fasting hyperglycemia ($p = 0.038$). Ones with altered cav1 distribution had wider waist ($p < 0.001$) and thighs ($p = 0.016$) circumference and more often normal blood pressure (X^2, $p = 0.048$).
Conclusion: Expression of caveolin-1 is high and distribution is altered in hepatocytes of patients with NAFLD compared to control group. This study implies the possible role of caveolin-1 in pathogenesis of NAFLD in humans but larger prospective studies are needed to confirm these pivotal results.

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Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 28, 2015 08:30–10:30
SCIENCE INFLUENCING CLINICAL PRACTICE IN BARRETT'S – ROOM E4

OP364 SQUAMOUS CELLULAR CARCINOMA ANTIGEN SERUM DETERMINATION AS A BIOMARKER OF BARRETT'S ESOPHAGUS AND ESOPHAGEAL CANCER: A PHASE III STUDY

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Introduction: The cost/effectiveness of surveillance in patients with Barrett's esophagus (BE) is still debated and the use of biomarkers in screening and surveillance not recommended. No information is available regarding SCCA-IgM determination in BE.
Aims & Methods: The study aimed at evaluating the potential role of the determination of the immunocomplexed form of Squamous Cell Carcinoma Antigen (SCCA-IgM) in screening for BE and in surveillance for esophageal adenocarcinoma (EAC).
SCCA-IgM levels were determined (ELISA) in 231 patients prospectively recruited in our Department among whom 53 with BE, 53 with EAC and 71 controls, including 42 blood donors and 65 patients with gastroesophageal reflux but with no endoscopic/ histologic diagnosis of BE (GERD). The cut-off levels for the determination of SCCA-IgM for BE/EAC versus controls and for Barrett "at risk" (long and/or dysplastic BE) versus BE "at low risk" (short non-dysplastic BE) were calculated by ROC curves. Immuno-staining for SCCA-IgM was obtained in a subgroup of patients.
Results: Median SCCA-IgM values were significantly higher in BE and EAC patients than in GERD ($p < 0.0001$). Patients with SCCA-IgM levels higher than the cut-off calculated on the basis of a ROC curve (91.5% sensitivity, 75.4% specificity, a positive predictive value 85.8%, negative predictive value 84.4%, AUC of 0.799) had a 33 times higher Relative Risk (RR) of harboring BE or EAC ($p = 0.0001$). Patients "at risk" (long or dysplastic BE) had SCCA-IgM levels significantly higher than those with short non-dysplastic BE ($p = 0.035$) and patients with SCCA-IgM above the calculated cut-off (sensitivity 85%, specificity 54%, PPV = 68%, NPV = 76%, AUC = 0.67) had a 15 times higher RR of having Barrett "at risk". SCCA was expressed in BE mucosa but not in cardiac- type gastric metaplasia.
Conclusion: Serum SCCA-IgM determination allows the identification of patients at risk for Barrett's esophagus and esophageal adenocarcinoma and the stratification of Barrett patients in subgroups with different cancer risk. Large, prospective studies are required to confirm this evidence in stage IV biomarker studies.
Disclosure of Interest: None declared

OP365 LONGITUDINAL SINGLE CELL CLONAL ANALYSIS REVEALS EVOLUTIONARY STASIS AND PRE-DETERMINED MALIGNANT POTENTIAL IN NON-DYSPLASTIC BARRETT'S ESOPHAGUS

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Introduction: Carcinogenesis is fundamentally an evolutionary process whereby cells that have acquired advantageous somatic mutations clonally expand via a process of Darwinian natural selection. Surveillance of Barrett's oesophagus allows us to study the evolutionary dynamics of a human neoplasm over time.
Aims & Methods: We used multicolor fluorescence in situ hybridization (FISH) on endoscopic brush cytology specimens collected from 320 non-dysplastic Barrett's patients to study clonal evolution at single cell resolution. For 195 of these patients we also analyzed material from a follow-up endoscopy (median interval 37 months). Patients were followed for a median of 43 months during which 20 patients (6.3%) progressed; 8 patients developed high-grade dysplasia (HGD) and 12 developed oesophageal adenocarcinoma after a median duration of 34 months. All samples were scored for abnormalities by FISH at seven markers including CEP7, CEP17, *p53, p16, Her-2/neu*, *20q*, and *MYC*, organized into two probe sets to measure clonal composition and clonal diversity within the Barrett's segment (i.e. Shannon diversity, Simpson diversity, richness, and average pairwise distance).
Results: Higher levels of clonal diversity at baseline were associated with increased risk of progression to HGD or cancer, this result being largely robust to the choice of diversity statistics, and the FISH probes included in the measure; univariate Cox proportional-hazards analysis showed that out of the 9 statistically significant predictors of progression, 7 were diversity-based, the two others being aneusomy and age (respectively 7th and 8th most significant) and they were still significant after adjusting for age and Barrett's segment length. Baseline genetic diversity remained in a stable dynamic equilibrium over time. Clonal expansions were rare; after correction for multiple testing, binomial analysis revealed 27 statistically significant clonal expansions and 45 clonal contractions over 993.6 patient years of observation, an average of 1 detectable clonal expansion by these methods every 36.8 patient years and 1 clonal contraction every 22.1 patient years. However, clonal expansions were not associated with progression in our cohort.
Conclusion: Our data indicated that the level of clonal diversity measured at baseline in non-dysplastic BE was indicative of progression risk, and that this level of diversity did not change significantly over time. This suggests a lack of strong clonal selection in Barrett's and that the malignant potential of 'benign' Barrett's lesions is predetermined, with important implications for surveillance programs.

Disclosure of Interest: M. Timmer: None declared, P. Martinez: None declared, C. Lau: None declared, S. Meijer: None declared, F. ten Kate: None declared, R. Mallant-Hent: None declared, A. Naber: None declared, A. van Oijen: None declared, L. Baak: None declared, P. Scholten: None declared, C. Böhmer: None declared, P. Fockens: None declared, J. Bergman: None declared, C. Maley: None declared, T. Graham: None declared, K. Krishnadath Conflict with: Dr. Krishnadath has a patent 10999US01 issued.

WEDNESDAY, OCTOBER 28, 2015 08:30–10:30

A TAILORED APPROACH TO ADVANCED RECTAL CANCER – ROOM E2

OP366 CLINICAL OUTCOMES OF RECTAL NEUROENDOCRINE TUMORS AFTER ENDOSCOPIC RESECTION : A KASID MULTI-CENTER STUDY

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Introduction: Recently, an incidental detection of rectal neuroendocrine tumors (NET) is increasing as the rise of diagnostic sigmoidoscopy and/or colonoscopy. However, the clinical outcomes of these tumors, especially after endoscopic treatment, remain elusive.
Aims & Methods: We are aimed to evaluate the long-term clinical outcomes of endoscopically treated rectal NETs through conducting a large, multicenter study.
This study retrospectively analyzed the medical records of patients, who were endoscopically resected rectal NETs and followed for more than 24 months, from January 2000 to November 2011 in 15 university hospitals. End outcomes were determined by assessing local or distant recurrence or metachronous NETs.
Results: Of a total of 405 patients with rectal NETs, the mean tumor size was 5.9 ± 3.2 mm (range 1.0–22.0 mm) and synchronous rectal NETs were noted in four patients. Resection margin status was positive in 82 patients (20.2%) and indeterminate in 72 patients (17.8%). Of them, 15 patients (9.7%) underwent salvage treatment and residual tumors were found in 5 patients. During the follow-up (56.6 ± 34.4 months), 4 patients had local recurrence and there was no recurrence at distal organs. In addition, rectal metachronous NETs were found in 4 patients. In the 8 cases (2.0%) with recurrence or metachronous NETs, a tumor size < 10 mm at initial resection was observed in 6 patients (75%). Tumor size and synchronous rectal NET at diagnosis was a significant predictor for recurrence and metachronous lesion, respectively.
Conclusion: In the rectal NETs after endoscopic resection, recurrence or metachronous NETs are observed in not negligible proportion of cases during the follow-up. Tumor size and synchronous rectal NET at diagnosis is significantly associated with the risk of recurrence and metachronous lesion, respectively.
Disclosure of Interest: None declared

OP367 VE1 (BRAF V600E) IMMUNOHISTOCHEMISTRY IN COLORECTAL CANCER: ASSESSMENT OF ANTIBODY PERFORMANCE, HISTOPATHOLOGY, PROGNOSIS AND HETEROGENEITY IN THREE COLORECTAL CANCER COHORTS

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Introduction: $BRAF^{V600E}$ mutation occurs in approx. 9-12% of colorectal cancers (CRC). In addition to its diagnostic role in Lynch syndrome, $BRAF^{V600E}$ is a prognostic factor in metastatic CRC (and possibly other disease stages) and a potential predictive biomarker for future combined therapies.
Aims & Methods: Here, we validate the VE1 antibody against $BRAF^{V600E}$, assess regional heterogeneity of VE1 in primary and matched metastatic sites and investigate clinicopathological associations and survival in CRC patients stratified by VE1. VE1 immunohistochemistry was performed on eight formalin-fixed and paraffin-embedded CRC cell lines, on whole tissue sections and on a next-generation tissue microarray (ngTMA) of 65 cases including 34 CRCs, 23 malignant melanoma and 8 thyroid cancers, all with known mutational status for BRAF. Inter-observer agreement was assessed by three observers. First, in order to investigate heterogeneity within/among primary cancers and within/among matched distant metastatic lesions, all tumor blocks from 14 CRC patients with synchronous metastases were interrogated for VE1 on an ngTMA (n = 100 areas; 0.6mm cores). Second, prognostic and histopathological questions were addressed using a multiple-punch ngTMA of colon cancers with six cores/tumor (n = 259 patients; 0.6mm cores). Thirdly, preoperative biopsies from 125 surgically treated CRC patients with full clinicopathological and survival/follow-up information were mounted onto an ngTMA (1mm core) and investigated for clinical and histopathological differences.
Results: Using cell lines and the test cohort of 65 cases, VE1 was found to be homogeneously expressed and was 100% concordant with mutational status. Inter-observer agreement was 100%; however all observers assigned incorrect VE1 positivity to a single BRAF wild-type CRC. This tumor showed mucinous histology and patchy, discontinuous staining. Therefore, sensitivity and specificity were 100% and 93%. Evaluating all CRC tumor blocks from each case, primary CRC showed no heterogeneity. Four cases had $BRAF^{V600E}$ in primary cancers that were found in the corresponding metastatic lesions. VE1-positivity correlated with older age ($p = 0.0455$), mucinous histology ($p = 0.0277$), right-sided location ($p = 0.001$), tumor grade ($p < 0.001$), MLH1-deficiency ($p < 0.0001$), and poor prognosis in pM1 patients ($p < 0.0001$).
Conclusion: VE1 is highly specific and sensitive for $BRAF^{V600E}$. Results from the application on human tumor samples suggest that $BRAF^{V600E}$ mutation is not acquired during the metastatic process. Positive VE1 correlates with expected clinicopathological features associated with $BRAF^{V600E}$. Because of homogeneous expression throughout the tumor samples, TMA studies using VE1 are reliable.
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 28, 2015 08:30–10:30

COLORECTAL CANCER: BIOMARKERS AND SCREENING – ROOM E3

OP368 SIGNIFICANT RISK OF POST-COLONOSCOPY COLORECTAL CANCER DUE TO INCOMPLETE ADENOMA RESECTION - RESULTS OF A NATION-WIDE POPULATION-BASED COHORT STUDY

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Introduction: Resection of adenomas detected during colonoscopy decreases the risk of subsequent colorectal cancer (CRC). It does however not preclude the occurrence of CRC within a few years after colonoscopy. Many of these post-colonoscopy CRCs (PC-CRCs) are preventable, as they are thought to be due to missed or incompletely resected adenomas.
Aims & Methods: The aims of this study were to assess the overall incidence rate of PC-CRC in patients with one or more adenomas, to determine the risk of PC-CRC due to incomplete adenoma resection, and to identify adenoma characteristics associated with a high risk of PC-CRC due to incomplete adenoma resection. We performed a population-based cohort study identifying all patients with a first colorectal adenoma between 2000 and 2010 in PALGA, the nationwide Dutch Pathology Registry. Outcomes were the incidence rate of PC-CRC overall and of PC-CRC due to incomplete adenoma resection, defined as the occurrence of CRC between 6 months and 5 years after adenoma removal in the same colon segment. We performed a multivariable cox proportional hazard regression analysis to identify adenoma-related factors associated with both outcomes.
Results: During the study period, 119,233 patients were diagnosed with a first adenoma. Mean age was 64.0 years (standard deviation 12.8) and 53.9% were male. We excluded 11,489 patients in whom prevalent CRC was found (CRC before or within 6 months after the first adenoma). Of the remaining 107,744 patients, 1031 (0.96%) developed PC-CRC anywhere in the colon within 5 years (incidence rate 1.9/1000 person years). PC-CRC due to incomplete adenoma resection occurred in 324 of 133,519 adenomas (0.24%). Mean follow up per adenoma was 4.4 years (SD 1.1). The incidence rate of CRC due to incomplete adenoma resection was 0.6 per 1000 years of follow up. High-grade dysplasia (hazard ratio (HR) 2.54, 95% confidence interval (CI) 1.99-3.25), villous (HR 2.63, 95% > CI 1.79-3.87) and tubulovillous histology (OR 1.80, 95% > CI 1.43-2.27) were risk factors for PC-CRC due to incomplete adenoma resection.
Conclusion: In this nationwide cohort, PC-CRC due to incomplete endoscopic resection occurred in one in four hundred adenomas and even more frequently in adenomas with high-grade dysplasia and villous or tubulovillous components. Our results suggest that enhanced surveillance is indicated after removal of adenomas with high-grade dysplasia or villous components.
Disclosure of Interest: None declared

OP370 CIRCADIAN CHANGES IN CELL-FREE DNA AMOUNT, METHYLATED SEPTIN 9 AND TUMOR MARKERS IN PATIENTS WITH COLORECTAL CANCER

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Introduction: Methylated Septin 9 (SEPT9) is a sensitive and specific blood-based biomarker for colorectal cancer (CRC). However, its circadian rhythm and the relationship to the circadian cycle of cell-free DNA (cfDNA) amount and blood-based tumor markers have not been described yet. Therefore the aim of this study was to compare the circadian rhythm of SEPT9 with the cycle of cfDNA amount and the nowadays used blood-based tumor markers, such as CEA, AFP, CA19-9, TPA and CA72-4.

Aims & Methods: Plasma samples were collected four times a day (06:00, 12:00, 18:00 and 0:00) from 9 patients with CRC (5 with Stage I-II and 4 with Stage III-IV), from one with adenoma and from one healthy control. CfDNA was isolated from 3.5 ml plasma and bisulfit-converted using Epi proColon Plasma Quick Kit and methylated SEPT9 was detected by Sensitive PCR kit (Epigenomics AG). Cell-free DNA was extracted additionally with High Pure Viral Nucleic Acid Large Volume Kit (Roche) and measured by Qubit dsDNA HS Assay (Life technologies). Tumor markers (CEA, AFP, CA19-9 and CA72-4) were measured from plasma samples, as well.

Results: The lowest cfDNA amounts (mean 16.5 ng/ml) were observed out of the 4 times measurements at 0:00 in 83.3% (5/6) of Stage I-III patients. In Stage IV samples this low level (mean 41.1 ng/ml) was observed in other times of the day (6:00, 12:00 and 18:00). Within each stage, the highest cfDNA levels (mean 32.6 ng/ml) were measured at 6:00 and 12:00 in CRC I-III Stages and at 0:00 in Stage IV samples (mean 138.9 ng/ml). Comparing the cfDNA changes, higher differences were found in higher CRC stages (48%) than Stage I (22%). In normal control plasma, although cfDNA showed the lowest level (mean 14.3 ng/ml) compared with others, it showed a circadian rhythm and SEPT9 negativity at the same time. At 0:00, all cancer (100%) and adenoma cases were positive for SEPT9 methylation. At other times (6:00, 12:00 and 18:00) only 77.7% of CRC samples showed SEPT9 positivity. Stage I cancer samples were SEPT9 positive only at 0:00. Interestingly, the highest SEPT9 methylation level was found at 0:00 in most CRC cases. In 7 of 6 advanced tumors (Stage II-IV) highest DNA level and SEPT9 methylation showed high correlation. The cycle threshold (CT) level was altered by 3.2 CT values in Stage II, 2.5 CT values in Stage III and 1.9 CT values in Stage IV during 24 hours. In Stage I, SEPT9 was methylated only at 0:00. The level of tumor markers correlates with the amount of cfDNA during the four times measurement. Changes of CEA differences between Stage I-IV were 9-21%. This difference was 17-22% in AFP, 13-23% in CA19-9, 23-44% in TPA and 6-12% in CA72-4 markers.

Conclusion: In cases with low amount of cfDNA, such as adenoma and early stage cancer (Stage I), the time of blood draw for SEPT9 detection as CRC screening is essential, since positive results were measured only in the early hours. Contrarily, in CRCs from Stage II, SEPT9 methylation can be determine confidently, however it still follows a circadian rhythm.

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Disclosure of Interest: None declared

OP371 INCREASED DETECTION OF COLORECTAL CANCER WITH A COMBINATION FAECAL AND BLOOD SCREENING TEST

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Introduction: Screening with a faecal occult blood test (FOBT) leads to early detection and decreased mortality from colorectal cancer (CRC). In practice, however, FOBT screening programs have uncovered a number of challenges including relatively low compliance rates in some studies. Different types of tests may increase screening participation. Surveys suggest that people would prefer to complete a combination screening test involving a FOBT and a blood test if it had higher accuracy than the standard tests (1).

Aims & Methods: The aim of this study was to determine the CRC detection rate with a screening test combining a FOBT with a blood test, compared to FOBT alone.

Patients who were scheduled for colonoscopy completed a immunochemical FOBT (faecal immunochemical test (FIT), one sample, OC Sensor, Eiken) within two weeks of the colonoscopy, followed by a CRC blood test (Colovantage Plasma, Clinical Genomics) immediately before colonoscopy. FITs were analysed for haemoglobin content, and samples with $\geq 10\mu g$ haemoglobin/g faeces were deemed positive. Plasma was assayed for methylated *BCAT1* and *IKZF1* DNA, with the detection of either methylated gene considered positive. Colonoscopy and pathology reports were assessed and clinical parameters associated with test positivity were evaluated.

Results: The primary colonoscopy diagnosis in the 1381 people who completed both tests included cancer (4.8% of cases), high-risk adenoma (defined as the presence of adenoma with villous or serrated morphology, $\geq$10mm, high-grade dysplasia, or more than two tubular adenomas; 13.7%), low-risk adenoma (18.8%) and no neoplasia found (62.8%). The FIT was positive in 309 patients, and detected 78.8% of the cancers (52/66) and 42.3% of the high-risk adenomas (80/189). The specificity of the FIT in the cases without significant neoplasia was 84%. In the FIT-negative patients, the blood test detected an additional 7 cancers and 8 high-risk adenomas. These additional cancers were more likely to have lymphovascular invasion than cancers positive for FIT alone (50% vs 11%, $p = 0.04$), with a slightly higher prevalence of these cancers in males (85.7% vs 55.6%). The combined test sensitivity (for either test positive) was 89.4% for CRC and the specificity was 77.8%. Cases with CRC that were positive for both tests (34/61) had a relative risk of 23.0 for cancer when compared to those cases without a double positive result.

Conclusion: Combining FIT and blood test increased sensitivity over either test alone using an "either or" rule. Cancer cases positive by the blood test alone appeared to be phenotypically different to FIT positive cancers, which might have implications for therapy.

Reference

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Disclosure of Interest: E. Symonds: None declared, S. Pedersen Shareholder: Employed by Clinical Genomics Pty Ltd., R. Baker Shareholder: Employed by Clinical Genomics Pty Ltd., G. Gopalsamy: None declared, D. Worthley: None declared, D. Murray Shareholder: Employed by Clinical Genomics Pty Ltd., P. Bampton: None declared, R. Fraser: None declared, S. Cole: None declared, L. LaPointe Shareholder: Employed by Clinical Genomics Pty Ltd., G. Young Financial support for research: This work was co-funded by Clinical Genomics Pty Ltd., Consultancy: G Young is a paid consultant of Clinical Genomics Pty. Ltd

OP372 NEW VOLATILE MARKER TEST TO DETECT COLORECTAL LESIONS

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Introduction: An ideal colorectal cancer (CRC) screening test would identify not only cancer but also high-risk colonic adenomas. There is still a space to improve the performance of non-invasive tests for CRC screening. Volatile marker tests based on nanoarray sensor technologies are presenting an attractive approach for screening and wide population-based applications being non-invasive, easy-to-use and low-cost diagnostic tools.

Aims & Methods: The study was aiming to investigate the feasibility of CRC and adenoma detection by measuring volatile organic compounds (VOCs) in the exhaled breath.

Alveolar exhaled breath samples were collected from 71 CRC patients, 13 patients with non-advanced adenomas (NAA), 10 – with high-risk adenomas (HRA), and 131 control patients. VOCs in the exhaled breath were measured by two different **Methods:** 1) gas chromatography coupled to mass-spectrometry (GCMS) and 2) cross-reactive nanomaterial-based sensor technology by using gold nano-particles and single-wall carbon nanotube combined with a pattern recognition method. For the latter approach classification success was calculated by (i) building an algorithm for 70% of the samples as a training set and (ii) randomly blinding 30% of the samples as a validation set.

Results: GCMS analysis revealed 5 VOCs having significant differences between the groups; these were ethanol, acetone, ethyl acetate, 4-methyl octane, and styrene.

The nanoarray analysis made it possible to differentiate CRC from the control group (validation set) with 85% sensitivity, 90% specificity, and 88% overall accuracy. Similarly good performance was demonstrated to detect adenomas, and differentiate between high- and low-risk lesions, although the small group size has to be mentioned as the limitation (see Table for details).

The table below is demonstrating the performance characteristics of nanomaterial-based sensor technology to detect colorectal cancer and adenomas.

	Sensitivity	Specificity	Accuracy
CRC (63) vs. controls (131)	85%	90%	88%
CRC (16) vs. Adenomas (16)	94%	88%	91%
Controls (16) vs. Adenomas (16)	94%	94%	94%
NAA (8) vs. HRA (8)	100%	88%	94%

CRC – colorectal cancer; NAA – non-advanced adenomas; HRA – high-risk adenomas

Conclusion: There is a good potential of VOC detection in exhaled breath by nanoarray sensor technology in diagnosing CRC and colonic adenomas. This testing approach should be further validated in CRC screening settings.

Disclosure of Interest: None declared

OP373 METFORMIN EFFICACY AND SAFETY FOR COLORECTAL POLYPS: A DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL

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Introduction: Colorectal cancer is one of the major neoplasms and a leading cause of cancer death worldwide, and new preventive strategies are needed to lower the burden of this disease. Metformin, a biguanide, which is widely used for treating diabetes mellitus, has recently been suggestive to have a suppressive effect on tumorigenesis and cancer cell growth. In a previous study conducted in non-diabetic subjects, we showed that oral short-term low-dose metformin suppressed the development of colorectal aberrant crypt foci (ACF). ACF have been considered as a useful surrogate biomarker of CRC, although the biological significance of these lesions remains controversial. We conducted a prospective randomized controlled trial to evaluate the chemopreventive effect of metformin against metachronous colorectal polyps and the safety of this drug in non-diabetic post-polypectomy patients.

Aims & Methods: This study is a multi-center, double-blind, placebo-controlled, randomized controlled trial to be conducted in non-diabetic patients with a recent history of undergoing colorectal polypectomy. All adult patients visiting the Yokohama City University hospital or affiliated hospitals for polypectomy was recruited for the study. Eligible patients were allocated randomly into either one of two groups: the metformin group and the placebo group. Patients in the metformin group received oral metformin at 250 mg per day, and those in the placebo group received an oral placebo tablet. At the end of 1 year of administration of metformin/placebo, colonoscopy was performed to evaluate the polyp formation.

Results: A total of 150 subjects were enrolled the study and allocated randomly into two group. The number of polyps (hyperplastic polyp and adenoma) at 1 year after the treatment was significantly lower in the metformin group in comparison with that in the placebo group (27/70 (38.6%) vs. 36/64 (56.3%), $p = 0.041$). Metformin at a low dose of 250 mg/d did not produce any severe side effects, including lactic acidosis, hypoglycemia, in this 1-year study.

Conclusion: This is the first study to explore the effect of metformin against colorectal polyp formation. Metformin activates AMPK, which inhibits the mammalian target of rapamycin (mTOR) pathway. The mTOR pathway plays an important role in the cellular protein translational machinery and cell proliferation. Patients with type 2 diabetes taking under treatment with metformin have been reported to be at a lower risk of cancer development than those not taking under treatment with metformin. We showed in this study that metformin suppressed the formation of metachronous colorectal polyps. Metformin has potential the colorectal cancer chemoprevention. Further study is needed.

Disclosure of Interest: None declared

OP374 THE MANAGEMENT OF MALIGNANT POLYPS IN COLORECTAL CANCER SCREENING PROGRAMS: AN ITALIAN MULTICENTRE SURVEY

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Introduction: Recognition of colorectal malignant polyps is increasing, mainly due to the diffusion of screening programs.

Although more and more information are being gathered regarding their management, treatment plans lack the evidence of randomized trials and still rely on observational studies, with high variability in clinical behaviour.

In 2012, a European panel has issued new guidelines in colorectal cancer (CRC) screening and diagnosis, including an update in histologic reporting [1].

Aims & Methods: We carried out a survey on all malignant polyps detected during CRC screening programs at 5 centres of North-Eastern Italy.

In all participating centres the followed protocol implies a colonoscopy in subjects aged 50-69 years of both sexes, who tested positive at immunochemical faecal occult blood test.

Cases diagnosed before the introduction of new histologic guidelines were reviewed by specialized pathologists

Results: In the period 2008-2013 306 malignant polyps were observed in 306 patients at 5 institutions located in the Veneto/Trentino region (Trento, Rovereto, Bassano del Grappa, Padova – Sant'Antonio Hospital, Feltre).

63% of patients were males. Mean age was 62.6 years (range 50-69).

The site distribution of the lesions was the following: rectum 24.3%, left colon 56.1%, right colon 19.6%.

72 patients (23.6%) were sent to direct surgery. 234 received an endoscopic treatment. 56.8% of them were sent to post-polypectomy radicalization surgery, and 12.8% of those had evidence of residual disease. As regards method of endoscopic treatment, an en bloc resection has been performed in 75.5% of cases. Involved, unsafe (<1mm) or invaluable resection margins and sessile morphology represented the most frequent determinants in the decision of subsequent surgery.

The mean number of lymph-nodes harvested during direct surgery was 9.6, whereas in the post-polypectomy surgery the mean number was 7.1 ($p = 0.027$, Student T test).

During a mean follow-up of 44 months (range 24-54), no recurrence of disease was diagnosed in endoscopically-treated population; 3 recurrences (2 cases of distant metastases and one case of lymph-nodal involvement) were observed in the high-risk population sent to radicalization surgery.

A histologic second opinion was acquired in 125 cases (53% of endoscopic resected lesions) and led to a change in the patient risk class in 18 cases (14.4%). 9 patients shifted from low to high risk class, 9 from high to low.

Conclusion: Although our rate of surgical treatment following endoscopic resection complies with other series, the rate of residual disease at surgery lies below the majority of international experiences.

Therefore, bearing in mind the potential risk of overtreatment in these patients, and given the fact that the lack of margin evaluation (mainly related to specimen fragmentation) has proved to be a frequent cause of attribution to high risk class, resection/handling of the lesion should be a major concern for endoscopists.

Finally, we believe that adhering to new histological reporting system and respecting guidelines on lymph-node harvesting (which recommend the resection of at least 12) may help in positively influencing the patient's prognosis.

Reference

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Disclosure of Interest: None declared

OP375 VALIDATION OF A SCORING SYSTEM TO PREDICT PROXIMAL NEOPLASIA FOR COLORECTAL CANCER SCREENING: A PROSPECTIVE STUDY

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Introduction: Flexible sigmoidoscopy (FS) and colonoscopy are two commonly used screening modalities. The risk of proximal neoplasia (PN) could influence the choice between these two screening tests. FS is now more popularly perceived, especially in European countries – following the publication of findings from landmark randomized trials.

Aims & Methods: This study developed a clinical scoring system to predict the risks of proximal neoplasia (PN), irrespective of the presence of distal neoplasia. Neoplasia include adenoma and advanced neoplasia, but not hyperplastic polyps. "Proximal" refers to a location in the colon which is proximal to the splenic flexure; whilst "distal" refers to the rectum, sigmoid and descending colon. We prospectively recruited 5,789 Chinese asymptomatic screening participants who received colonoscopy in Hong Kong (2008-2014). From random sampling of 2,000 participants, the independent risk factors were evaluated for PN using binary regression analysis. The odds ratios for these factors were used to develop a scoring system. The score range is 0-3 with two categories: 'average risk' (AR): 0-1 and 'high risk' (HR): 2-3. The other 3,789 screening participants formed an independent validation cohort. Each subject was scored based on their risk factors, and we evaluated the performance of the scoring system devised.

Results: The proportion of PN in the derivation and validation cohorts was 17.4% and 17.5%, respectively. According to the adjusted odds ratios from the derivation cohort, the following predictors of PN were used to assign scores to each subject: age 50-55 years (0), 56-70 (1), male gender (1), female gender (0), BMI < 25 kg/m^2 (0), BMI ≥ 25 kg/m^2 (1). Based on age, gender, and body mass index, 54% and 46% in the derivation cohort were classified as AR and HR, respectively. Among all subjects, the prevalence of PN in the AR and HR groups was 12.8% and 22.9%, respectively. Participants in the HR group had 1.67-fold (95% CI = 1.45 to 1.92, $p < 0.001$) increased risk of PN compared to the AR group (Table 1). The Hosmer-Lemeshow goodness-of-fit statistic evaluating the reliability of the validation sets had p values of 0.381, indicating a close match between predicted risk and real risk.

Conclusion: The scoring system bears potential to predict the risk of PN. It is anticipated that its use in clinical practice could assist physicians to risk stratify subjects for colorectal cancer screening, and offer an informed choice between FS and colonoscopy based on individual risk of PN. Future research should evaluate

Abstract number: OP375 Table 1: Prevalence of proximal neoplasia by risk tier

Derivation cohort			Validation cohort		
Risk Tier(Risk Score)	**No. of Subjects (%)**	**ProximalNeoplasia* (%)(95% CI)**	**No. of Subjects(%)**	**ProximalNeoplasia(%)(95% CI)**	**RelativeRisk(95% C.I.)**
Average Risk(0-1)	1,051(54.0)	120 (11.4)(9.6-13.5)	2,149(56.6)	288 (13.4)(12.0-14.9)	1.00
High Risk(2-3)	895(46.0)	212 (23.7)(21.0-26.6)	1,651(43.4)	370 (22.4)(20.4-24.5)	**1.67(1.45-1.92)P < 0.001**
Total	1,946 (100)	332 (17.1)(15.4-18.8)	3,800(100)	658 (17.3)(16.1-18.6)	

the scoring system in other countries with different ethnicity. The projected cost-effectiveness, acceptability, and practicality to implement this prediction tool in screening practices should be further addressed.
Disclosure of Interest: None declared

OP376 THE FAS (FECAL HEMOGLOBIN CONCENTRATION, AGE AND SEX) MODEL: DEVELOPMENT AND EXTERNAL VALIDATION OF A SIMPLE PREDICTIVE MODEL FOR COLORECTAL CANCER DETECTION IN SYMPTOMATIC PATIENTS

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Introduction: Predictive models for colorectal cancer (CRC) detection in symptomatic patients are based on subjective clinical criteria with low diagnostic accuracy. Simple to calculate predictive models based on easy to obtain objective variables are required.
Aims & Methods: The COLONPREDICT study is a prospective blind diagnostic test study aimed at developing a CRC predictive model in symptomatic patients. Fecal hemoglobin concentration was measured in the1572 patients included (CRC prevalence: 13.7%). We stratified fecal hemoglobin concentration into four groups; 0, 1-19.9, 20-199 and ≥200 μg Hb/g feces to build this model. A simpler predictive model (FAS) for CRC detection based on Fecal hemoglobin concentration, Age and Sex was developed using binary logistic regression. The validation cohort consisted of 1035 patients included in two studies done in Scotland, a pilot study (FITS) involving 280 patients (6 CRC) presenting in primary care with symptoms, a larger follow-up study (FITS+) with 755 individuals (28 CRC) and a third study performed in Barcelona (Bellvitge) involving 1030 patients (30 CRC). Fecal hemoglobin concentration was determined in all studies with the OC-Sensor®. We compared the diagnostic accuracy between initial and validation cohorts with ROC curves and AUC. At pre-established sensitivity thresholds in the initial cohort (90% and 99%), we determined if there were differences in the sensitivity and specificity between initial and validation cohorts with the Chi-square test.
Results: The Odds Ratio of the variables included in the FAS model were: age (year) 1.03 (95% confidence interval, CI: 1.02-1.05); male sex 1.6 (95% CI: 1.1-2.3); fecal hemoglobin concentration 1-19.9 2.0 (95% CI: 0.7-5.5); 20-199 16.8 (95% CI: 6.6-42) and ≥ 200 μg Hb/g feces 65.0 (95% CI: 26-164). The AUC of FAS model was 0.87 (95% CI: 0.85 to 0.90) in the initial cohort and 0.92 (95% CI: 0.89 to 0.94) in the overall validation cohort ($p = 0.01$). The overall diagnostic accuracy was increased in FITS (0.95, 95% CI: 0.92-0.99; $p < 0.001$) and Bellvitge studies (0.94, 95% CI: 0.91-0.97; $p = 0.001$) cohorts. However, no differences were found with the FITS+ cohort (0.89, 95% CI: 0.93-0.94; $p = 0.6$). At the pre-established FAS model cut-off yielding 90% sensitivity (B coefficient: 4.5), no differences in sensitivity were found between initial (89.8%) and validation cohorts, both globally (87.5%; $p = 0.6$) or separately (FITS 100%; $p = 1.0$, FITS+ 82.1%; $p = 0.2$, Bellvitge 90.0%; $p = 1.0$). However, specificity was superior in the validation cohort (initial 71.3%, validation 85.9%, FITS 86.8%, FITS+ 85.4%, Bellvitge 87.5%; $p < 0.001$). At the pre-established cut-off with a 99% sensitivity (B coefficient: 2.12), the sensitivity in all the cohorts was 100%. In contrast, the specificity in the initial cohort was inferior (initial 13.9%, validation 22.1%, FITS 25.2%, FITS+ 26.3%, Bellvitge 25.2%; $p < 0.001$).
Conclusion: FAS is a simple method to calculate CRC predictive model from easily obtainable variables. Although we found differences in specificity, its sensitivity is similar in different settings and transferable over geography.
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 28, 2015 08:30–10:30
UPPER GI CANCER: MANAGEMENT PERSPECTIVES – ROOM E5

OP377 THE EFFECT OF HELICOBACTER PYLORI ERADICATION ON METACHRONOUS GASTRIC CANCER AFTER ENDOSCOPIC SUBMUCOSAL RESECTION

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Introduction: There are many epidemiologic studies about prophylactic effect of *Helicobacter pylori* (*H. pylori*) eradication on metachronous gastric cancer after endoscopic resection in patient with early gastric cancer. However, their results are controversial. We performed the study to evaluate whether *H. pylori* eradication could reduce the occurrence of metachronous gastric cancer after endoscopic submucosal dissection (ESD) in patient with early gastric cancer.
Aims & Methods: Between November 2005 and August 2013, the patients who were treated by ESD for early gastric cancer were enrolled (n = 484), and the follow-up data was reviewed retrospectively.
Results: We divided patients into three groups: those without *H. pylori* infection(n = 336), those who successfully underwent *H. pylori* eradication (n = 88), those who failed or didn't take *H. pylori* eradication (n = 60).
Metachronous recurrence was diagnosed in 20 patients (4.1%) in all patients, including 15 (4.5%) in the *H. pylori*-negative group, 3 (3.4%) in the eradicated, and 2 (3.3%) in the non-eradicated groups. Median time to metachronous recurrence was 30.1 months (range, 2 – 71 months). The odds ratio in the non-eradicated group compared with the *H. pylori*-negative and eradicated groups were 1.355 (P value = 1, 95% CI = 0.302 – 6.083) and 1.024 (P value = 1, 95% CI = 0.166 – 6.317), respectively.
H. pylori eradication didn't reduce metachronous recurrence of early gastric cancer. The risk factor of subsequent gastric metachronous cancer was a degree of mucosal atrophy. Odds ratio was 4.273 between the mild to moderate mucosal atrophy group and severe mucosal atrophy group. (P value = 0.002)
Conclusion: *H. pylori* eradication doesn't have prophylactic effect about the occurrence of metachronous gastric cancer after endoscopic resection in patients with early gastric cancer. And the risk factor of metachronous gastric cancer is the degree of mucosal atrophy.
Disclosure of Interest: None declared

OP378 THE PREDICTIVE INDICATORS FOR METASTASIS IN NON-AMPULLARY DUODENAL NEUROENDOCRINE TUMORS MEASURING 20 MM OR LESS IN GREATEST DIMENSION: A RETROSPECTIVE MULTICENTER STUDY

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Introduction: The algorithm of treatment (i.e., endoscopic resection (ER) or surgical resection) of non-ampullary duodenal neuroendocrine tumors (NAD-NETs) usually depends upon the size of the lesions. ER is generally recommended for NAD-NETs < 10 mm in diameter, but the clinical algorithm of proceeding to the additional treatment following ER has not been established. In addition, the treatment strategy for NAD-NETs of 10–20 mm in diameter has not been determined either.
Aims & Methods: In this study, we aimed to evaluate the detailed clinicopathological characteristics of NAD-NETs measuring ≤20 mm in diameter to clarify the predictive indicators of subsequent metastasis. The patients with NAD-NETs ≤20 mm in diameter treated at 12 institutions between May 1992 and April 2013 were enrolled in this retrospective study. Those with follow-up periods of < 24 months, unless metastasis was clinically identified, were excluded. Clinical records were retrieved, and histopathological findings of all cases were centrally reviewed by two expert pathologists who were blinded to any clinical information. We then analyzed the predictive indicators of metastasis using univariate analysis. As for independent variables, age (≤60 and > 60 years), gender, the number of the tumor (single and multiple), the presence of functional or hormonal syndrome, multiple endocrine neoplasia type 1, tumor size (≤10 and 11–20 mm), depth of the tumor invasion (confined to submucosa, and muscularis propria or deeper), World Health Organization (WHO) grade (G1 and G2), lymphovascular invasion, and peptide hormone and amine products were evaluated as categorical variables in this study.
Results: We could study 49 patients with a mean follow-up period of 66.5 months. There were 7 lymph node metastases (14.3%) and 3 distant metastases (6.1%). Thirty-five patients were initially treated with ER, and 14 with surgery. Correlation coefficient for Ki67 index and mitotic index obtained by two pathologists were extremely high, 0.9967 and 1.0, respectively. A univariate analysis revealed that the predictive indicators for metastasis were lymphovascular invasion (odds ratio [95% confidence interval] = 12.5 [2.01-77.9]; $P = 0.007$), multiple tumors (9.75 [1.46-65.4]; $P = 0.019$), a tumor size of 11–20 mm (6.67 [1.21-36.6]; $P = 0.029$), and WHO grade G2 (7.13 [1.16-43.9]; $P = 0.034$). Five-year overall and disease-specific survival rates were 86.1% and 97.2%, respectively. NAD-NETs were demonstrated to have immunoreactivity for gastrin, somatostatin, and serotonin in 75.5%, 36.7%, and 40.8% of the cases, respectively, but only 4 cases had a functional syndrome (Zollinger-Ellison syndrome).
Conclusion: This is the first study to demonstrate that the predictive indicators of metastasis in NAD-NETs ≤20 mm in diameter were lymphovascular invasion, multiple tumors, a tumor size of 11–20 mm, and WHO grade G2. These findings could provide clinically important information for determining the appropriate therapeutic approach and the clinical strategy of treatment following ER.
Disclosure of Interest: None declared

OP379 RANDOMISED TRIAL OF POST-DISCHARGE ENTERAL FEEDING FOLLOWING SURGICAL RESECTION OF AN UPPER GASTROINTESTINAL MALIGNANCY

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Introduction: Patients undergoing upper gastrointestinal surgery often eat poorly post operatively, despite dietetic input. The benefit of nutritional supplementation following hospital discharge is unknown. We examined the benefit of 6 weeks nutritional supplementation, via the patients feeding jejunostomy, on fatigue, quality of life and independent living.

Abstract number: OP379

	Energy %*		MFI-20^		EQ5D^		QLQ-OES18+	
	Active	Control	Active	Control	Active	Control	Active	Control
Discharge	58 (54,74)	65 (55,80)	42 (34,58)	58 (42,65)	10 (9,12)	12 (10,13)	35 (28,39)	27 (25,30)
3 weeks	114 (96,127)	79 (67,96)	47 (39,62)	60 (37,72)	12 (10,13)	12 (12,14)	32 (27,38)	30 (25,34)
6 weeks	117 (99,127)	75 (63,84)	64 (51,71)	67 (57,79)	12 (12,13)	13 (12,14)	29 (25,36)	29 (24,30)
12 weeks	72 (58,93)	101 (82,114)	62 (48,77)	66 (53,78)	12 (11,14)	14 (13,14)	30 (26,36)	30 (26,32)
24 weeks	78 (70,99)	81 (68,97)	61.9 (58,73)	66.4 (66,73)	13 (12,15)	15 (14,14)	29 (24,30)	28 (27,28)

*Percentage of calculated energy requirements taken^High score good, +Low score good

Aims & Methods: Patients undergoing oesophagectomy/gastrectomy for cancer had a feeding jejunostomy placed routinely at surgery. Jejunal feeding was instituted postoperatively. If jejunal feeding was tolerated at discharge consenting patients were randomly allocated (stratified by gastric/oesophageal) to nutritional supplementation (600Kcal/day) via their feeding jejunostomies or no jejunal supplement. All patients received oral supplements and dietetic input. Patients were assessed at discharge and 3, 6, 12 and 24 weeks following discharge for fatigue (MFI-20), quality of life (EORTC QLQ-OES18), health economic analysis (independent living: EQ5D) as well as completing 2 day dietary diaries. Results were analysed non-parametrically (Mann-Whitney) and data presented as medians with interquartile ranges.
Results: 44 patients (M:F 29:15) were randomised, 23 received jejunal supplements. There was no difference between the groups in age, sex, neo-adjuvant chemotherapy, ASA grade, type of operation, operative time, blood loss, length of hospital stay, and inpatient complications.
Percentage of calculated energy requirement actually received was greater in the supplemented group at weeks 3 and 6 ($p < 0.0001$). Jejunal supplementation did not suppress oral energy intake. There was no difference between the two groups for oral energy intake at any time period. No complications were seen from jejunal feeding in the community.
After hospital discharge, scores for MFI-20, EQ5D and EORTC QLQ-OES18 were not different between groups at any time point. From hospital discharge fatigue improved and plateaued at 6 weeks ($p < 0.05$ for both groups), independence at 12 weeks ($p < 0.05$ for both groups) but no improvement was seen in quality of life until 24 week in the active group alone ($p < 0.02$) and not at all in the control group.
Conclusion: Dietary intake following hospital discharge after oesophageal or gastric surgery is poor. Addition of jejunal feeding over and above dietary advice and sip feeds is effective in providing patients with an adequate energy intake. Increased energy intake however, produced no obvious improvement in measures of fatigue, quality of life or health economics. Interestingly improvement in fatigue and independence plateaued by 12 weeks whilst there was little evidence of improvement in quality of life at 24 weeks.
Disclosure of Interest: None declared

OP380 LONG-TERM OUTCOME OF MINIMALLY INVASIVE TREATMENT OF EARLY GASTRIC CANCER BEYOND ENDOSCOPIC SUBMUCOSAL DISSECTION

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Introduction: The prognosis of early gastric cancer chiefly depends on the presence of lymph node metastasis, which has been reported at rates from 2% to 18%, with the rate increasing in proportion to the depth of invasion. For this reason, the presence of nodal metastasis cannot be totally excluded following ESD of early gastric cancer.
Aims & Methods: The aim of this study was to evaluate the long-term outcomes of combined endoscopic submucosal dissection (ESD) with laparoscopic lymph node dissection (LLND) and endoscopic full-thickness resection (EFTGR) with laparoscopic regional lymph node dissection (hybrid natural orifice transluminal endoscopic surgery, hybrid NOTES) for early gastric cancer (EGC).
A total of 23 patients with EGC underwent combined ESD with LLND and hybrid NOTES for early gastric cancer beyond endoscopic submucosal dissection between February 2007 and August 2009. Then the patients received periodic endoscopicfollow-up over 5 years.The main outcome measures were curability, recurrent rate, and survival rates.
Results: The curative resection rate of all cases was 95.7% (ESD with LLND 90.0% vs. hybrid NOTES 100%, respectively). Incomplete resection was shown in 1 (tumor-positive vertical margin). Histologically, 11 cases were mucosal cancers, and 12 were submucosal cancers. And there were 12 undifferentiated cancers. The median tumor size was 3.4 cm (range, 1.2–5.7cm) in long diameter. The lymphovascular invasion was found in 3 cases with 1 lymph node metastasis. 5 patients underwent additional gastrectomy because of tumor-positive margins or treatment-related complications. During over 5 year follow-up periods, none showed local recurrence or lymph node metastasis. The 5 year overall survival rates and disease-free survival of the patients was100% in both.
Conclusion: Combined ESD with LLND and hybrid NOTES showed favorable long term clinical outcomes. They could be utilized as a bridge between ESD and gastrectomy in selected patients with a risk of lymph node metastasis.

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Disclosure of Interest: None declared

OP381 ANALYSIS OF RISK FACTOR IN SALVAGE ENDOSCOPIC RESECTION FOR LOCAL RECURRENCE AFTER CHEMORADIOTHERAPY FOR ESOPHAGEAL SQUAMOUS CELL CARCINOMA

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Introduction: Local failure after definitive chemoradiotherapy (CRT) is the major problem for patients with esophageal squamous cell carcinoma (ESCC). If the local failure is a superficial lesion without any metastasis, it can be treated with salvage endoscopic resection (sER). However, there are few reports about the clinicopathological risk factors of recurrence after sER for local failure.
Aims & Methods: The aim of this study was to clarify the risk factors of recurrence after sER for local failure after CRT for ESCC. We enrolled consecutive patients treated with sER for local recurrence between 1998 and 2013 in our institution, and excluded patients whose resected specimen was not contain cancer cells. The indication criteria for sER as followed: (1) no lymph node or distant metastasis after CRT, (2) absence of ulceration in primary site after CRT, (3) depth of tumor invasion evaluated as limited within T1. The procedure of sER was endoscopic mucosal resection (EMR) with 2 channel method or endoscopic submucosal dissection (ESD) using dual knife. Recurrence after sER was defined and divided in two patterns as follows: (1) locoregional recurrence: local recurrence which could not control with repeated endoscopic treatment and/or locoregional lymph node metastasis; (2) distant metastasis; distant lymph node or organ metastasis. All patients provided written informed consent before procedure and the study protocol was approved by institutional review board in our institution.
Results: A total of 72 patients were included in this analysis, and patient's characteristics before CRT were as follows: median age of 66 years (range: 44—83); male/female ratio of 68/4; baseline clinical TNM Classification (6th edition) cT1/T2/T3/T4: 37/8/23/4; cN0/N1: 44/28; cStage IB/IIA/IIB/III: 31/20/15/6. Characteristics of local failure before sER: residue just after CRT/ local recurrent: 19/53; Median tumor size, mm (range): 9.5 (3-43); Method of sER: EMR in 67/ ESD in 5. Pathological results of sER were as follows; depth of resected tumor T1a(M)/T1b(SM): 45/27; horizontal margin +/−: 11/61; vertical margin +/−: 8/64; lymphatic vessel invasion +/− 4/68; venous invasion +/−: 10/62. At a median follow-up period of 36 months (range, 3-175 months) after sER; 45 patients (63%) did not detect any recurrence, whereas 13 (18%) and 14 (19%) patients were detected locoregional recurrence and distant metastasis, respectively. And the progression free and overall survival at 3 years were 48.9% and 61.2%. Multivariate analysis revealed that advanced cT-stage (OR, 2.34; 95% CI, 1.13—4.84) and residual tumor (OR, 4.95; 95% CI, 1.21—20.20) after CRT were associated with a significantly higher risk of recurrence after sER.
Conclusion: The ER is one of the curative salvage treatment options for local failure after definitive CRT. The results from this study indicates that the characteristics of before CRT or sER are more influential risk factors for recurrence after sER compared with the pathological findings of endoscopic resected specimens.
Disclosure of Interest: None declared

OP382 SURVIVAL IMPACT OF POSTOPERATIVE BODY MASS INDEX IN GASTRIC CANCER PATIENTS UNDERGOING GASTRECTOMY

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Introduction: The relationship between body mass index (BMI) and the survival of postoperative gastric cancer patients is not clear, even though weight loss is inevitable after gastrectomy.

Aims & Methods: This study was to evaluate the relationship between BMI and long-term survival in gastric cancer patients undergoing gastrectomy. Patients who underwent gastrectomy for gastric cancer between 2000 and 2008 were included in the study (n = 1,909). Patients were divided into three groups based on their BMIs: low (< 18.5 kg/m^2), normal (18.5–24.9 kg/m^2), and high BMI (≥25.0 kg/m^2). Patient survival was compared according to BMI at two time points: baseline and 1 year after surgery. Laboratory data were obtained from patients who had surgery after 2006.

Results: Regarding BMI 1 year after surgery, overall survival, disease-specific survival, and recurrence-free survival were longer in the high BMI group than the low and normal BMI groups. In a Cox proportional hazards model, adjusting for the patient's age, sex, tumor stage, histology, and curative resection, a high BMI 1 year after surgery was associated with lower overall mortality compared to normal BMI (Hazard Ratio 0.51; 95% confidence interval, 0.26-0.98). However, BMI at baseline was not an independent prognostic factor. Total protein and albumin levels were slightly higher in the high BMI group 1 year after surgery.

Conclusion: BMI 1 year after surgery significantly predicted the long-term survival of patients with gastric cancer compared with the preoperative BMI. Aggressive nutritional support should be considered in these patients to improve their outcomes.

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Disclosure of Interest: None declared

OP383 LOW-TRAUMA FRACTURE AFTER GASTRECTOMY FOR GASTRIC CANCER: LONG-TERM FOLLOW-UP OBSERVATION STUDY

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Introduction: Gastrectomy is a known risk factor for decreased bone mass and it is expected to increase fracture incidence.

Aims & Methods: The aim of the study is to evaluate the incidence of low-trauma fracture in gastric cancer patients with gastrectomy and to figure out what predictive factors are.

We retrospectively reviewed 1687 patients who underwent gastrectomy for gastric cancer at St. Mary's hospital between September 1991 and December 2008. Patients with stage IV gastric cancer, history of cancer recurrence or other medical conditions that cause osteoporosis such as chronic liver disease, kidney disease and other cancer, were excluded. Among the patients with fracture, we excluded the patients with high energy injury. Low trauma fracture was diagnosed with annual bone scan, plain x-rays, MRI and medical records. We analyzed the incidence of low-trauma fracture by Kaplan-Meier analysis method. We evaluated the effects of age, sex, body mass index (BMI), anemia, tumor staging and type of gastrectomy.

Results: With median follow-up period of 94 months, the incidence of low-trauma fracture was 29.4% (332/1131). The cumulative incidence of fracture was 34.9 cases per 1000 persons-years. The cumulative incidence of fracture was 9.1% at 24th month after surgery, 19.6% at 48th month after surgery and it increased upto 24.8% at 60th month. Univariate analysis revealed that older age [Hazard ratio (HR) = 1.03, 95% confidence interval (CI) 1.02-1.04, $p < 0.001$], male (HR = 1.61; 95% CI = 1.25-2.07, $p < 0.001$), postmenopausal state (HR = 2.07; 95% CI = 1.27-3.36, $p = 0.003$), smoking (HR = 1.44, 95% CI = 1.14-1.80, $p = 0.002$) and stage III (vs. stage I; HR = 1.54; 95% CI = 1.08-2.18, $p = 0.016$) were risk factors for low trauma fracture after gastrectomy. Multivariate analysis showed that older age and smoking are risk factors. Type of gastrectomy and BMI did not significantly increase risk of fracture.

Conclusion: The incidence of low-trauma fracture was high in gastric cancer patients with gastrectomy, regardless of gastrectomy type. The patients with risk factors, such as old patients with smoking habits, require regular surveillance and medical interventions to prevent fracture.

Disclosure of Interest: None declared

OP384 DO ALL ELDERLY PATIENTS NEED TO UNDERGO ADDITIONAL SURGERY AFTER NON-CURATIVE ESD FOR EARLY GASTRIC CANCER?

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Introduction: When endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) results in a non-curative resection, additional surgery is recommended according to the Japanese gastric cancer treatment guidelines. However, for elderly patients, the contribution of additional surgery to their life prognosis is still controversial.

Aims & Methods: The aim of this study was to assess the survival outcomes of radical surgery compared with observation only in elderly patients after non-curative ESD. We reviewed existing data of all elderly patients (older than 80 years) who had undergone ESD for EGC at a prefectural Cancer Center between September 2002 and December 2012. We compared the overall and relapse-free survival rates after non-curative ESD between with and without additional surgery. According to the pathological results of ESD, the patients were divided into two groups: high-risk and low-risk. "High-risk" was defined as positive lymphatic or/and venous invasion, or submucosal deep (SM2) invasion. Cox proportional-hazards model was performed to estimate hazard ratio (HR) and 95% confidence interval (CI). Multivariate analysis was also performed to examine the effects of independent variables adjusted for the effects of each of the others.

Results: Of the 100 non-curative ESD patients, 20 patients underwent additional surgery and 80 were followed without surgery. There was no significant difference between the groups in Performance Status, American Society of Anesthesiologist score, comorbidities, and previous cancer history. Patients who did not undergo surgery tended to be older. The rate of high-risk patient was 95% in additional surgery group, and 49% in no additional surgery group. The median follow-up period in additional surgery group and no additional surgery group was 49.5 and 36 months, respectively. In additional surgery group, 2 patients (10%) died as a result of gastric cancer and 7 patients (35%) died from other causes. In no additional surgery group, 4 patients (5%) died from gastric cancer and 19 patients (24%) died from other causes. Overall 5-year survival rates in additional surgery group and no additional surgery group were 59 and 60% (log-rank p = 0.802, HR: 0.70 (95% CI 0.30-

Abstract number: OP383 Table 1: Cox proportional hazard models for cumulative incidence of low-trauma fracture in patients after gastrectomy

		Univariate analysis			Multivariate analysis		
Variables		HR	95% CI	*P* value	HR	95% CI	*P* value
Age		1.03	1.02-1.04	<.001	1.03	1.01-1.04	<.001
Male	vs. Female	1.61	1.25-2.07	<.001	1.18	0.36-3.91	.787
Postmenopausal	vs. Premenopausal	2.07	1.27-3.36	.003	1.49	0.89-2.49	.133
BMI		1.01	0.97-1.04	.786	0.99	0.96-1.03	.794
Diabetes mellitus		1.30	0.87-1.96	.202	1.11	0.73-1.68	.614
Smoking		1.44	1.14-1.80	.002	1.33	1.02-2.08	.038
Stage III	vs. Stage I	1.54	1.08-2.18	.016	1.46	0.37-1.20	.174
Subtotal gastrectomy	vs. Total gastrectomy	1.08	0.84-1.39	.528	1.04	0.81-1.35	.753

HR, hazard ratio; CI, confidence interval

1.62)). There was no significant difference in overall and relapse-free survival (log-rank p = 0.695, HR: 0.86 (95% CI 0.42-1.95)) between the groups. In high-risk patients, overall 5-year survival rate tended to be higher in additional surgery group than no additional surgery group (63% vs 53%). According to multivariate analysis, additional surgery was not an independent factor indicating a longer survival (HR: 1.70 (95% CI 0.60-4.58)).
Conclusion: In our retrospective study, additional surgery following non-curative ESD could not improve overall survival compared with non-surgical observation only. For the patients with histological findings of lymphovascular involvement or massive submucosal penetration, additional surgery might contribute to the extension of life expectancy. Thus, additional surgery after non-curative ESD may not be considered for all elderly patients, but for high-risk patients.
Disclosure of Interest: None declared

OP385 ADH1B AND ALDH2 ARE ASSOCIATED WITH METACHRONOUS SQUAMOUS CELL CARCINOMA AFTER ENDOSCOPIC RESECTION OF ESOPHAGEAL SQUAMOUS CELL CARCINOMA

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Introduction: A previous genome-wide association study identified two novel esophageal squamous cell carcinoma (ESCC) susceptibility genes, *ADH1B* and *ALDH2*. We investigated the characteristics of ESCC, and the relationship between "metachronous esophageal and/or pharyngeal squamous cell carcinoma (SCC) " and "the *ADH1B* & *ALDH2* risk alleles".
Aims & Methods: One hundred and twelve ESCC patients who had been treated by endoscopic resection were followed up by endoscopy for 12 months or longer. First, we performed a replication study to confirm the relationship between ESCC and "the *ADH1B* & *ALDH2* risk alleles" using 112 ESCC cases and 1,125 healthy controls. Next, we investigated the incidence and genetic/environmental factors for metachronous SCC development after endoscopic resection. We also analyzed the potential risk factors for metachronous SCC development using Cox's proportional hazards model.
Results: Rs1229984 located on *ADH1B* and rs671 located on *ALDH2* were significantly associated with ESCC progression ($P = 2.96 \times 10^{-15}$ [AA vs AG + GG], and $P = 9.14 \times 10^{-10}$ [TC vs TT + CC]). Patients with rs1229984, those with rs671, smokers, and heavy alcohol drinkers (43.5 g/day ethanol) developed metachronous SCC more frequently ($P = 2.34 \times 10^{-3}$, 1.53×10^{-3}, 5.39×10^{-3}, and 0.018, respectively), and the hazard ratios were 2.91 (95% confidence interval [CI] 1.46-5.81), 4.19 (95% CI 1.47-11.96), 4.45 (95% CI 1.56-12.73), and 2.53 (95% CI 1.17-5.46), respectively. Multiple logistic regression analysis revealed that rs1229984, rs671, and smoking status were independently associated with the risk of metachronous SCCs.
Conclusion: Our findings elucidated the crucial role of multiple genetic variations in *ADH1B* & *ALDH2* as metachronous biomarkers for ESCC patients.
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 28, 2015 08:30–10:30
DIAGNOSIS AND TREATMENT OF PANCREATIC TUMORS – ROOM E6

OP386 DISCRIMINATING PANCREATIC CYST TYPE AND GRADE USING CLINICAL CRITERIA: THE RESULTS OF A LARGE RETROSPECTIVE COHORT

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Introduction: The current preoperative classification of pancreatic cystic neoplasms is based on a combination of imaging and clinical criteria. However, the diagnostic performance of such criteria is relatively inaccurate. The aim of this study was to design an improved combination of preoperative features to enhance the classification of pancreatic cysts.
Aims & Methods: We retrospectively analyzed 1026 patients with pancreatic cystic neoplasms who underwent surgical resection. To determine which preoperative clinical and radiological features that best predicted cyst type and grade of dysplasia, various combinations of features were analyzed using the Multivariate Organization of Combinatorial Alterations (MOCA) algorithm. Millions of feature combinations were tested and the most informative features were then used to design composite clinical markers for each cyst category. This model was then validated in an independent cohort consisting of 130 patients.
Results: The first cohort consisted of 584 patients with intraductal papillary mucinous neoplasms (IPMN), 332 with serous cystadenomas (SCA), 78 with mucinous cystic neoplasms (MCN), and 42 with solid-pseudopapillary neoplasms (SPN). Composite clinical markers were identified that classified SCAs with 95% sensitivity and 83% specificity; SPNs with 89% sensitivity and 86% specificity; MCNs with 91% sensitivity and 83% specificity, and IPMNs with 94% sensitivity and 90% specificity. None of the individual features were as accurate as the composite markers. A composite marker was also developed that correctly identified SPN, MCNs or IPMNs with high-grade dysplasia or associated carcinoma, with 84% sensitivity and 81% specificity. When applied to an independent cohort of 130-patients, the composite clinical markers had high sensitivity for SCAs, SPNs, and MCNs (100%, 89%, and 90%, respectively), and modest sensitivity for IPMNs. The specificities of the composite clinical markers ranged from 71% to 88% for SCAs, SPNS, MCNs and IPMNs.
Conclusion: The composite markers identified here integrate clinical and radiologic observations into a coherent framework. These composite markers have improved performance characteristics over individual clinical features and offer the potential for a more accurate classification of pancreatic cystic neoplasms.
Disclosure of Interest: D. Masica: None declared, M. Dal Molin: None declared, C. Wolfgang: None declared, T. Tomita: None declared, M. Ostovaneh: None declared, A. Blackford: None declared, R. Moran: None declared, J. Law: None declared, T. Barkley: None declared, M. Goggins Conflict with: inventor royalties, M. Canto: None declared, M. Pittman: None declared, J. Eshleman: None declared, S. Ali: None declared, E. Fishman: None declared, I. Kamel: None declared, S. Raman: None declared, A. Zaheer: None declared, N. Ahuja: None declared, M. Makary: None declared, M. Weiss: None declared, K. Hirose: None declared, J. Cameron: None declared, N. Rezaee: None declared, J. He: None declared, Y. J. Ahn: None declared, W. Wu: None declared, Y. Wang: None declared, S. Springer: None declared, L. Diaz, Jr. Conflict with: inventor royalties, N. Papadopoulos Conflict with: inventor royalties, R. Hruban Conflict with: inventor royalties, K. Kinzler Conflict with: inventor royalties, B. Vogelstein Conflict with: inventor royalties, R. Karchin: None declared, A. M. Lennon: None declared

OP387 PATTERN OF RECURRENCE IN RESECTED IPMN OF THE PANCREAS: PRELIMINARY RESULTS FROM A MULTI-INSTITUTIONAL INTERNATIONAL STUDY

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Introduction: The natural history of the pancreas remnant in patients who have had partial pancreatectomy for IPMN has been investigated in studies containing a relatively small number of patients and with short follow-up.
Aims & Methods: The aim of this study is to collect a large number of patients underwent partial pancreatectomy for IPMN and then followed for a long period of time to better understand the natural history of this disease. A trial was planned in the European Study Group for Cystic Tumors of the Pancreas in order to investigate the recurrence pattern and the prognostic factors influencing the recurrence of IPMN after partial pancreatectomy. A preliminary analysis on data coming from 1686 patients included in the study is presented in this report.
Results: The overall recurrence rate was 15.7%. In 12.5% of patients the recurrence was represented by progression of clinically significant IPMN in the pancreas remnant, 2.2% developed liver metastasis, 0.4% peritoneal carcinomatosis, 0.3% local recurrence and 0.2% new onset pancreas cancer. The overall risk of progression of the diseases at 1, 5 and 10 yrs was 7%, 14% and 21% respectively. Comparing the 1, 5 and 10 yrs risk of progression in different morphologic types, mixed-type IPMN showed a worse prognosis (5%, 24.3% and 37.6%) compared to main duct type (4.3%, 18.2% and 25.7%) and branch duct type (6%, 15% and 28.7%) (p = 0.01). Comparing histology, patients with pancreatico-biliary type showed a 1, 5 and 10 yrs risk of recurrence (7.2%, 50.2% and 62.2%) higher than gastric (2.4%, 17.1% and 18.7%), intestinal (2.6%, 11.4% and 18.6%) and oncocytic (5.8%, 15.3% and 15.3%) ($p < 0.0001$). Data on frozen section of the resection margin was available in 747 patients. A positive resection margin was associated with an increased risk of recurrence at 1, 5 and 10 yrs (7.6%, 27.4% and 35.5% vs 3%, 12.6% and 18.5% respectively; $p < 0.0001$).
Conclusion: Our data show that mixed type IPMN, pancreatico-biliary histology and a positive resection margin are negative prognostic factors for recurrence in patients with IPMN who have had partial pancreatectomy.
Disclosure of Interest: None declared

OP388 PANCREATIC JUICE CYTOLOGY WITH THE CELLBLOCK METHOD IN PATIENTS WITH BRANCH-DUCT TYPE INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS OF THE PANCREAS: USEFULNESS FOR PREOPERATIVE DIAGNOSIS OF MALIGNANCY AND PATHOLOGICAL SUBTYPING

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Introduction: In recent years, we have attempted to improve the preoperative diagnosis of malignant branch duct intraductal papillary mucinous neoplasms (BD-IPMN) by introducing the cellblock method for pancreatic juice cytology (CB-PJC).
Aims & Methods
Aim: To elucidate the efficacy and safety of CB-PJC for the determination of surgical indication in patients with BD-IPMN.

Subjects: One hundred and thirty-eight patients (the total number of ERCPs: 168) with BD-IPMN from whom pancreatic juice was collected under ERCP for CB-PJC at our medical center between December 2005 and August 2014 were recruited to this study.
Methods: In these 138 subjects, we retrospectively evaluated the following: (1) the diagnostic efficacy of CB-PJC for Papanicolaou's classification and for identification of histological subtypes in 28 subjects with resected IPMNs, (2) the percentage of IPMN lesions which developed into invasive cancer and the progression of IPMN lesions in 66 subjects who underwent follow-up for more than 1 year after CB-PJC, and (3) post-ERCP adverse events in 168 ERCPs. The definition of malignancy by CB-PJC was determined to be Class IIIb-V according to Papanicolaou's classification system, and that for resected specimens was determined to be high-grade dysplasia (HGD) and invasive carcinoma derived from IPMN (IC). Pathological subtypes were classified as follows: gastric (G), intestinal (I), pancreatobiliary (PB), and oncocytic (O). The antibodies used for the immunostaining of CB-PJC and resected specimens were as follows: Ki-67, p53, MUC1, MUC2, MUC5AC, MUC6, and CDX-2.
Results: (1) In the 28 resected specimens, the pathological grade was IC in 9 patients, HGD in 5, and low-intermediate grade dysplasia (L-IGD) in 14. The sensitivity, specificity, and accuracy of CB-PJC for preoperative diagnosis of malignancy were 50%, 100%, and 68%, respectively, with only HÿŸE stain and AB-PAS stain, while they were 79%, 100%, and 89%, respectively, by adding immunohistological staining. The agreement rate of the preoperative subtype by CB-PJC with the subtype of resected specimens was 93%. (2) Details of 66 subjects were as follows: median follow-up period was 3.4 years, the rate of the existence of mural nodules was 18%, the rate of BD-IPMN 30 mm or more in size was 41%, and the subtype of CB-PJC was G in 57 patients, I in 4, and PB + G in 5. All 4 patients who underwent surgery during follow-up were pathologically diagnosed as L-IGD. In the remaining 62 patients without resection of IPMN during follow-up, the imaging onset of IC was not detected at all, while the progression of IPMN was detected in 14 patients (21%). Multivariate analysis revealed the risk factor of progression to be non-gastric type. The cumulative 5-year progression rate in this group was 89%. (3) The percentage of post-ERCP pancreatitis was 7.7% (13/168: mild, 12; moderate, 1).
Conclusion: The diagnostic efficacy of preoperative CB-PJC for malignant BD-IPMN was good. The results such as the excellent diagnostic yield of the pathological subtyping by CB-PJC and the impact of pathological subtype on the progression of follow-up IPMN may suggest the feasibility of applying preoperative subtyping by CB-PJC to decisions as to whether surgery is indicated.
Disclosure of Interest: None declared

OP389 COMPARATIVE ANALYSIS BETWEEN SENDAI GUIDELINES AND THE EUROPEAN EXPERTS CONSENSUS STATEMENT ON BD-IPMN OF THE PANCREAS

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Introduction: Management decisions on Branch-duct Intraductal Papillary Mucinous Neoplasms (BD-IPMN) of the pancreas are mainly based on imaging features. However, several consensus guidelines proposed different features predicting malignancy and no clarity exists about which lesions will progress to malignancy ultimately.
Aims & Methods: The aim was to perform a comparative analysis between Sendai guidelines and the European experts consensus statement on BD-IPMN. This retrospective study included 120 consecutive patients (65 males, mean age: 57.75 years) with a BD-IPMN histologically proven between 2006 and 2014. Neoplasms were classified as malignant if high-grade dysplasia or invasive carcinoma were detected. Symptoms, mural nodule and wirsung > 6mm were considered as indications for surgery according to the European consensus. Patients with one or more worrisome features or high-risk stigmata were considered as Sendai-positive. Finally, agreement between both guidelines and predictive values for malignancy were analyzed.
Results: The global malignancy rate was 30% (n = 36). Among the 93 European-positive patients, 31(33.3%) harbored a malignant tumor (sensitivity: 86.1%, specificity: 26.2%, accuracy: 45.8%), with 5 false-negative cases (4.2%). By contrast, within 89 Sendai-positive patients, 34 malignant BD-IPMN (38.2%) were found and only 2 false-negative cases (1.7%)(sensitivity: 94.4%, specificity: 34.5%, accuracy: 52.5%). There were 46 cases (38.3%) in disagreement, being 7 of them malignant forms. The features predicting malignancy within the 21 Sendai-positive European-negative patients were cyst size ≥ 30mm (n = 7), wirsung ≥ 5mm (n = 6), abrupt change in caliber of the Wirsung (n = 5) and thickened/enhancing walls (n = 12). The 25 Sendai-negative European-positive cases underwent surgery for relief of symptoms.
Conclusion: Sendai guidelines have a higher accuracy. Both consensus increased surgical indications.
Disclosure of Interest: None declared

OP390 COMPARING PROCORE NEEDLE WITH FINE NEEDLE IN ENDOSCOPIC ULTRASOUND-GUIDED TISSUE SAMPLING FOR SUSPECTED PANCREATIC CANCER

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Introduction: Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is widely used for diagnosis of pancreatic mass lesions. In order to overcome some limitations of FNA, Endoscopic ultrasound-guided fine-needle biopsy (EUS-FNB) with ProCore needle was developed. A recent randomized trial showed that diagnostic sufficiency, technical performance, and safety profiles of FNA and ProCore needles were comparable for solid pancreatic mass.[1] However, there wasn't reported study to compare the diagnostic accuracy of both FNA and ProCore needle in the same patient yet.
Aims & Methods: This study aimed to compare the diagnostic accuracy of both FNA and ProCore needles in patients with suspected pancreatic cancer. We conducted crossover randomized control study at Samsung Medical Center between July 2013 and February 2015. A total of 60 consecutive patients who was suspected to have an unresectable pancreatic cancer were enrolled. We performed four needle passages on each patient with twice by 22G FNA (EZ Shot2; Olympus) and twice by 22G ProCore (EchoTip ProCore; Cook Medical) needle. The order which needle should be used first was randomized. The primary outcome was diagnostic accuracy and the secondary outcomes included specimen quality, and rate of complication.
Results: The mean age of 60 patients was 61.6 ± 10.0 years, and 58.3% of them were male. The mean size of 60 lesions was 3.13 ± 0.85 cm. The locations of them were respectively 26.7%, 11.7%, 41.7% and 20% in the head, uncinated process, body, and tail. The overall diagnostic accuracy did not differ between ProCore and fine needle (94.9% vs. 93.3%, p = 1.000). Furthermore, the adequacy, cellularity and blood contamination of specimen was comparable between two needles. None of the complications including bleeding, infection and pancreatitis were reported after procedure.

Table 1: Total diagnostic accuracy

	FNA		FNB		
	N	%	N	%	*P*
Cytologic diagnosis					0.743
No	6	10.0	4	6.8	
Yes	54	90.0	55	93.2	
Histologic diagnosis					0.670
No	16	26.7	13	22.0	
Yes	44	73.3	46	78.0	
Diagnosis					1.000
No	4	6.7	3	5.1	
Yes	56	93.3	56	94.9	

Conclusion: The diagnostic accuracy, specimen quality, and safety profiles are comparable between ProCore and fine needle in suspicious unresectable pancreatic cancer. (Clinical trial registration number: NCT01876069)

Reference

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Disclosure of Interest: None declared

OP391 INTERACTION BETWEEN SURGICAL AND ONCOLOGICAL PALLIATIVE THERAPIES IN PANCREATIC CANCER UNRESECTABLE AT SURGERY

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Introduction: Pancreatic cancer (PC) is frequently diagnosed at highly recalcitrant stages. In patients with locoregional disease, curative-intent resection may significantly prolong survival and improve quality of life; however, up to 30% are found to be unresectable at exploratory laparotomy (EXL) due to unexpected locally advanced or metastasized (LA/M) disease. A prophylactic double bypass (PDB, hepaticojejunostomy and gastroenterostomy) to prevent malignant bile and duodenal obstruction, represents the standard of care; however, minimal-invasive on-demand strategies are under debate. The aim was to compare PDB with EXL alone regarding postoperative outcome, subsequent initiation of palliative chemotherapy (PCT) and disease-specific survival (DSS) in unexpected LA/MPC.

Aims & Methods: An observational cohort study was conducted between 2004 and 2013 on patients found to have locally advanced or metastasized PC at EXL. The diagnosis was confirmed histologically. Demographics, operative and post-operative data were recorded together with outcomes of postoperative PCT and observation/supportive care (OSC). DSS was determined using the Kaplan-Meier method, pairwise comparison was performed using the log-rank test, prognostic interactions between PDB, EXL, PCT and OSC were investigated using Cox's regression model.
Results: Of 503 patients with pancreatic cancer who preoperatively had been considered resectable, 104 were found to be unresectable at laparotomy (38 locally advanced PC, 36 liver metastasis, 30 carcinomatosis, unresectability rate 20.7%). Patients with non-disseminated LAPC had a longer survival (9.9 months; 95%CI 8.2, 11.5) than patients with systemically disseminated PC (liver metastasis 3.6 months; 95%CI 2.4, 4.8; $p = 0.002$, peritoneal carcinomatosis 3.7 months; 95%CI 2.4, 5.0; $p = 0.264$). Seventy-four patients underwent PDB (30 EXL +/- GE). PDB was associated with longer operation time, higher blood loss, higher rate of major complications and prolonged length of stay; however, EXL/PDB groups showed no differences regarding 30/90-days mortality, PCT initiation rate or median DSS (EXL 6.7, PDB 8 months, $p = 0.174$). Compared to OSC, PCT was associated with significantly prolonged median DSS for locally advanced (16 vs 6 months, $p = 0.046$) and metastasized PC (10 vs 2 months, $p < 0.001$). PCT receivers with prior EXL had a significantly better median survival than PCT receivers with prior PDB (18.5 vs 11.6 months, $p = 0.023$).
Conclusion: The data of the present study indicate that patients with pancreatic cancer found to be unresectable at laparotomy may not have long-term benefits from prophylactic double bypass procedures. In the light of new, more effective chemotherapy regimens and less invasive alternatives to surgical bypass, this vulnerable patient group deserves additional prospective studies to define optimum palliation strategies.

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Disclosure of Interest: None declared

OP392 PROGRESSION OF PANCREATIC CANCER WITH LUNG METASTASIS IS RELATIVELY SLOW

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Introduction: Lung metastasis from pancreatic cancer is rare and the prognosis after lung metastasis is unknown.
Aims & Methods: We investigated the prognostic factors in patients with pancreatic cancer with lung metastasis. Medical records from prospectively registered database for unresectable or recurrent pancreatic cancer receiving chemotherapy between September 2007 and December 2014 were reviewed and those who met the following criteria were analyzed. 1. Certain distant metastasis was found on CT scans, 2. The diagnosis of adenocarcinoma was confirmed from primary or metastatic lesions, and 3. Performance status (PS) was 0 or 1.Background characteristics (sex, age, PS, metastatic site (lung alone or others), the values of CEA, CA19-9, WBC, Hb, ALP, CRP, Alb) were analyzed for overall survival (OS) by univariate and multivariate analyses and prognostic factors were determined. Survival from the final chemotherapy (BSC survival) was also analyzed in these factors.
Results: A total of 335 patients were included in the analyses. Median OS and median BSC survival was 200 days and 64 days, respectively. Lung metastasis, PS, CEA, CA19-9, WBC, and ALP were significant prognostic factors for OS in univariate analysis and lung metastasis (hazard ratio (HR) = 1.68, 95% CI, 1.033-2.727; $p = 0.036$), PS, CA19-9 and WBC were independent prognostic factors in multivariate analysis. Lung metastasis, PS, CEA, CA19-9 and WBC were significant prognostic factors for BSC survival in univariate analysis and lung metastasis (HR = 1.73, 95% CI 1.076-2.795, $p = 0.024$), PS, CA19-9 and WBC were independent prognostic factors in multivariate analysis.OS and BSC survival in patients with lung metastasis were 311 days and 121 days, respectively.
Conclusion: Lung metastasis alone from pancreatic cancer indicates slow progression compared to other metastasis.
Disclosure of Interest: None declared

OP394 CATHETER DRAINAGE VERSUS RELAPAROTOMY FOR SEVERE PANCREATIC FISTULA AFTER PANCREATODUODENECTOMY: A MULTI-CENTRE PROPENSITY-MATCHED ANALYSIS

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Introduction: Postoperative pancreatic fistula (POPF) after pancreatoduodenectomy is a potentially life-threatening complication. Treatment consists of catheter drainage or relaparotomy. We compared these treatment strategies in a multicentre study.
Aims & Methods: In a retrospective observational cohort study all patients with severe POPF (ISGPF grade B/C) following pancreatoduodenectomy between January 2005 and September 2013 in 9 centres of the Dutch Pancreatic Cancer Group were analysed. Patients were divided in two groups based on the initial intervention for POPF: catheter drainage or relaparotomy. We performed propensity score matching to correct for selection bias. Primary endpoint was mortality. Secondary endpoints included new onset organ failure.
Results: Out of 2196 of pancreatoduodenectomies, 309 patients underwent an intervention primarly for a severe POPF: 227 patients (73%) underwent primary catheter drainage while 82 (27%) underwent primary relaparotomy. Of all patients treated with primary catheter drainage, 83% was treated with catheter drainage only. A total of 75 patients undergoing primary relaparotomy were successfully matched to 75 patients undergoing primary catheter drainage (i.e. had well balanced baseline characteristics). Mortality was significantly lower after primary catheter drainage than after primary relaparotomy (17% vs. 36%; risk ratio [RR] 0.48, 95% confidence interval [CI] 0.28-0.80, $P = 0.007$), as was multiple-organ failure (20% vs. 39%, RR 0.51, 95% CI 0.29- 0.30, $P = 0.02$).
Conclusion: Primary catheter drainage is associated with better clinical outcomes, including lower mortality, compared to primary relaparotomy in patients with severe pancreatic fistula after pancreatoduodenectomy.
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 28, 2015 08:30–10:30
INTERVENTIONAL BILIARY ACCESS AND DRAINAGE – ROOM B3

OP395 EVALUATION OF UTILITY OF DIAGNOSTIC AND THERAPEUTIC ERC USING A SHORT DOUBLE-BALLOON ENDOSCOPE IN PATIENTS WITH ALTERED GASTROINTESTINAL ANATOMY: A JAPAN MULTICENTER PROSPECTIVE DB-ERC STUDY

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Introduction: Endoscopic approaches for pancreatobiliary diseases in patients with surgically altered gastrointestinal anatomy had been difficult. However, newly developed double-balloon endoscope (DBE) facilitated a variety of endoscopic interventions in such patients. The aim of this study was to make a prospective assessment on the efficacy and safety of ERC using a short DBE (DB-ERC) in postoperative patients with various types of gastrointestinal reconstruction.
Aims & Methods: This study was conducted as a multicenter, single arm, prospective trial at 5 tertiary care academic centers and 3 community based hospitals in Japan (UMIN-CTR number, 000010375). Biliary disease patients with altered gastrointestinal anatomy were enrolled. The primary endpoint was the success rate of reaching a targeted site (major papilla or choledochojejunostomy anastomosis). The secondary endpoints were assessment of safety, success rate of cannulation and contrast injection of the targeted bile duct, and success rate of treatments relevant to ERC.
Results: From June 2013 to May 2014, 316 patients were invited to the study and 2 patients declined. A total of 314 patients were enrolled, though 3 patients were cancelled prior to procedures. The reasons for cancellation were; 1 patient died from the primary disease, another suffered from bradycardia caused by sedative, and the other spontaneously passed biliary stones. The final figure of participants was 311. The success rate of reaching the targeted site defined as the primary endpoint was 97.7% (304/311). The respective success rates of ERC-related

interventions defined as the secondary endpoints were; diagnosis 96.4% (293/304) and therapy 97.9% (283/289). Regarding adverse events, the occurrence rate was 10.6% (33/311). Additionally, the success rates of reaching the targeted site by type of surgical reconstruction methods were; Roux-en-Y (R-Y): 97.0% (197/203), Billroth II (B-II): 96.2% (25/26), pancreaticoduodenectomy (PD): 100% (44/44), pylorus-preserving pancreaticoduodenectomy (PpPD): 100% (31/31), and others: 100% (7/7). The diagnostic success rates by type of surgical reconstruction methods were; R-Y: 97.0% (191/197), B-II: 100% (25/25), PD: 98.0% (43/44), PpPD: 90.0% (28/31), and others: 85.7% (6/7). The therapeutic success rates by type of surgical reconstruction methods were; R-Y: 97.9% (185/189), B-II: 100% (24/24), PD: 100% (43/43), PpPD: 96.3% (26/27), and others: 83.3% (5/6). The occurrence rates of adverse events by type of surgical reconstruction methods were; R-Y: 10.3% (21/203), B-II: 23.1% (9/26), PD: 2.3% (1/44), PpPD: 6.5% (2/31), and others: 0% (0/7).

Conclusion: DB-ERC for biliary diseases in patients with altered gastrointestinal anatomy is extremely effective and safe for reaching the targeted site and for completing the ERC-related interventions. DBE provides high and stable performance in assisting ERC in such patients, and especially the use of a short type DBE should be recommended.

Disclosure of Interest: None declared

OP396 INTERNATIONAL MULTICENTER COMPARATIVE TRIAL OF EUS-GUIDED BILIARY DRAINAGE VS. ENTEROSCOPY-ASSISTED ERCP IN PATIENTS WITH SURGICAL ANATOMY AND BILIARY OBSTRUCTION

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Introduction: ERCP is challenging in patients with surgically altered UGI anatomy with reported cannulation rates of enteroscopy-assisted ERCP (e-ERCP) between 48 and 70%. EUS-BD techniques potentially offer multiple advantages in these patients. It is currently unknown how e-ERCP and EUS-BD compare in such patients.

Aims & Methods

Aims: 1) to compare efficacy and 2) safety of both techniques and 3) study predictors of these outcomes.

Methods: This was an international multicenter comparative cohort study at 10 tertiary centers (3 US, 3 European, 3 Asian and 1 South American; 2 centers with published expertise on e-ERCP and 8 centers on EUS-BD) between 2008 and 2014. All patient with altered UGI anatomy who presented with benign or malignant biliary obstruction and subsequently underwent e-ERCP (2 centers) or EUS-BD (8 remaining centers) were included. Outcomes data included technical success (biliary access with cholangiography and stent placement (when indicated)), clinical success (resolution of biliary obstruction) and adverse events (graded according to the ASGE lexicon).

Results: A total of 98 patients (mean age 58yr, female 67%, malignant biliary obstruction 36%) underwent EUS-BD [n = 49; Hepatogastrostomy (HG) 33 (67.4%), antegrade stenting (AG) 10 (20.5%), rendezvous 2 (4%), Hepatojejunostomy 3 (6.1%), Hepatoduodenostomy 1 (2%)] or e-ERCP [n = 49; single balloon enteroscopy (SBE)-ERCP 5 (10.2%), double balloon enteroscopy (DBE)-ERCP 42 (85.7%), or colonoscope-ERCP 2 (4.1%)]. There was higher frequency of malignant obstruction in the EUS-BD group ($p < 0.0001$), but higher frequency of Roux-en-Y (RY) anatomy ($p < 0.0001$) and native ampulla ($p < 0.0001$) in the e-ERCP group. Technical success was achieved in 48 (98%) patients in the EUS-BD group as compared to 32 (65.3%) patients in the e-ERCP group (OR 12.48, $p = 0.001$). Clinical success (intention-to-treat) was attained in 88% of patients in EUS-BD group as compared to 60.4% in the e-ERCP group (OR 2.83, 95% CI 1.10-7.31, $p = 0.03$). Procedural time was significantly shorter in the EUS-BD group (55min vs 95min, $p < 0.0001$). Adverse events occurred more commonly in EUS-BD group (20% vs. 4%, $p = 0.01$). However, majority (90%) of complications were mild/moderate. Length of stay was significantly longer in the EUS-BD group (6.6d vs. 2.4d, $p = < 0.0001$). On multivariate analysis, EUS-BD was independently associated with increased rate of clinical success (OR 4.31, $p = 0.02$) and adverse events (OR 8.74, $p = 0.01$).

Conclusion: EUS-BD offers multiple advantages over e-ERCP in patients with surgical UGI anatomy, including higher technical success, higher clinical success, and reduced procedural times. However, EUS-BD is also associated with increased rate of adverse events, although severe events are uncommon.

Disclosure of Interest: M. Khashab Consultancy: Boston Scientific, Olympus America, Xlumena, M. El Zein: None declared, K. Sharzehi: None declared, F. Marson: None declared, O. Haluszka: None declared, A. Small: None declared, Y. Nakai: None declared, D. H. Park: None declared, R. Kunda: None declared, A. Teoh: None declared, I. Peñas: None declared, M. Perez-Miranda Consultancy: Boston Scientific, Xlumena, V. Kumbhari: None declared, S. Ngamruengphong: None declared, A. Messallam: None declared, S. Van der Merwe Consultancy: Boston Scientific, Cook endoscopy, E. Artifon: None declared, A. Ross: None declared

OP397 OUTCOMES OF PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAPHY FOR THE RELIEF OF MALIGNANT JAUNDICE IN ENGLAND BETWEEN 2001 AND 2014

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Introduction: Percutaneous transcutaneous cholangiography (PTC) is widely utilised to relieve malignant obstructive jaundice, especially when endoscopic retrograde cholangiopancreatography (ERCP) has failed or surgical resection is not indicated. Recent local audit data suggests PTC carries a high peri-procedural mortality and complication rate and there is a lack of national outcome data.

Aims & Methods: Using Hospital Episode Statistics (HES), subjects with cancer of the pancreas, biliary tree, gallbladder, small intestine and liver that underwent PTC were identified. Mortality, major complication rates, readmission and variation in outcomes between healthcare providers were examined. Associations between age, sex, comorbidity, cancer type and mortality were examined using multivariate regression analysis.

Results: Between April 2001 and March 2014, 15,390 subjects were identified (49.8% male). 2,175 underwent surgical resection after PTC and 13, 216 had no surgical intervention. The crude 30-day mortality was 9.7% for subjects undergoing surgery after PTC and 27.7% for palliative subjects and three-month mortality 25.8% and 55% respectively. The 30-day readmission rate for palliative subjects was 19.7%. The major complication rate was 25.9% in the surgical resection group and 24% in the palliative group. The most common complications were cholangitis (28.1%), acute kidney injury (21.4%), displacement or blockage of the stent (15.4%) and other sepsis (22.2%). In subjects undergoing PTC for palliation, increasing age was strongly associated with 30-day mortality (65-74 years OR 1.88(95% CI 1.31-2.71), p 0.001, 75-84 years 2.51(1.74-3.61), $p < 0.001$ and > 85 years 3.53(2.43-5.12), $p < 0.001$). 30-day mortality was also associated with a higher Charlson medical co-morbidity score of 10-14 (1.16(1.05-1.28), p 0.002) and > 20 (1.23(1.09-1.39), p 0.001). Female subjects had a better outlook at 30 days (0.83(0.76-0.89), $p < 0.001$). The type of cancer causing biliary obstruction was not associated with 30-day mortality. There was a large variation in 30-day mortality between healthcare providers for palliative subjects. Excluding providers that performed less than 5 PTCs per year, 30-day mortality varied between 6.3 and 50%. In the five healthcare providers that performed more than 250 PTCs per year, 30-day mortality was less than 30%.

Conclusion: In subjects undergoing PTC for the palliative relief of malignant jaundice, 30-day mortality is 27.7%, major complications occur in 24% and readmission occurs in 19.7%. There is a large variation in outcomes between healthcare providers. Mortality is highest in older males with increasing co-morbidity and careful multidisciplinary selection of patients who will benefit from PTC for relief of significant symptoms from jaundice or as a bridge to chemotherapy is clearly merited.

Disclosure of Interest: None declared

OP398 MULTICENTER RANDOMIZED PHASE II STUDY: PERCUTANEOUS BILIARY DRAINAGE VS EUS GUIDED BILIARY DRAINAGE : RESULTS OF THE INTERMEDIATE ANALYSIS

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Introduction: Since 10 years, EUS guided biliary drainage is an option as EUS guided choledoco-duodenostomy or Hepatico-gastrostomy. Two small randomized studies showed no difference between EUS guided BD vs Percutaneous drainage. The aim of this work was to evaluate in a multicenter randomized study the percutaneous biliary drainage (PBD) vs EUS guided biliary drainage (EBD) in patients with an obstructive jaundice when ERCP failed or impossible due do duodenal involvement or previous Surgery as gastrectomy or Wipple resection.

Aims & Methods: Inclusion criteria were: Benign or malignant obstructive jaundice with failure of ERCP.

Exclusion criteria were : ascites, Blood coagulation disorders, stenosis of the right bile duct.

Randomization ratio was 1 : 1, with a stratification by indication (benign vs malignant) and by centers (4 centers were included). The route of the biliary drainage was randomized as PTB (arm A) and EGD (arm B). But the choice of the EGD technique was free for the operator as (Anterograde transpapillary stenting, choledoco-duodenostomy, hepatico-gastrostomy). The main goal was to evaluate the specific morbidity and mortality during the 30 days following the biliary drainage in each arm. To prove a decrease of 50% of the morbidity rate in the EGD arm (A = 30%, B = 15%), 55 patients should be included in the EGD arm (B) as a Simon plan in 2 steps with an intermediate analysis to exclude severe adverse events in the EGD arm.

Results: Forty seven patients from 4 centres were included between 2011 to 2013. Six patients were excluded. Forty one patients were randomized(Arm A ; n = 21/ Arm B ; n = 20). The 2 groups were similar except the sex ratio (Female : Arm A, n = 11 ; Arm B, n = 2 ; p = 0.0036). The biliary stenosis was

malignant in 37 cases (Arm A, n = 19 ; Arm B, n = 18). Biliary access was successful in 100% in the Arm A and in 95% in the Arm B. Technical success was respectively 17/21 (85%) in the Arm A and 19/20 (95%) in the Arm B. No difference was showed regarding the decrease of the bilirubin level after the drainage in the two arms. Hospitalization time was significatively shorter in the Arm B (6 days range 3-30 days) than the Arm A (12 days range 2-52 days) p = 0.02. Nine patients died 30 days following the biliary drainage, 6 deaths were directly due to the procedure (Arm A = 3, Arm B = 3). A specific complication occurred in Twelve patients (60%) in the Arm A vs 7 (35%) in the Arm B : Bleeding (A = 4[19%], B = 1 [5%]), Cholangitis (A = 3 [15%], B = 1 [5%]), Sepsis not related to cholangitis (A = 7 [35%], B = 5 [25%]), Bile leakage (A = 1[5%], B = 1 [5%]).

Conclusion: Complication rate was higher in the Arm A (60%) vs Arm B (35%), we have decided to stop the Arm A and to continue to include patients only in the EGD Arm up to reach the total number of 55 patients.

Disclosure of Interest: None declared

OP399 EUS-GUIDED BILIODIGESTIVE ANASTOMOSIS FOR DRAINAGE OF MALIGNANT DISTAL BILIARY OBSTRUCTION USING A NOVEL CAUTERY-TIPPED LUMEN-APPOSING STENT DELIVERY SYSTEM: A LARGE RETROSPECTIVE MULTICENTER EUROPEAN STUDY

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Introduction: EUS-guided biliary drainage (EUS-BD) is a minimal invasive alternative for palliative treatment of unresectable malignant distal biliary obstruction in patients who failed ERCP. A novel lumen-apposing, self-expanding fully covered metal stent incorporated in an electrocautery enhanced delivery system has been developed to facilitate creation of bilio-digestive anastomosis and decrease the risk of complications. The aim of our study was to evaluate the safety, feasibility and clinical effectiveness of this new device for EUS-BD in these patients.

Aims & Methods: Retrospective analysis of all consecutive patients with unresectable malignant distal biliary obstruction who failed ERCP and who between August 2013 and April 2015 underwent EUS-BD using the study device (Hot-Axios™, Xlumena Inc., Mountain View, California, USA) in 5 European tertiary referral centers. Technical success was defined by adequate placement of stent with established drainage. Clinical success was defined by ≥90% decrease of obstructive parameters. Procedural complications as well as need for re-interventions were evaluated.

Results: 49 patients (Mean age 73 ± x yrs.; M/F: 23/26) were included. Cause of biliary obstruction was pancreatic cancer (28), bile duct cancer (11) and others in 10 cases. Indication for EUS-BD was duodenal obstruction in 27and failed cannulation in 22. CBD access was used 38 patients and gallbladder (GB) access in 11. The procedure was performed transduodenally in 41 and transgastrically in 8. Mean CBD diameter was 16.6mm (10-30). In 22 patients access of the target was achieved using a 19G needle with guidewire placement, which was followed by insertion of the Hot-Axios, while in 27 direct access with Hot-Axios was performed. Stent diameters were 6x8mm (16), 8x8mm (12) and 10x10mm (22). Technical success was achieved in all but one patient (97.9%). All procedures were performed under primary EUS guidance with help of endoscopic and/or fluoroscopic guidance at the discretion of the endoscopist. Clinical success was achieved in 46 of the 48 patients (95.8%) with successful stent placement. Failures were due to bile peritonitis in one case requiring surgery and unsuccessful drainage due to involvement of cystic duct by the malignant process in another one drained through the GB. During follow up, 2 patients (4.2%) suffered from cholangitis that was successfully treated with placement of a plastic stent through the Hot-Axios. Two additional patients required reinterventions for lithotripsy of bile duct stones via Axios stent. In all 40 (100%) patients with follow up ≥ 2 weeks the stent was patent at the end of follow up (mean 128d; range 18-595). 23 patients in the group have follow ≥3month (mean: 196d, range 93 -595), 20 (86.9%) of them showed stent patency without any reintervention.

Conclusion: EUS-BD by creating a biliodigestive anastomosis with the CBD or the GB using the Hot-Axios delivery system for palliative treatment of obstructive malignant jaundice after failed ERCP is feasible, safe and highly clinically effective. Long-term patency of the stent is encouraging and future multicenter prospective studies are warranted to further explore this issue.

Disclosure of Interest: None declared

OP400 EUS-GUIDED BILIARY DRAINAGE FOR MALIGNANT BILIARY TRACT OBSTRUCTION COMPARED TO ERCP WITH TRANSPAPILLARY BILIARY DRAINAGE: RANDOMIZED CONTROLLED TRIAL IN SINGLE INSTITUTION

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Introduction: Obstructive jaundice is a major adverse effect of pancreatic or biliary carcinoma. This adverse event requires treatment, especially in patients who cannot be treated surgically due to concurrent chemotherapy. ERCP with biliary stenting is a gold standard method of treatment for obstructive jaundice. However, this method is associated with several problems, such as post-endoscopic ERCP pancreatitis. In addition, ERCP with biliary stent insertion cannot be performed in patients with selective cannulation failure of the major papilla or an inaccessible papilla due to duodenal invasion or altered anatomy due to previous surgeries. The alternative method under these conditions is PTBD. However, PTBD can lead to several adverse events, such as cholangitis, bile leakage and pneumothorax. Moreover, the frequency of major complications, such as prolonged hospital stay and permanent adverse sequelae, is 4.6% > 25%, and that of procedure-related deaths is 0% > 5.6%. Cosmetic issues due to external drainage also compromise the patient's quality of life. Endoscopic ultrasound-guided biliary drainage (EUSBD) has been developed and performed by experienced endoscopists

Aims & Methods: The aims of this study was to compare success rate in both technical and functional as well as procedure-related complications between ERCP with biliary stent insertion and EUBD. The prospective randomized controlled study was conducted and 30 patients were enrolled; 15 for each EUSBD and ERCP with biliary stent insertion arm. (http://clinicaltrials.gov/show/NCT01421836)

Results: There was the total of 30 patients with extrahepatic malignant biliary tract obstruction (19 male, 11 female). There were 27 patients with unresectable PDACs, 1 patient with distal CBD cancer and 2 patients with metastatic LN compressing distal biliary tract: lung cancer, colorectal cancer. The median OS of the study patients were 8.8 months (0.8 ~36 mo) and there was no significant difference between the two groups: EUSBD 9.1 mos vs. ERCP 8.4 mons (p = 0.5). There were no significant difference between stent patency and both technical and functional success rate. There was one patient with post-ERCP pancreatitis in ERCP biliary biliary stent group and chemotherapy schedule was delayed around 5-7 days. However, it was not statistically significant in terms of complications.

Conclusion: This study showed that EUSBD was not only safe but also as efficient as compared to conventional ERCP with biliary stent insertion in patients with malignant biliary obstruction. In addition, EUSBD technique has a great advantage over the patients not feasible to ERCP with bilary stent and can avoid PTBD for their quality of life.

Disclosure of Interest: None declared

OP401 EUS-GUIDED GALLBLADDER DRAINAGE FOR ACUTE CHOLECYSTITIS IN HIGH SURGICAL RISK PATIENTS USING A NOVEL CAUTERY-TIPPED LUMEN-APPOSING STENT DELIVERY SYSTEM: A LARGE RETROSPECTIVE MULTICENTER EUROPEAN STUDY

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Introduction: Percutaneous gallbladder drainage (PTGBD) is the treatment of choice in high-risk surgical patients with acute cholecystitis (AC). Continuous drainage, however, is associated with patient discomfort and risk of inadvertent drain removal, which may lead to bile leakage and need for re-intervention. Recently EUS-guided transmural gallbladder drainage (EUS-GBD) has become a minimal invasive alternative to PTGBD. We evaluated the safety, the feasibility and clinical effectiveness of a novel lumen-apposing, self-expanding fully covered metal stent incorporated in an electrocautery enhanced delivery system, which facilitates direct puncture of the target, insertion and stent release in a one-step-fashion.

Aims & Methods: Retrospective analysis of all consecutive patients with AC who, between October 2013 and April 2015, underwent EUS-GBD using the study device (Hot-Axios™, Boston Scientific Corp., Natick, MA, USA) in 6 European tertiary referral centers. Technical success was defined by adequate placement of the stent with established drainage. Clinical success was defined by resolution of AC. Procedural complications as well as need for re-interventions were evaluated.

Results: 28 patients (Mean age 72yrs; 41-96); M/F: 13/15) with AC (16 calcolous, 12 acalcolous) not eligible for surgery because of severe comorbidity or advanced malignancy underwent EUS-GBD. The procedure was performed transduodenally in 16 cases and transgastrically in 12. In 16 patients access to the GB was achieved using a 19G needle with guidewire placement, which was followed by insertion of the Hot-Axios, while in 12 direct access with Hot-Axios was done. Stent was placed under EUS/Endoscopic control in 11 cases, while in 17 cases occasional use of fluoroscopy was utilized. Stent diameters were 10x10mm (26) and 15x10 (2). Technical success was achieved in all but one patient (96.4%), in whom gastric wall perforation occurred that required cholecystectomy and suturing of the perforation. Clinical success was achieved in all patients with successful stent placement (100%). Long-term complications occurred in 2 patients (7.4%). One had recurrent cholecystitis that was successfully treated by insertion of a pigtail through the Axios stent. The other patient developed Bouveret's syndrome necessitating lithotripsy. One patient needed reintervention for lithotripsy of cholecystolithiasis for maintaining of stent patency and healing of preexisting cholecystocutanous fistula. In all 22 (100%) patients with technical success and

follow up ≥14 days the stent was patent at the end of follow up (mean 143d; range 14-407).
Conclusion: EUS-guided gallbladder drainage in patients with high surgical risk using the Hot-Axios delivery system is feasible, safe and highly clinically effective. Randomized controlled studies comparing EUS-GBD performed with the study device with PTGBD are needed before this procedure can become the standard of care.
Disclosure of Interest: None declared

OP402 ENDOSONOGRAPHY-GUIDED GALLBLADDER DRAINAGE VERSUS PERCUTANEOUS CHOLECYSTOSTOMY AS A DEFINITIVE MANAGEMENT FOR ACUTE CHOLECYSTITIS IN PATIENTS THAT ARE UNFIT FOR SURGERY

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Introduction: Percutaneous cholecystotomy (PC) is the standard treatment for acute cholecystitis in patients that are unfit for surgery. Recently, endosonography-guided gallbladder drainage (EGBD) has emerged as a potential alternative treatment in these high-risk patients. However, there is no data on how the procedure compares to percutaneous cholecystostomy as a definitive management for acute cholecystitis in patients that are unfit for surgery.
Aims & Methods: This was a retrospective review of all patients who suffered from acute cholecystitis and received EGBD between October 2011 and August 2014 in the Prince of Wales Hospital and the University Hospital Rio Hortega. The patients that received EGBD were matched with those that received PC based on sex, age and American society of anesthesiology grading. All patients included were deemed unfit for surgery by surgeons or anesthesiologist. EGBD was performed using a linear echoendoscope (GF-UCT180 Olympus, Japan) and a lumen apposing stent (AXIOS, Xlumena, CA, USA), draining the gallbladder to the stomach or duodenum. The primary outcome was the overall adverse event rate. Secondary outcomes included technical and clinical success rates, hospital stay, the number of unplanned admissions and mortality.
Results: A total of 116 patients were included (EGBD vs PC = 58:58). There were no significant differences in background demographics. All procedures were technically successful (100% vs 100%) and the clinical success rates were comparable (93.1% and 100%, P = 0.119). When comparing EGBS with PC, significantly more patients in PC group suffered from overall morbidities (25.9% vs 70.7%, P < 0.001) and required more frequent unplanned admissions (6.9% vs 70.7%, P < 0.001). The most common causes of readmission in the PC group were due to tube dislodgement and blockade. Whilst in the EGBD group, procedural adverse events were significantly higher (17.2% vs 0%, P = 0.001) and the most common procedural adverse event was stent malposition. The rates of recurrent acute cholecystitis were low in both groups (0% vs 3.4%, P = 0.717) and no difference in overall mortality was observed (P = 0.115).
Conclusion: EGBD and PC were both effective means of obtaining gallbladder drainage. In the absence of percutaneous tubing, EGBD reduced the overall morbidities and number of unplanned admissions. While, the higher rate of procedural adverse events may be related to the learning curve associated EGBD. Thus, EGBD may potentially replace PC as the treatment of choice in patients that are unfit for surgery.

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Disclosure of Interest: None declared

OP403 PROSPECTIVE INTERNATIONAL MULTICENTER STUDY ON EUS-GUIDED BILIARY DRAINAGE FOR PATIENTS WITH MALIGNANT DISTAL BILIARY OBSTRUCTION AFTER FAILED ERCP

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Introduction: EUS-guided biliary drainage (EUS-BD) has emerged as an alternative to traditional radiologic and surgical drainage procedures. However, prospective multicenter data are lacking.
Aims & Methods: The primary outcome of this prospective study (NCT01889953) was to assess the clinical success of EUS-BD. Secondary outcomes included technical success, rate and severity of adverse events, and long-term outcomes. **Methods:** All consecutive patients at 12 tertiary centers (5 US, 5 European, 1 Asian, 1 South American) with malignant distal (≥ 2cm from the hilum) biliary obstruction and failed ERCP underwent EUS-BD using either rendezvous (REN), direct transluminal (TL) [Choledochoduodenostomy (CDS), Hepatogastrostomy (HGS), Hepatoduodenostomy (HDS)], or antegrade (AG) stenting techniques. Technical success was defined as successful stent placement in the desired position. Clinical success was defined as drop in bilirubin by 50% at 2 weeks or to below 3 at 4 weeks. Adverse events were prospectively tracked and graded according to the ASGE lexicon's severity grading system. Overall survival and duration of stent patency were calculated using Kaplan-Meier estimate.
Results: A total of 95 patients (mean age 66yr, female 44%, pancreatic cancer 55%) underwent EUS-BD [REN 11, AG 12, TL 72 (CDS 53, HGS 15, HDS 4)]. Reason for EUS-BD was obscured ampulla by invasive cancer or enteral stent (n = 49), altered anatomy (n = 9), failed deep biliary cannulation (n = 20), gastric outlet obstruction (n = 17). Electrocautery was used during 66.67% of procedures (coaxial 38.67%, non-coaxial 28%). EUS-guided cholangiography was successful in 94 (99%) patients. Technical success was achieved in 91 (95.7%) patients (metallic stent 83, plastic stent 8). Mean procedure time was 41 minutes (range 8-207). Clinical success was achieved in 85 patients (95%, intention to treat; 89.4%, per protocol analysis). There was significant decrease in bilirubin at 4 weeks (13.9 vs. 1.86, p < 0.0001). A total of 10 (10.5%) adverse events occurred: pneumoperitoneum (n = 2), sheared wire (n = 1), bleeding (n = 1), bile leak (n = 3), cholangitis (n = 2), and perforation (n = 1): 4 graded as mild, 4 moderate, 1 severe, and 1 fatal (due to perforation). There were no predictive factors of clinical success or occurrence of adverse events (all p > 0.05). A total of 24 (25%) patients died of disease progression during the study period. The median patient survival was 491 days. The mean stent patency was 536 days (95% CI 383-689) and the one-year stent patency was 61%.
Conclusion: This is the first prospective international multicenter study on EUS-BD and demonstrates the excellent efficacy and safety of EUS-BD when performed by experts. Based on these results, a study comparing EUS-BD to percutaneous drainage is being planned.
Disclosure of Interest: M. Khashab Consultancy: Boston Scientific, Olympus America, Xlumena, S. Van der Merwe Consultancy: Boston Scientific, Cook endoscopy, R. Kunda: None declared, M. El Zein: None declared, A. Teoh: None declared, F. Marson: None declared, C. Fabbri: None declared, I. Tarantino: None declared, S. Varadarajulu: None declared, R. Modayil: None declared, S. N. Stavropoulos: None declared, I. Peñas1: None declared, S. Ngamruengphong: None declared, V. Kumbhari: None declared, J. Romagnuolo: None declared, R. Shah : None declared, A. Kalloo: None declared, M. Perez-Miranda Consultancy: Boston Scientific, Xlumena, E. Artifon: None declared

WEDNESDAY, OCTOBER 28, 2015 08:30–10:30
ABSTRACTS ON FIRE: GUT MICROBIOTA IN LOWER GI DISEASES – HOTSPOT

OP404 IDENTIFICATION OF A GUT MICROBIAL SIGNATURE LINKED TO SEVERITY OF IRRITABLE BOWEL SYNDROME

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Introduction: Irritable bowel syndrome (IBS) is the most common functional gastrointestinal disorder affecting around 10-15% of the western population. Alteration in gut microbiota composition has been reported in IBS patients or IBS subgroups in some studies (Rajilić-Stojanović *et al.*, 2011; Jeffery *et al.*, 2012) with different microbial ecology outcomes. Larger sample size studies are needed to take into account the heterogeneity of IBS pathophysiology.
Aims & Methods: In our study, 130 subjects including 95 IBS (ROME III, all subtypes, n = 78 severe IBS, IBS-SSS > 300) and 35 healthy controls were thoroughly characterized for symptom severity (IBS-SSS, GSRS), psychological comorbidities (HAD, FIS, PHQ-15, VSI) and quality of life (IBSQoL). A combined nutrient and lactulose challenge test (Le Nevé *et al.,* 2013) with symptom assessment and measurement of exhaled H_2 and CH_4 was performed in all subjects. Unprepared sigmoid colon biopsies and stool samples were obtained. Paired fecal and mucosal microbiota were then analyzed by 16S rRNA targeted pyrosequencing with LOTUS v1.32 using USEARCH v7 to identify Operational Taxonomical Units (OTUs, 97% identity, molecular species similarity levels), and GreenGenes database (release version 13.8 August 2013). Microbial enterotype stratification was identified using previously described methods with the Dirichlet multinomial bayesian statistics (Holmes

et al., 2012). Machine learning procedure to identify microbial IBS signature was carried out using L1 regularized logistic regression using the LIBLINEAR library (Fan *et al*., 2008) validated through a ten-fold independent cross-validation. In addition, quantitative PCR was used to detect archaea methanogens in stool samples.
Results: 16S rRNA microbiota OTU-based data complexity was reduced using a machine learning procedure into a "species-specific IBS severe signature", consisting of ~100 bacterial OTUs (extracted out of 2,900 total OTUs detected in the dataset) linked to IBS severity as assessed by IBS-SSS. This IBS severity microbial signature has been further confirmed in sigmoid mucosal microbiota (n = 57, AUC = 0.80) and an external validation stool set (n = 46, AUC = 0.68), allowing to discriminate severe IBS from mild/moderate IBS patients and healthy controls. Using this OTUs based signature, IBS symptom severity score was, as a gradient, significantly and negatively associated to 1) exhaled CH_4, 2) presence of Archaea methanogens 3) microbial species richness and 4) enterotypes enriched either with *Clostridiales* or *Prevotella* species. This IBS severity signature was independent from age, gender, BMI and exhaled H_2.
Conclusion: Overall, our study indicates that IBS symptom severity is associated with a distinct signature at the fecal microbiota level. Exhaled CH_4, enterotypes stratification and mucosal microbiota are linked with this signature. Whether this indicates a causal role of gut microbiota alteration in the genesis of IBS symptoms remains to be investigated.

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OP405 SEROLOGIC PREDICTOR OF SMALL INTESTINAL BACTERIAL OVERGROWTH IN IRRITABLE BOWEL SYNDROME

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Introduction: Small intestinal bacterial overgrowth (SIBO) is common in the irritable bowel syndrome (IBS). Up to now, little is known about study regarding serologic markers of small intestinal bacterial overgrowth. The purpose of the present study was to determine possible serologic markers of small intestinal bacterial overgrowth in irritable bowel syndrome.
Aims & Methods: We reviewed the charts for patients who showed irritable bowel syndrome symptoms with documented results for lactulose breath test. Univariate and multivariate models were used to identify which markers were useful in predicting small intestinal bacterial overgrowth, and receiving operating characteristics curves were used to find the specificity, sensitivity, and the negative and positive predictive values.
Results: Of the 740 patients, 243 (32.8%) were found to have SIBO. Subjects with SIBO had significantly higher total bilirubin than those without SIBO. On multivariate analysis, SIBO was independently associated with serum total bilirubin. The best cut-off of serum bilirubin was ≥4.5 mg/ dL [AUROC 0.67 (95% CI 0.63–0.72)] predicting SIBO with sensitivity 63%, specificity 63%, positive predictive value 62% and negative predictive value 75%.
Conclusion: Increased total bilirubin is serologic predictor for the presence of small intestinal bacterial overgrowth in irritable bowel syndrome patients.
Disclosure of Interest: None declared

OP406 EPIDEMIOLOGY OF POST INFECTIOUS IRRITABLE BOWEL SYNDROME FOLLOWING CLOSTRIDIUM DIFFICILE INFECTION

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Introduction: Infectious gastroenteritis (IGE) is the most commonly identified risk factor for development of irritable bowel syndrome (IBS). Long-term gastrointestinal sequelae have been reported after IGE caused by bacterial, viral and parasitic pathogens. However, there is very limited epidemiological information for post infectious (PI)-IBS development following *Clostridium difficile* infection (CDI).
Aims & Methods: Our aim was to determine the incidence and risk-factors for PI-IBS development among culture-confirmed cases of CDI. We sent postal surveys to 683 cases of CDI reported to the Mayo Clinic microbiology laboratory during Sep 2012-Nov 2013. Phone calls were made to reach non responders. Participants were asked to complete the Rome III IBS questionnaire for current and pre-CDI GI symptoms and details on the CDI episode. Electronic medical records were reviewed. Predictive modelling was done using logistic regression to evaluate demographic, CDI and psychological characteristics as risk-factors for PI-IBS development.
Results: The overall survey response rate was 46.1% (315/683). 205 of the 315 *C. difficile* cases that responded were known to be at-risk for PI-IBS development (excluding cases with pre-existing IBS prior to the *C. difficile* episode, cases with missing data and cases with an alternative diagnosis such as inflammatory bowel disease or microscopic colitis). Those with repeated infections after the index episode were excluded prior to defining them as PI-IBS. 25.4% of those at risk (52/205) met the Rome III criteria for IBS. The IBS phenotype was mixed in 27 (52%), diarrhea-predominant in 21 (40.4%), constipation-predominant in 2 (3.9%), and undifferentiated in 2 (3.9%). The mean (±SEM) IBS symptom severity score was 238.3 (13.8). The Table lists comparsion of demographic, enteritis-related and psychological variables among PI-IBS cases and controls.

Variable	PI IBS (52)	Controls (153)	p- value
Mean age (±SEM)	55.7 (± 2.4)	58.3 (±1.5)	0.39
Gender, Females	61.5%	54.9%	0.40
Bloody diarrhea during CDI	22.4%	32.9%	0.18
Fever during CDI	26%	38.5%	0.12
Duration of CDI symptoms > 7 days	78.8%	60.4%	0.02
Hospitalized during CDI	59.6%	57.9%	0.83
Mean (± SEM) HADS anxiety score	9.8 (±0.4)	8.1 (±0.2)	<.0001
Mean (± SEM) HADS depression score	8.5 (±0.2)	8.5 (±0.1)	0.78

From a multivariable model, CDI symptoms > 7 days (p=0.03) and current anxiety score on Hospital Anxiety and Depression Scale ($p < 0.001$) were associated with development of PI-IBS following *C. difficile* infection.

Conclusion: Like other bacterial infections, CDI is associated with the risk of development of IBS. Longer duration of CDI symptoms and current anxiety are associated with the diagnosis of *C. difficile* PI-IBS. This chronic sequela of PI-IBS should be considered during active management and follow up of patients with CDI.
Disclosure of Interest: None declared

OP407 FECAL MICROBIOTA TRANSPLANTATION FOR RECURRENT C. DIFFICILE INFECTION: A 2-YEAR EXPERIENCE FROM A EUROPEAN REFERRAL CENTRE

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Introduction: Fecal microbiota transplantation (FMT) from healthy donors is considered an effective treatment against recurrent *Clostridium difficile* infection (rCDI). To date, however, FMT is available only in few Centers worldwide. FMT was implemented in our Centre since June 2013
Aims & Methods: To report outcomes of a large series of patients treated with FMT for rCDI in a European academic tertiary care Centre after 2 years of experience. All patients treated with FMT for rCDI in our Centre were prospectively identified. Follow-up data, including diarrhea, *C. difficile* toxin status and adverse events were collected and analyzed.
Results: 35 subjects (M/F: 17/18; mean age 69, range 31-91) received FMT from healthy donors because of rCDI (mean n° of recurrences: 3, range 2-6). Mean Charlson Comorbidity Index score was 3. Inpatient/outpatient ratio was 2.2. Eight patients received multiple infusions, for a total of 47 procedures. All procedures were performed by colonoscopy. In 9 patients, endoscopic appearance of pseudomembranous colitis (PMC) was observed. The mean follow-up was 9 months (range 1-22 months). Resolution of rCDI occurred in 33 of the 35 treated patients (94%). No patients experienced further recurrences after FMT. Fecal material was provided by unrelated donors in 45% of cases. Both fresh and frozen feces were used. *K. Pneumoniae*-related sepsis occurred in one patient (3%) 24 h after the transplant, and resolved after antibiotic treatment. In 2 patients (6%), all suffering from concomitant urinary infections, a transient, self-limiting bacteriemia was observed 1 to 6 days after FMT. Two subjects died because of overwhelming CDI from 1 to 10 days after FMT failure. Eight patients died 6 to 12 months after FMT, because of their own comorbidities (mainly cardiovascular disease) not relatable to the procedure.
Conclusion: FMT by colonoscopy achieved a 94% resolution rate of rCDI in our series. Our results confirm the efficacy of FMT in the treatment of rCDI in a large series of European patients, with a mean follow-up of 9 months. Dissemination of FMT is warranted to provide a better management of patients with rCDI.
Disclosure of Interest: None declared

OP408 ABOLISHED NEED FOR SURGERY IN C. DIFFICILE INFECTION AFTER THE IMPLEMENTATION OF FECAL MICROBIOTA TRANSPLANTATION IN AN ACADEMIC TERTIARY CARE CENTRE

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Introduction: *C. difficile* infection (CDI) is increasing in both incidence, severity and mortality. Total abdominal colectomy is recommended to manage complicated severe infection. Nevertheless, surgery is associated with poor long-term survival and significant morbidity. CDI recurrences greatly increase the risk of severe complications and the need for surgery. Fecal microbiota transplantation (FMT) is considered an effective treatment against recurrent CDI (rCDI). FMT is available at our Centre since June 2013.
Aims & Methods: To assess the evolution of the need for surgery in CDI after the implementation of FMT programme in an academic tertiary care centre. Medical charts of all patients referring our hospital from January 2010 to April 2015 because of CDI were reviewed retrospectively. Total number of subjects with CDI/year, as well as raw numbers and annual rates of CDI-related surgery and FMT procedures were respectively assessed.
Results: Throughout the study period, 901 patients with CDI were identified. Overall, 18 patients underwent surgery because of severe rCDI. No patients at first infection who required surgery were identified. Thirty-five patients underwent FMT, and 37% of them had severe disease.
Number of patients diagnosed with CDI increased gradually over years, being, respectively, 54 in 2010, 116 in 2011, 200 in 2012, 212 in 2013, 268 in 2014, and 71 in 2015 (until April 2015).
Surgery rates (n° of surgical procedures/patients with CDI), despite an initial increase (from 2010 to 2012), rapidly decreased over years, until their complete abatement, concomitantly with the implementation of FMT, being, respectively, 1.9% in 2010, 2.6% in 2011, 5% in 2012, 1.9% in 2013, 0% in 2014, and 0% in 2015. FMT rates (n° of FMT procedures/patients with CDI), instead, progressively increased over years since 2013 (3.3% in 2013, 6% in 2014, 22.5% in January-April 2015).
The raw numbers of surgical and FMT procedures were, respectively: 1 and 0 in 2010, 3 and 0 in 2011, 10 and 0 in 2012, 4 and 7 in 2013, 0 and 16 in 2014, 0 and 12 in 2015 (April 2015).
Conclusion: In our retrospective series, the implementation of FMT was associated with the abatement of surgical procedures for CDI, despite the increasing epidemic of the infection. This may be explained both by the prevention of further recurrences and complications of CDI provided by FMT and by the increased attention to CDI by physicians. Should our findings be confirmed by further studies, FMT may assume an even greater importance in the management of rCDI.
Disclosure of Interest: None declared

OP409 A SUBSET OF PATIENTS WITH NON-INFECTIOUS DIARRHEA HAVE ALTERED GUT MICROBIOTA SIMILAR TO C. DIFFICILE INFECTION

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Introduction: Non-infections diarrhea is commonly associated with chronic gastrointestinal disorders such as functional diarrhea, irritable bowel syndrome, inflammatory bowel disease, and microscopic colitis. The pathophysiology of diarrhea remains poorly understood, but recent data suggests a role for alterations in the gut microbiota.
Aims & Methods: The aim of this study was to assess gut microbial alterations in patients with non-*Clostridium difficile* diarrhea in comparison to patients with *C. difficile* infection (CDI) and healthy volunteers.
Stool samples from patients with *C. difficile*-negative diarrhea, active CDI, and healthy volunteers were collected and stored at -80°C. MoBio DNA isolation kits were used for stool DNA extraction. Sequencing was performed on the 16S rRNA V4 region using an Illumina MiSeq platform. Data analyses were conducted in QIIME and R-3.1.2.
Results: We profiled gut microbial communities from 115 patients with *C. difficile*-negative diarrhea (76 females, age 46.5 ± 1.6 years) and compared them to 92 patients with CDI and 110 healthy volunteers. Among the patients with *C. difficile*-negative diarrhea, 16 (14%) had Crohn's disease, 13 (11%) had ulcerative colitis, 7 (6%) had viral gastroenteritis, 21 (18%) had IBS, and 56 (49%) had other causes of diarrhea. Gut microbial communities from patients with CDI were significantly different (PERMANOVA $p < 0.05$) from healthy volunteers as assessed by the unweighted UniFrac distance metric (β diversity). A subset of patients with *C. difficile*-negative diarrhea (n = 54 of 115) had markedly altered gut microbial communities characterized by lower relative abundances of *Bacteroidetes* and higher relative abundances of *Proteobacteria*. These alterations resembled gut microbial changes in patients with CDI. Additionally, these alterations were associated with clinical risk factors commonly linked to the development of CDI: recent antibiotics (odds ratio; 95% confidence interval; 0.24; 0.08-0.67; p = 0.003), immunosuppression (0.32; 0.13-0.77; p = 0.006), current hospitalization (0.21; 0.06-0.68; p = 0.004), recent hospitalization (0.26; 0.07-0.83; p = 0.01), and prior CDI (0.06; 0.001-0.43, $p < 0.001$). The remaining *C. difficile*-negative patients (n = 61 of 115) had gut microbial communities that resembled those of healthy volunteers.
Conclusion: A subset of patients with *C. difficile*-negative diarrhea but clinical risk factors associated with CDI - including hospitalization, prior CDI, recent antibiotics, and immunosuppression - exhibit gut microbial alterations similar to those seen in patients with CDI. These clinical risk factors may instigate changes in the gut microbial community resulting in diarrhea and increased susceptibility to CDI.

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Disclosure of Interest: None declared

OP410 SELECTIVE DECONTAMINATION OF THE DIGESTIVE TRACT AT THE INTENSIVE CARE UNIT PROMOTES SPREAD OF CLOSTRIDIUM DIFFICILE INFECTION

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Introduction: An outbreak of a single clone of *Clostridium difficile* ribotype 027 occurred at the VU University Medical Center, involving 19 medical departments. Several risk factors for CDI are known, but factors specifically associated with hospital-wide outbreaks are less well defined.
Aims & Methods: Primary aim is to determine risk factors associated with hospital-wide spread of clonal *Clostridium difficile*-infection (CDI) due to ribotype 027.
We performed a case control-study during an outbreak of CDI due to a single clone of *C. difficile* ribotype 027 in a 750-bed tertiary care medical centre.
Microbiological ***Methods:*** *C. difficile* isolates were characterised by ribotyping, Amplified Fragment Length Polymorphism, and Multi Locus Sequence Typing. A selection of strains (n = 10) was also characterised by Whole Genome Sequence analysis.
Participants: cases (n = 79) were diagnosed with CDI due to *C. difficile* ribotype 027 during hospitalization between May 2013 and March 2014. Each case was matched to 4 controls for age and medical specialty (n = 316); controls stayed on the same ward as the index patient within 48 hours of diagnosis and had no known history of CDI.
Variables: medical charts were reviewed for demographic, clinical and healthcare associated characteristics.
Statistical Methods: Odds Ratios (OR) and their 95% Confidence Intervals (95% CI) were calculated by univariate and multivariate conditional logistic regression (SPSS version 20).
Results: Nearly all patients with CDI (75/79) had used antibiotics prior to CDI, compared to 176/316 of controls (OR 7.37; 95% CI 2.44 to 22.30). Cases were more likely than matched controls to have stayed on a high care ward like ICU or MCU (OR 5.64; 95% CI 2.03 to 15.65), had a longer length of stay (11-25 days: OR 3.50; 95% CI 1.19 to 10.30; > 25 days: OR 4.38; 95% CI 1.31 to 14.68), and had been recently (< 90 days) admitted before this admission (OR 2.19; 95% CI 1.06 to 4.55). Cases were less likely to have been admitted to a ward with a known CDI patient that was nursed in isolation (OR 0.24; 95% CI 0.09 to 0.63). There was no significant association with the number of ward transfers or the use of proton pump inhibitors (PPI). The overall 30-day mortality was 18% for cases and 8% for controls (HR 2.25; 95% CI 1.06 to 4.76). For participants that stayed on a high-care ward during their hospital admission (cases n = 45; controls n = 81), the use of selective decontamination of the digestive tract (SDD) was strongly associated with acquiring CDI, also when adjusted for sex, Apache IV score, Charlson comorbidity index and length of stay (OR 9.95; 95% CI 3.29 to 30.08).
Conclusion: In this large outbreak, caused by a single clone of *C. difficile* ribotype 027, antibiotic use appeared as a prerequisite for acquisition of this outbreak strain. We identified stay on a high-care unit but especially the use of SDD as a major risk factor for acquisition of CDI. Restriction of SDD use during an outbreak of CDI might be a possible measure to prevent furher spread that merits further investigation.
Disclosure of Interest: None declared

OP411 GENETIC INFLUENCE ON COMPOSITION OF THE INTESTINAL BACTERIA IN HEALTHY FIRST DEGREE RELATIVES (FDR) OF CROHN'S DISEASE (CD) SUBJECTS

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Introduction: Genome-wide association studies (GWAS) have identified numerous genetic associations with inflammatory bowel disease (IBD) most of which

encode proteins involved in immunity, host defense against microbes, and gut homeostasis. IBD patients have a dysbiosis. However as inflammation influences the composition of the microbiota, it is unknown whether these differences are a cause or result of intestinal inflammation.

Aims & Methods: In order to determine if the composition and diversity of gut microbiota are associated with host genetic makeup we assessed the stool microbiome in a cohort of 1,273 healthy Caucasian FDR of CD patients. 16S rDNA were sequenced from the stool and MiSeq sequences were processed using the QIIME pipeline. After rarefaction at 30,000 reads per sample, bacterial alpha diversity was estimated. Genotyping and imputation was performed using the HumanCoreEXOME chip and IMPUTE2. Polygenic heritability (H2R) of the gut microbiota was calculated using SOLAR software. Analysis of 50 demographic and environmental factors identified age as the most important factor associated with microbial makeup and it was included as covariate in subsequent analysis. Genome-scans at every microbial taxonomic level were carried out on imputed SNPs with a minor allele frequency $>5\%$. We used a generalized estimating equation assessing the association between the taxa and potential genetic effects controlling for age, sex, and the first three genetic principal components in European origin subjects. We performed a sensitivity analysis using two models: a log-normal model on the non-zero outcomes and a two-part log-normal model fitting both a logistic model on the absence/presence of the taxa and the log-normal model described before.

Results: Overall, the dominant phyla in these samples were Firmicutes (relative abundance of $64.2\% \pm 14.1$, (mean $\pm$ SD)), Bacteroidetes ($26.9\% \pm 15.0$), and Actinobacteria ($5.0\% \pm 5.2$). A total of 91 out of 253 taxa showed significant heritability ($25\% < H2R < 67\%$, $3.2 \times 10^{-6} <$ p-value < 0.05). No significant associations were observed between genotype and bacterial alpha diversity and no associations were observed among 123 SNPs known to be associated with IBD. However among 3,727,707 high-quality SNPs, as many as 65 SNPs reach genome-wide significance (p-value $< 5 \times 10^{-8}$) for association with the relative abundance of 34 microbial taxa.

Conclusion: These results suggest that host genetic variants are associated with differences in intestinal microbiota composition in healthy FDR. This study differs from prior analysis of microbiota in patients with CD where the composition of the microbiota was influenced by the effects of treatment and the inflammatory process itself. It remains to be determined if the genetic associations with microbiome differences identified are related to the risk of developing Crohn's disease.

Disclosure of Interest: None declared

OP412 THE DYSBIOSIS INDEX DOES NOT DISTINGUISH CHILDREN WITH CROHN'S DISEASE FROM HEALTHY SIBLINGS

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Introduction: Patients with Irritable Bowel Syndrome (IBS) are often used as controls in studies of the Crohn's disease (CD) microbiome. However, digestive symptoms among the IBS-controls could be associated with microbial dysbiosis. An alternative design is to use healthy siblings of CD patients as controls. As healthy siblings should be free from such symptoms, comparisons with CD patients should be more straightforward. Further, familial controls offer the possibility to tease out hereditary or dietary factors.

Aims & Methods: Our aims were to compare the microbial community composition of stool samples from healthy siblings and pediatric CD patients, to characterize their microbiomes at the functional level and to investigate the familial effect on measurements of community diversity and the potential relationship between dysbiosis and the CD phenotypes, using the Dysbiosis Index (DI), a recent measure of microbial dysbiosis, which was originally derived from a dataset dominated by biopsy samples taken from CD patients, and was shown to be associated with clinical disease severity.

Metagenomic sequences from stool samples of 5 pediatric CD patients and their siblings were obtained using MiSeq on both whole-metagenome sequencing and16S ribosomal RNA fragments. Microbial composition profiles based on 16S ribosomal RNA genes were derived from the green genes database. To obtain functional assignment, sequences were searched against 28 representative KEGG (Kyoto Encyclopedia of Genes and Genomes) pathways, with putative functions ultimately assigned by using HUMAnN. Microbial composition profiles were analyzed using QIIME and STAMP, and functional profiles were inferred using STAMP and BiomeNet. Microbial dysbiosis was determined for each sample as implemented in QIIME.

Results: Examination of phylotypes that contribute to the dysbiosis index revealed that considerable among-sample variability was shared between siblings. For example, some pairs of healthy and CD siblings exhibited highly similar frequencies of phylotypes that contribute to the dysbiosis index. Clearly, in these cases it is inappropriate to attribute the CD phenotype to the presence of those lineages. Furthermore, none of the samples scored as dysbiotic according to the ensemble index, and there was no consistent relationship between sibling pairs in terms of the magnitude of their scores. Similar results were obtained at the functional level. Bayesian modeling of metabolic structures via BiomeNet also revealed a close association between many healthy and CD siblings.

Conclusion: The DI of stool samples is not able to distinguish healthy siblings from pediatric patients with Crohn's disease. We hypothesize that this is because the DI is based on too few microbial lineages. We suggest that the dysbiosis index might be improved by inclusion of more indicator lineages and functional information. Comparison to sibling controls indicates that there is a strong familial effect on both microbiome composition and function that can vary considerably among sibling pairs. This effect must be accommodated if microbiome-derived information is going to make a practical contribution to clinical care in the future.

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Disclosure of Interest: K. Dunn: None declared, J. Connors: None declared, B. MacIntyre: None declared, A. Stadnyk: None declared, J. Bielawski: None declared, N. Thomas: None declared, A. Otley: None declared, J. Van Limbergen Financial support for research: Abbvie, Lecture fee(s): Abbvie, Janssen, Nestle, Consultancy: Nestle

OP413 EXCLUSIVE ENTERAL NUTRITION TREATMENT RESTORES THE MUCOSA-ASSOCIATED INTESTINAL MICROBIOME IN CHILDREN WITH CROHN'S DISEASE

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Introduction: Aberrant host immune responses to the intestinal microbiome are likely to contribute to Crohn's disease (CD) pathogenesis. Intestinal microbiome dysbiosis is reported in both adult and pediatric CD. Exclusive enteral nutrition treatment (EEN), by sterile liquid formula as the only intake of nutrients for 6-8 weeks as monotherapy, is recommended as remission induction treatment in pediatric CD. However, the mechanisms by which EEN induces remission in pediatric CD is still obscure. We hypothesize that EEN exerts its action by restoring the intestinal microbiome.

Aims & Methods: The aim was to compare the mucosa-associated intestinal microbiome before and after eight weeks of EEN in treatment-naive children with CD. Mucosal biopsies from ileum and left colon were collected from eight children with newly diagnosed CD before and at the end of eight weeks of EEN. Biopsies were frozen in liquid nitrogen and stored in -70 C. To determine the microbiome the16S™ Metagenomics Solution (Thermo Fisher Scientific) was used. After DNA extraction, seven hypervariable regions (V2, V3, V4, V6, V7, V8, and V9) of bacterial 16S rRNA were amplified using Ion 16S™ Metagenomics Kit (Thermo Fisher Scientific). The amplified fragments were sequenced on the Ion PGM™System (Thermo Fisher Scientific). The Ion Reporter™ Software was used for initial data processing and analysis.

Results: All children were in clinical remission at the end of EEN, and a repeat colonoscopy revealed macroscopic and histologic improvement but not full mucosal remission. In all children the mucosa-associated intestinal microbiome in both ileum and left colon changed radically with an increased overall bacterial diversity. Also, a shift in microbiome composition followed EEN, with decreased abundance in bacterial orders bacteroidales and enterobacteriales.

Conclusion: The positive clinical and histological response to EEN in children with CD correlated to an increased diversity in the mucosa-associated intestinal microbiome. These findings support the hypothesis that EEN exerts its effects in pediatric CD by restoring the mucosa-associated intestinal microbiome.

Disclosure of Interest: None declared

OP414 THE GUT MICROBIOME DIFFERENTIATES CLINICAL PHENOTYPES IN MODERATE TO SEVERE CROHN'S DISEASE: RESULTS FROM THE CERTIFI STUDY

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Introduction: The aim of this study was to investigate the relationship between the fecal microbiome and clinical phenotypes in subjects with moderately to severely active Crohn's disease (CD). Specifically, the potential of the microbiome to differentiate among Crohn's patient sub-groups as defined by specific clinical traits was examined.

Aims & Methods: CERTIFI was a Phase 2b multicenter, randomized, double-blind, placebo controlled clinical trial to evaluate the efficacy and safety of ustekinumab therapy in subjects with moderately to severely active CD who had previously not responded to anti-TNFα therapy. Fecal samples from 100 subjects, collected at screening, week 4, week 6, and week 22 study visits, and stored at -80°C, were selected for microbiome analysis. Bacterial DNA was extracted from the fecal samples using the MoBio PowerSoil DNA Isolation kit and subjected to 16S rRNA sequencing and shotgun metagenomic sequencing. 16S rRNA sequencing was performed on the GS-FLX 454 Titanium platform and the sequences were assigned genus-level annotations. Metagenomic sequencing was performed on the Illumina HiSeq 2000 using 100 base pair paired-end processing. Filtered sequences were mapped against the MetaCyc database of metabolic pathways and enzymes. Spearman correlation, LEfSe, logistic regression, and Adonis were applied to identify bacterial taxa or metabolic pathways that were associated with clinical variables of interest.

Results: The gut microbiome of individuals with CD was characterized by pronounced inter-personal variation in the presence and relative abundance of specific bacterial taxa. Despite this heterogeneity, bacterial abundances and metabolic pathways correlated with patient sub-groups defined by specific baseline clinical traits. The baseline CDAI score significantly associated with the relative abundance of several bacteria, including Parabacteroides (rho = -0.42, P < 1e-4). The metagenomic data supported this result, demonstrating correlation between specific metabolic pathways and CDAI score. Baseline CRP, fecal calprotectin (FCALP), and lactoferrin (FLACT) concentrations also correlated with baseline bacterial abundances of specific taxa, including Dialister (rho = 0.36, P = 3e-4, Spearman correlation with FCALP), and with metagenomic data. Previous response to anti-TNFα therapy did not significantly correlate with the abundance of any specific bacteria or with metagenomic data.
Conclusion: The fecal microbiome demonstrated the ability to discriminate clinical phenotypes in moderately to severely active CD patients who had previously not responded to anti-TNFα therapy. The strongest associations between metadata and the microbiome, supported by 16S and metagenomic data, were observed for CDAI score, FCALP, and FLACT. The results suggest the potential application of the fecal microbiome as a molecular marker of disease severity in CD.
Disclosure of Interest: T. Ding Financial support for research: Janssen R & D, LLC, S. Telesco Conflict with: Employee Janssen R & D, LLC, C. Monast Conflict with: Employee Janssen R & D, LLC, C. Brodmerkel Conflict with: Employee Janssen R & D, LLC, T. Yatsunenko Financial support for research: Janssen R & D, LLC, A. Das Conflict with: Employee Janssen R & D, LLC, P. Schloss Financial support for research: Janssen R & D, LLC

OP415 THE IMPORTANCE OF THE MUCOSAL ANTIMICROBIAL PEPTIDE EXPRESSION AND GUT MICROBIOTA IN ANTI-TNF THERAPY RESPONSE IN PATIENTS WITH ULCERATIVE COLITIS

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Introduction: Anti-TNF therapy is a common treatment for patients with ulcerative colitis (UC). However, about 30-50% of the patients do not respond to the treatment and it is not understood why some patients respond while others do not. Antimicrobial peptides (AMPs), a part of the innate defense against intestinal microorganisms, and the gut microbiota are essential for gut homeostasis and may be of importance for treatment effects of anti-TNF therapy.
Aims & Methods: The aim of this study was to determine AMP and microbiota profiles in patients with UC before start of anti-TNF therapy and correlate these data to therapy outcome.
Blood, biopsy and fecal samples were obtained before anti-TNF treatment from anti-TNF therapy-naïve UC patients. Therapy response was assessed by Mayo score 12-14 weeks after treatment initiation, and response was defined as a decrease in Mayo score of $\geq$3 points. Biopsies were cultured for 24h and used for quantitative proteomic analysis by mass spectrometry or directly frozen for rtPCR analysis. AMP levels in serum were measured by ELISA. Microbiota analysis of fecal samples was performed using the GA-map^{TM} Dysbiosis Test (Genetic Analysis AS, Oslo, Norway) where dysbiosis indexes of 1-2 are considered normal while 3-5 denotes increasing dysbiosis. Multivariate factor analysis (SIMCA-P+ software; Umetrics, Umeå, Sweden) was used to examine relationship between AMP levels and bacterial content to therapy outcome.
Results: Among the 31 included patients, 17 patients responded to the therapy. According to the proteomic analysis of cultured biopsies (from 3 responders and 3 non-responders) Defensin 5 (Def5), eosinophil cationic protein (ECP) and bactericidal/permeability-increasing protein (BPI) were recorded in responders but not in non-responders. Gene expression of 11 AMPs or genes associated with AMP expression were analyzed in biopsies: Def5, ECP, BPI, Cathelicidin (CAT), Lysozyme, hβ-defensin 2, HMGB1, HMGN2, HistoneH1.5, 40S ribosomal protein S19 and HDAC1. Multivariate data analysis showed that responders and non-responders clustered differently when studying mRNA levels of the 11 genes. The most important nominators for therapy response were increased expression of Def5 (median (IQR), resp vs. non-resp; 0.598 (0.079-2.694) vs. 0.034 (0.005-0.211), p = 0.006) and ECP (0.00025 (0.00013-0.00053) vs. 0.00012 (0.00009-0.00014), p = 0.03) and decreased expression of CAT (0.0040 (0.0016-0.0133) vs. 0.0133 (0.0057-0.0498), p < 0.05). Responders also had higher serum levels of ECP compared with non-responders (33.7 ng/ml (18.7-98.9) *vs.* 7.5ng/ml (3.4-41.3) p = 0.03). Microbiota analysis of fecal samples (4 responders and 3 non-responders) revealed that non-responders tended to have higher dysbiosis indexes compared to responders (4.7 (4-5) vs. 3.3 (2-5), p = 0.097). Also, non-responders had low levels of Faecalibacterium prausnitzii while responders showed normal levels.
Conclusion: Anti-TNF therapy responders and non-responders display different patterns of mucosal AMP expression and gut microbiota before start of therapy. This indicates that infliximab therapy benefits from a defined anti-microbial defense pattern and that the intestinal microbial composition may be different in the two patient cohorts.
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 28, 2015 11:00-12:30
VIDEO CASE SESSION - ROOM F1

OP416 RAPID AND SAFE ENDOSCOPIC TREATMENT OF ZENKER'S DIVERTICULUM WITH A NEW SCISSOR LIKE ESD DEVICE

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Introduction: Zenker's diverticulum (ZD) represents a diverticulum of the mucosa of the pharynx above the cricopharyngeal muscle. Traditionally, ZD has been treated by neck surgery or rigid endoscopy. Endoscopic therapy is based on cutting the septum between the ZD and the esophageal lumen. Therefore, a variety of endoscopic methods have been used, including laser, stapler, harmonic scalpel, argon plasma coagulation, or needle knives. Here, we present the potential of a novel device originally developed for endoscopic submucosal dissection (ESD) for rapid and safe therapy of Zenker's diverticulum.
Methods: For the purpose of this study, the Clutch Cutter (Fujifilm, Tokyo, Japan) was used. The device was introduced late October 2014 to the European market and is a forceps-type resection device for ESD. The device has a 0.4mm wide and 3.5mm long serrated cutting edge. The device is rotatable and the outer side of the forceps is insulated to avoid burning of surrounding tissue. With a diameter of 2.7mm the device is compatible with most conventional endoscopes. For electrocautery, the Vio 200 D-system (Erbe, Tübingen, Germany) with the following settings was used: Forced coagulation 30W, Endo Cut Q with effect 1, duration 3, interval 1.
Results: With the patient under conscious sedation a single channel endoscope (Olympus, Tokyo, Japan) is carefully advanced in the esophagus. Directly below the upper esophageal sphincter one can clearly identify the Zenker's diverticulum which is also highlighted by the barium swallow examination. After inspection of the duodenum and the stomach the endoscope is withdrawn and a conventional feeding tube is placed through the nose of the patient. Afterwards, a clear distal cap is attached to the endoscope. The feeding tube is placed under endoscopic visualization in the gastric antrum. Afterwards, the endoscope is placed in front of the septum between the ZD and the esophageal lumen and the Clutch Cutter is advanced through the working channel of the endoscope. Subsequently, the forceps of the Clutch Cutter is opened and pushed against the septum to grasp the tissue. Electrocautery is applied and the procedure is repeated until the septum is completely cut. Of note, the Clutch Cutter device allows to selectively catch and dissect the muscle fibers. Neither bleeding nor any post procedural complications occurred. Total procedure time was 6 minutes. The patient resumed a normal diet for 48 hours. Follow-up endoscopy after 2 days revealed a significant improvement.
Conclusion: The newly introduced ESD device Clutch Cutter is a promising device for rapid and safe endoscopic treatment of Zenker's diverticulum.
Disclosure of Interest: None declared

OP417 AN EFFECTIVE ENDOSCOPIC CLOSURE TECHNIQUE OF LARGE MUCOSAL DEFECTS AFTER GASTRIC ENDOSCOPIC SUBMUCOSAL DISSECTION USING ENDOLOOP AND ENDOCLIPS FOR PATIENTS ON ANTITHROMBOTIC DRUGS

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Introduction: Delayed bleeding after gastric endoscopic submucosal dissection (ESD) is more common in patients on antithrombotic drugs, occurring in 11.6% [1]. Little is known about the prevention of post-ESD bleeding in those patients. There are case reports of complete endoscopic closure using endoloop and endoclips after endoscopic resection [2]. We aimed to investigate the technical feasibility of this endoscopic closure technique after gastric ESD in patients at high risk of bleeding who were on antithrombotic drugs.
Methods: This pilot study included 15 patients on antiththrombotic drugs who underwent a total of 16 gastric ESDs followed by endoscopic closure using endoloop and endoclips between May 2013 and April 2015. An endoloop was opened through the first accessory channel of double channel endoscope and endoclip was also prepared through the other channel after gastric ESD. We hooked endoclip on the endoloop and then anchored the endoloop along the edge of the mucosal defect using the hooked endoclips. Then the mucosal defect was closed by tightening the fixed endoloop. Plural endoloops were used as necessary for large mucosal defects. Complete closure was defined as achieving visible endoscopic closure for the whole mucosal defect and successful closure was defined as that over three fourth endoscopically. We evaluated complete closure rate, successful closure rate, procedure time for closure and post-ESD bleeding.
Results: Patients characteristics were as follows; male/female = 13/2, median age = 78 year old (67-93), aspirin/cilostazol/ticlopidine/warfarin/novel oral anticoagulant/others = 6/5/2/3/2/3 (with overlapping). ESD locations were upper/middle/lower = 3/8/5 and median resected specimen size was 33.5mm (19-65). Median procedure time for closure was 13.5 min (7-43) and mean number of endoloops was 1.4 (1-3). Complete closure rate and successful closure rate were 75% and 88%, respectively. Delayed bleeding occurred in one ESD (6.3%), which failed in closure due to trouble in releasing endoloop.
Conclusion: Endoscopic closure of mucosal defect after gastric ESD using endoloop and endoclips was technically feasible. Further prospective study is warranted to investigate the prevention of post-ESD bleeding in patients on antithrombotic drugs.

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Disclosure of Interest: None declared

OP418 EUS-GUIDED GASTROJEJUNOSTOMY FOR MANAGEMENT OF GASTRIC OUTLET OBSTRUCTION OF BENIGN ETIOLOGY

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Introduction: Techniques to create an EUS-guided gastrojejunostomy (EUS-GJ) include direct EUS-GJ and balloon-assisted EUS-GJ. The balloon-assisted technique provides a target (fluid-filled balloon) for transgastric puncture. However, after transgastric needle puncture into the jejunum, there is a concern that the jejunal loop will fall away and the wire will be lost during tract dilation. To circumvent this, we attach a polypectomy snare to the balloon catheter and grasp the wire within the small bowel. Therefore, tension can be put on the wire without a concern of losing access. A 48-year-old male was referred for management of gastric outlet obstruction (GOO) secondary to a chronic calcific pancreatitis associated duodenal stricture. He had failed to respond to multiple through-the-scope balloon dilations and was not suitable for an enteral stent. After a multidiscliplinary meeting, the decision was made to proceed with EUS-GJ and lumen opposing stent insertion.

Methods: The duodenal stricture was dilated to 15mm allowing for passage of the paediatric colonoscope into the jejunum. Then a stiff 0.035-inch guidewire was passed through the working channel of the endoscope into the small bowel. Dilute contrast was injected into the small bowel and an enterogram was obtained. The endoscope was then exchanged out for the balloon/snare catheter which was passed over the wire and inflated in the jejunum. The fluid-filled balloon was localized transgastrically by EUS and was punctured with a 19-gauge needle. A stiff 0.035-inch wire is then advanced through the needle, through the open snare into the small bowel. The snare was then closed to secure the wire. The needle was exchanged out and the tract was subsequently dilated using modified needle-knife (bent tip) and a 4mm dilating balloon (stent delivery system is 10.8F in diameter). The lumen opposing stent was then advanced over the wire, deployed and subsequently the lumen was dilated to 15mm.

Results: Total procedure time was 43 minutes. The patient was kept nil per oral overnight and upper gastrointestinal series the following day demonstrated a patent stent. The patient was dicharged home with a 5-day course of prophylactic oral antibiotics and full-fluid diet for 10 days. The patient was subsequently commenced on a normal diet.

Conclusion: EUS-GJ is a minimally-invasive, effective and safe method of managing GOO. The duration of stent placement necessary to establish a permanent and patent fistula after stent removal needs to be ascertained.

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Disclosure of Interest: V. Kumbhari: None declared, S. Ngamruengphong: None declared, M. El Zein: None declared, A. Tieu: None declared, G. Aguila: None declared, M. Khashab Financial support for research: Cook Medical, Consultancy: Boston Scientific, Olympus America, Xlumena

OP419 CREATION OF GASTRO-GASTROSTOMY AND DUODENO-JEJUNOSTOMY USING LUMEN APPOSING STENTS FOR ACCESS TO CHOLEDOCHOJEJUNOSTOMY

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Introduction: Treatment of biliary diseases is challenging in altered anatomy. EUS-guided access using fully covered lumen apposing metal stents (FCLAMS) allows for safe creation of a fistula between lumens and stabilization of lumen walls for more direct access.

Methods: 28-year-old woman who had Roux-en-Y gastric bypass, had a cholecystectomy that was complicated by common bile duct injury and subsequent recurrent cholangitis requiring multiple surgeries, including choledochojejunostomy, resection of segments 5 and 6 with revision of Roux limb. Recurrent episodes of cholangitis required multiple percutaneous interventions. She was referred for endoscopic management of recurrent cholangitis with internalization of biliary drainage.

Entersocopy-assisted ERCP was unsuccessful in reaching the biliary anastomosis. Contrast injection through the PTC drain showed abutment of the Roux limb with the duodenum. Re-establishment of the native anatomy in order to access to the bile duct was planned. In the first step, a gastro-gastric fistula was created under EUS-guidance, and a FCLAMS was placed between the two gastric segments. Three weeks later the second step was performed in which an EUS scope was advanced through the stent to the native duodenum where the Roux limb was identified and a duodeno-jejunal fistula was created under EUS guidance. A FCLAMS was then advanced across the new duodenojejunal fistula and deployed. The EUS was removed and a pediatric colonoscope was inserted through both FCLAMS and the choledochojejunostomy was visualized. The bile duct was cannulated and a biliary stent placed. Afterwards the patient was able to have her PTC drains removed, had resolution of pain and no recurrence of cholangitis.

Results: We have successfully used multiple FCLAMS to achieve biliary access in a patient with gastric bypass and choledochojejunostomy. There were no complications. This access can be used for repeat long-term interventions.

Conclusion: This case demonstrates successful use of multiple FCLASs to establish access in a patient with altered anatomy in order to treat recurrent cholangitis.

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Disclosure of Interest: None declared

OP420 TRANSHEPATIC PERCUTANEOUS ENDOSCOPIC JEJUNOSTOMY TO THE AFFERENT LOOP USING LUMEN-APPOSING METAL STENT FOR TRANSPROSTHETIC ENDOTHERAPY

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Introduction: Percutaneous transenteric approaches allow ERCP when enteroscopy fails. Percutaneous-Assisted Transprosthetic Endotherapy (PATENT) uses large calliber metal stents to allow percutaneous duodenoscope passage into the GI tract. We present a triple modification of currently reported PATENT techniques: a) Transhepatic antegrade cholangioscopy and abdominal ultrasound to guide direct PEJ placement; b) Lumen-Apposing Metal Stent instead of tubular SEMS; and c) Direct cholangioscopy via PATENT. A patient with 9 prior laparotomies, including Billroth-2 gastro-jejunostomy and Roux-en-Y hepatico-jejunostomy had severe relapsing biliary sepsis and hepatholithiasis on MRI. Further percutaneous or surgical intervention was ruled out.

Methods: A three-staged intervention was carried out. 1st: EUS-guided Hepatico-Jejunostomy (EHJ) with two overlapping covered SEMS from the B2 afferent jejunal limb into the left hepatic duct. 2nd: Transhepatic antegrade cholangioscopy through the EHJ and the surgical hepaticojejunostomy into the Roux-en-Y afferent limb to guide D-PEJ. Transilumination was not obtained despite close proximity on fluoroscopy. Transabdominal ultrasound was used to monitor percutaneous puncture of the Roux-en-Y afferent limb. A 15 mm diameter Lumen-Apposing Metal Stent was placed as conduit for PATENT. 3rd: Retrograde percutaneous cholangioscopy via PATENT to dilate a dominant right hepatic duct stricture and to rule out residual hepatolithiasis.

Results: The patient recovered uneventfully and remains well at 7-month follow-up.

Conclusion: This case illustrates custom-made approaches combining emerging EUS & percutaneous transenteric procedures with novel stent technology to relieve biliary obstruction where standard approaches fail.

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OP421 WHAT ARE YOU DOING IN THERE? A CASE OF AN UNUSUAL PANCREATIC LESION

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Introduction: Schwannomas are benign spindle cell tumors derived from the Schwann cells that line the nerve sheaths. Extracranial neuromas typically occur in the peripheral extremities. Visceral location of these tumors is rare. Pancreatic schwannomas are uncommon and often difficult to diagnose given their similarity with more common pancreatic cystic lesions.

Methods: A 62-year-old female with a past medical history of type II Neurofibromatosis presents with a two-year history of abdominal pain and 15

pound unintentional weight loss. Patient had a recent normal upper endoscopy and colonoscopy. No change in her symptoms with proton pump inhibitors or anti-spasmodic therapy. MRI of the abdomen and pelvis revealed a multilobulated circumscribed mass between the uncinate process of pancreas and C-loop of duodenum measuring 2.7 x 2.0 cm. Mass showed increased signal on T2 as well as prominent surrounding lymph nodes. Endoscopic ultrasound showed a complex of hypoechoic masses in the uncinate process, the largest of which measured 2.3 cm. In some views, there were cystic components to these lesions. FNA revealed a spindle cell neoplasm which stained positive for S-100, consistent with schwannoma.

Results: Pancreatic schwannomas arise from the nerve sheath of the branches of the vagus nerve which courses through the pancreas. These tumors are slow growing and rarely malignant. They are typically located in the head and body of the pancreas. 60% of these lesions are cystic, and as such can mimic more common cystic pancreatic lesions such as cystadenoma, intraductal papillary mucinous neoplasm, and pseudocysts. These tumors are typically asymptomatic on presentation, but can present with abdominal pain and weight loss. On cytology, schwannomas are composed of spindle cells with indistinct cytoplasmic borders with wavy nuclei embedded in a collagenous matrix. Schwannomas stain strongly positive for S-100 protein. Given their slow growth and low rate of malignant transformation, treatment is typically enucleation or watchful waiting if asymptomatic.

Conclusion: Although pancreatic schwannoma is a rare and benign disease, it should be considered in the differential diagnosis of pancreatic lesions with cystic changes. The diagnosis of pancreatic schwannoma is difficult given its common appearance and low yield of specimen collection with fine needle aspiration.

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Disclosure of Interest: None declared

OP422 ENDOSCOPIC BAND LIGATION: AN EFFECTIVE THERAPY FOR ACTIVE DIVERTICULAR BLEEDING

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Introduction: Colonic diverticular bleeding is the most common cause of lower gastrointestinal bleeding in adults. Recently, new endoscopic techniques have been developped to identify the responsible diverticulum and achieve immediate mechanical hemostasis. Band ligation has been proposed as a safe and effective endoscopic approach and recent studies defend this technique is superior to hemoclips and should therefore be attempted as the initial therapy for active diverticular bleeding.

Methods: The authors present a video case of diverticular bleeding successfully diagnosed and treated by endoscopy using band ligation technique. The gastroscope *GIF-Q165, Olympus®*, and the band-ligator device *SpeedbandSuperview Super, Boston Scientific®*, were used in this procedure.

Results: A 84-year-old female patient with past medical history of hypertension, cerebral vascular disease and end-stage kidney disease under dialysis, not on anticoagulation or antiplatelet therapy, was admitted with sudden, painless severe hematochezia, hypovolemic shock and acute severe anemia (hemoglobin 6.9 g/dL). After bowel preparation, a full colonoscopy with ileoscopy was performed, showing bright red blood in the transverse and left colon and multiple sigmoid diverticula. Vigorous water lavage was performed, allowing identification of a diverticulum with active bleeding in the sigmoid colon. A marking clip was placed near to the responsible diverticulum. After switching to a conventional gastroscope with the band-ligator attached to the tip, aspiration and eversion of the bleeding diverticulum was performed and an elastic band was placed around its base, producing immediate hemostasis. Then, the opposite colonic wall was tattooed. Within a 3-months follow-up, no complications and no rebleeding were documented.

Conclusion: Band ligation proved to be a safe and effective endoscopic treatment for active diverticular bleeding.

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Disclosure of Interest: None declared

OP423 EMR DISSECTION OF A 100MM 90% CIRCUMFERENTIAL LATERALLY SPREADING TUMOUR OF THE RECTUM

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Introduction: We present the case of a 80-year-old man presenting with PR bleeding. At colonoscopy he was found to have a 100mm Paris 0-IIa/Is Kudo IV laterally spreading tumour of the rectum, from 7 to 17 cm from the anal verge. He was referred to Westmead Hopsital, Sydney for endoscopic resection.

Methods: The resection of this lesion was performed piecemeal by endoscopic mucosal resection (EMR). The specific techniques involved are demonstrated including snare placement, multiple snare types and resection of a wide margin of normal tissue to prevent recurrence [1]. Snare tip soft coagulation is demonstrated as an effective method to control intraprocedural bleeding [2]. Use of multiple angles, multiple resections and retroflexion over a fold is shown to be required in the complete resection of the lesion.

Results: A new technique described at Westmead is also demonstrated in the video. EMR dissection describes the technique required to perform EMR of large lesions with Paris Is components and extending over folds. Numerous resections are often required to delineate the plane of the resection and isolate the Is component with that component resected last if possible and en bloc. Submucosal invasion is more likely in lesions with Is components and is most likely beneath the Is area [3]; en bloc resection allows ease and accuracy of histopathological assessment once this area has been dissected from the surrounding tissue.

Conclusion: We have demonstrated the possibilities of a novel resection technique termed EMR dissection, alongside multiple standard techniques. This type of lesion is presenting more frequently to endoscopists as the boundaries of possibility with endoscopic resection are extended. We hope this video is informative to our European colleagues who encounter such lesions in their centres.

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Disclosure of Interest: None declared

OP424 POCKET CREATION-TUNNELING METHOD FOR TREATMENT OF RECTAL GIANT (18 CM) LATERAL SPREADING TUMOR WITH ENDOSCOPIC SUBMUCOSAL DISSECTION

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Introduction: Endoscopic submucosal dissection(ESD) is an effective and safe method, enabling en-bloc complete resection of lesions. Pocket-creation method is an ESD technique which helps safe dissection of the submucosal area and en-bloc resection of the lesion(1). We report a case of laterally spreading tumor (LST) in rectum 18cm in size which was successfully resected by ESD using two different techniques.

Methods: Procedure was performed after the patient was sedated with spinal anesthesia technique at endoscopy unit. Submucosal invasion was evaluated by chromoendoscopy and by endoscopic ultrasonography before ESD. To achieve en-bloc resection and benefit from gravity, ESD was planned as follows: open a tunnel at anal site of the lesion to proximal site when the patient is on left lateral position and then connect the tunnel to the right site of the lesion. Afterwards for the benefit of gravidity and clear sight re-position the patient to right lateral, join the tunnel to the left site of the lesion. A mixture of sodium hyaluronate, indigo carmine was injected for submucosal elevation. After 2-3 cm of dissection the mixture of saline, epinephrine and indigo carmine was used for quicker injection. ESD was performed using Dual Knife.

Results: The patient was a 61-years-old male with giant LST at rectum starting at 3 cm from the anal canal and extending proximally measured 13 cm endoscopically. The resected tumor was taken out as en-bloc and measured 179*108 mm. The procedure time was 224 minutes. Pathologic examination showed intramucosal carcinoma, lateral and vertical margins were clear. No complication occurred during or after the procedures. Two months later no residual tissue was seen on colonoscopic examinations.

Conclusion: Two different techniques; Pocket creation tunnelling method (PCM-t) and gravidity effect of standard ESD, were used together for an effective and controlled dissection of giant lesion which was successfully removed en-bloc. As the lumen of colon is narrow, with standard ESD technique the dissected lesion can completely block the lumen, decrease maneuver capacity of the endoscope. When PCM-t is performed, dissection can be done with control because dissected lesion does not fall directly into the lumen. Colorectal ESD is an effective and safe method for large lesions in experienced hands and using both techniques together may provide en bloc resection.

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Disclosure of Interest: None declared

OP425 A CASE OF PERFORATION DURING COLORECTAL ESD WITH NO SERIOUS ADVERSE EVENTS AFTER APPLICATION OF POLYGLYCOLIC ACID SHEETS AND FIBRIN GLUE

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Introduction: Endoscopic submucosal dissection (ESD) for large colorectal tumors is an effective method of treatment with a high curative resection rate, but is also accompanied with a relatively high rate of perforation. In cases where perforation cannot be endoscopically closed, emergency surgical treatment is frequently required. The use of polyglycolic acid (PGA) sheets, a surgical suture material, adhered with fibrin glue, has been reported to prevent leakage after surgical resection. However, there have been no reports on the efficacy of PGA sheets with fibrin glue after perforation during colorectal ESD.
Methods: An asymptomatic 72-year-old male patient underwent colonoscopy due to positive fecal occult blood tests, resulting in the discovery of a laterally spreading tumor in the descending colon. The patient was referred to our institute, and preoperative magnifying endoscopy examination revealed characteristics that were suggestive of adenoma. However, there were irregular areas within the lesion, and early stage adenocarcinoma could not be ruled out. ESD was advised for en bloc resection.
Results: ESD was performed at our endoscopy unit under conscious sedation. Treatment began smoothly, but as ESD progressed, the target submucosal layer regressed into a fibrotic layer. During dissection of the fibrotic layer perforation occurred, which further widened as dissection of the fibrotic layer continued, and eventually led to an enormous perforation with the underlaying omentum clearly visible. Endoscopic clip closure of the perforation was attempted, but complete closure was technically unfeasible. Clip closure of the perforations was discontinued, and as an emergency measure the perforation was covered with multiple strips of polyglycolic acid sheet, and adhered with fibrin glue. After this procedure, there was no visible perforation remaining and no apparent signs of continuous gas leakage, achieving clinical complete closure of the perforations. The patient displayed a slight fever the day after ESD, but was otherwise asymptomatic, with no significant changes in laboratory findings. Postoperative CT findings revealed free air in the abdominal cavity, but with no signs of peritonitis. Oral diet was begun on day 7 after ESD, and the patient was discharged with no adverse events.
Conclusion: This is a case report of colorectal perforation where the application of polyglycolic acid sheets and fibrin glue was effective in closure of perforation. In cases where complete clip closure of colorectal perforation is not technically feasible, this novel method may be useful for minimizing adverse events. Further evaluation is required for confirmation.
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WEDNESDAY, OCTOBER 28, 2015 11:00–12:30
RECENT ADVANCES IN DIVERTICULAR DISEASE AND MICROSCOPIC COLITIS – ROOM E3

OP426 PREDICTIVE VALUE OF THE "DICA" ENDOSCOPIC CLASSIFICATION ON THE OUTCOME OF THE DIVERTICULAR DISEASE OF THE COLON: AN INTERNATIONAL STUDY

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Introduction: The endoscopic classification DICA (Diverticular Inflammation and Complication Assessment) has been recently developed for patients suffering from diverticulosis and diverticular disease.
Aims & Methods: The aim of this study was to assess its predictive value on the outcome of the disease. We reassessed retrospectively patients in whom endoscopic videos and/or photos and/or clinical follow-up were available. For each patient, we recorded: age at the time of disease occurrence; severity of DICA (grade 1, 2 or 3) at the time of diagnosis; months of follow-up; therapy taken during the follow-up; occurrence/recurrence (in months) of diverticulitis.
Results: The study enrolled 1651 patients (793 M, 858 F, mean age 66.6 ± 11.1 years): 939 (56.9%) patients were classified as DICA 1, 501 (30.3%) as DICA 2 and 211 (12.8%) as DICA 3. The mean follow-up was 29.5 ± 28.7 months. Acute diverticulitis (AD) occurred/recurred in 263 (15.95) patients ; surgery was necessary in 57 (21.7%) of those cases.
DICA was the only factor significantly associated to the occurrence of diverticulitis ($p < 0.0001$) and surgery ($p < 0.0001$) either at univariate or multivariate analysis. At each level of DICA classification a significant increase of diverticulitis occurrence was detected (HR (95% CI): DICA 1 vs DICA 3: 18.992 (12.267 to 29.406); $p < 0.0001$).
Therapy with various regimens was taken by 869 (52.6%) patients during the follow-up. With respect to prevention of occurrence/recurrence of diverticulitis, assumption of therapy was effective only in DICA 2 patients with HR (95% CI) of 1.796 ($p = 0.002$); therapeutic regimens including mesalazine were the only effective therapies to reduce diverticulitis occurrence/recurrence compared to no therapy (HR (95% CI) mesalazine-based therapies vs no therapy: 0.2103 (0.122 to 0.364), $p < 0.0001$).
Conclusion: DICA classification is a valid parameter to predict the risk of diverticulitis occurrence/recurrence in patients suffering from diverticular disease of the colon.
Disclosure of Interest: None declared

OP427 EFFICACY OF RIFAXIMIN AND DIETARY FIBER ON SYMPTOMS OF UNCOMPLICATED DIVERTICULAR DISEASE OF THE COLON

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Introduction: Dysbiosis is common in patients with diverticular disease of the colon. Available data show the efficacy of poorly absorbed antibiotics and dietary fiber in achieving symptomatic relief in patients with uncomplicated diverticular disease. However, their value in the prevention of inflammatory complications of the disease needs to be further explored.
Aims & Methods: The aim of the study was to comparatively evaluate the long-term efficacy of Rifaximin and dietary fibers in reducing symptoms and to prevent both recurrent attacks and complications such as diverticulitis. 282 patients (161 males, 121 females, age 65.4 ± 7.4 years) from two gastroenterological units were enrolled in the study in two treatment schedules in a randomized fashion: Group 1 (172 pts) rifaximin 400 mg BID; Group 2 (110 pts) dietary fiber supplementation (Colon Help 20 gr/day). Treatments were administered 10 days every month for 9 months. Inclusion criteria were: endoscopic and/or radiologic evidence of diverticular disease of the left colon and the presence of symptoms attributable to diverticular disease without signs of diverticulitis.
Results: Clinical evaluations (Global Symptomatic Score – GSS), endoscopic and imagistic evaluations were performed at admission and at 3 month intervals. Analysis of standardized deviates showed that both treatments were effective in reducing tenesmus, bloating, diarrhea, well-being and bleeding ($p < 0.0001$; $p = 0.01$; $p = 0.01$; $p = 0.01$; $p = 0.04$ and $p = 0.03$, respectively after 9 months). GSS declined in both groups, but a greater reduction was evident in the rifaximin group (intention-to-treat analysis 3.31 ± 2.68 vs 5.86 ± 4.55, $p < 0.001$; per-protocol analysis: 3.50 ± 2.56 vs 6.32 ± 4.21, $p < 0.001$). The patients treated with rifaximin showed a more marked reduction in symptom frequency. Complications occurred in 5 patients of group I (3 cases of rectal bleeding and 2 of diverticulitis) and in 9 patients of the fiber group (3 cases of intestinal infections, 2 of rectal bleeding and 4 of diverticulitis) – $p = 0.031$. Side effects occurred in 7 patients of the rifaximin group and 5 patients of the fiber group ($p = NS$).
Conclusion: Cyclic administration of rifaximin and dietary fiber is effective for the symptomatic relief of uncomplicated diverticular disease of the colon. Some symptoms and complications showed greater improvement with rifaximin, which is safe and well-tolerated by patients.
Disclosure of Interest: None declared

OP428 DISTRIBUTION OF HISTOLOGICAL LESIONS OF MICROSCOPIC COLITIS (MC): OVER 9 MC OUT OF 10 CAN BE DIAGNOSED BY A LEFT COLONOSCOPY: RESULTS OF THE FRENCH NATIONAL COHORT ANGH

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Introduction: The aims of this study were to evaluate the characteristics and topography of histological diagnosis lesions of MC, lymphocyte (LC) and collagen (CC), from the national cohort COLMI (1) conducted between September 2010 and June 2012 in 26 French general hospitals.

Aims & Methods: The patients of the cohort with MC were included. The diagnosis of CC or LC was made by colonoscopy with multiple biopsies of the rectum and colon. Collagenous colitis was defined by a sub epithelial collagen layer reaching or exceeding 10 mm thickness, and LC by an increased intra-epithelial lymphocytes count reaching or exceeding 20 lymphocytes per 100 epithelial cells. Diagnoses of CC and LC were made according to these predefined criteria by the pathologists working in each center. It has been established that the diagnosis of MC is highly reproducible (2).

Results: 129 had MC (LC 87 and 42 CC): 99 patients (72 LC and 27 CC) had colonic biopsies in each segment and were retained for analysis. The median thickening of the collagen membrane significantly increased of the rectum to the right colon, respectively 14.5+/-15.8 microns, 15.2+/-20, 20+/-11.8, 22.5+/-16.2. The median rate LIE was significantly lower in the rectum (22.5%+/-21.5) and identical at the level of the left, transverse and right colon, respectively 30%+/-22.2, 23.4+/-30%, 30%+/-22.3. The diagnostic sensitivity of the biopsies was maximal in the right colon, respectively 93% and 97% for CC and CL, and minimum in the rectum, 77% and 74% for CC and CL. The achievement of rectal and left colic biopsies allowed the diagnosis of CC and CL in 93% and 94% of cases. Performing additional biopsies beyond the splenic flexure allowed to diagnose all of MC. In case of CC, a lesser collagen thickening of the basement membrane was significantly associated with the presence of an autoimmune disease ($p = 0.02$). No significant correlation was observed between the intensity of the histological lesions and clinical and biological severity. In case of CL, a rate higher of intra-epithelial lymphocytes count was significantly associated with the absence of abdominal pain ($p = 0.01$) and a shorter duration of diarrhea ($p = 0.001$).

Conclusion: The diagnostic sensitivity of colonic biopsies is maximal in the right colon and minimum in the rectum. The achievement of rectal biopsies and colic left in a short colonoscopy to diagnose more than 9 microscopic colitis out of 10.

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Disclosure of Interest: None declared

OP429 RISK OF COLORECTAL POLYPS AND CANCER IN MICROSCOPIC COLITIS

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Introduction: Microscopic colitis (MC) is a disease characterized by chronic watery diarrhea, normal radiological and endoscopic appearance but microscopic inflammation. MC includes two distinct entities: lymphocytic (LC) and collagenous colitis (CC). Following the biology of MC, prolonged and increased colonic inflammation could increase the risk of colorectal polyps, adenomas and cancer.

Aims & Methods: The aim of this study was to assess the risk of colorectal polyps, adenomas and colorectal cancer (CRC) in patients with MC.

We conducted a cohort study using a nationwide population-based pathology database (PALGA) from the Netherlands (1991-2014). All incident (newly diagnosed), histologically confirmed cases of MC (lymphocytic, collagenous or unspecified) among adults (≥18 years) were identified and followed until first occurrence of colorectal polyp, adenoma or cancer, death (life expectancy of Dutch standard population was assumed) or end of study period. As a measure of the relative risk, the observed number of CRC events in the MC cohort was compared to the number of expected events in the general Dutch population (based on Dutch cancer registry), yielding the standardized incidence ratio (SIR) with 95% Confidence Intervals (CI). The one-year and five-year risk of CRC after MC diagnosis was calculated by Kaplan Meier analysis.

Results: Out of 10,826 potential MC cases, 7,897 were classified as incident MC cases (n = 4.397 collagenous; n = 2.671 lymphocytic; n = 954 unspecified type) of whom 56% were female. Median age at MC diagnosis was 60 years (IQR 49-71) with 2.5% having celiac disease at time of MC diagnosis. During follow-up (median 7.2 years IQR 3.7-11.5), a total of 702 patients were diagnosed with colorectal adenomas, yielding an incidence rate (IR) of 1155.0 (95% CI: 1071.9-1242.8) per 100,000 person-years (PYs); 321 with polyps (other than adenomas) resulting in an IR of 511.6 (95%CI: 457.9-569.9) per 100,000 PYs; and 91 with CRC yielding an IR of 142.4 (95%CI: 115.3-173.9) per 100,000 PYs. IRs were particularly high in the first year following MC diagnosis, and lowered over time. The SIR for CRC was 1.8 (95% CI: 1.4-2.2) over all time periods. When divided in time after MC diagnosis SIR was 5.6 (95%CI: 4.0-7.7) in the first year after MC diagnosis, 1.6 (95%CI: 0.7-3.3) in the second year after MC diagnosis and 1.8 (95%CI: 1.3-2.3) thereafter. The risk of CRC in the first year after MC diagnosis was 0.46% (0.32-0.62) and five years was 0.84% (0.66-1.09).

Conclusion: The risk of colorectal cancer was higher among incident microscopic colitis patients in this large Dutch nationwide cohort as compared to the general population. The increased incidence may be due to prolonged and continued colonic inflammation. Particularly in the first year following MC diagnosis high incidences of colorectal polyps, adenomas and cancer were observed, potentially because of more medical attention, which decreased over time. Whether surveillance for colorectal cancer should be considered in patients with MC needs further investigation.

Disclosure of Interest: None declared

OP430 RIFAXIMIN TREATMENT INCREASES LACTOBACILLUS ABUNDANCE IN PATIENTS WITH DIFFERENT GASTROINTESTINAL AND LIVER DISEASES

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Introduction: Rifaximin is a non-absorbable antibiotic with beneficial effects in several gastrointestinal diseases (ulcerative colitis UC, Crohn's disease CD, irritable bowel syndrome I, diverticular disease DD) and in hepatic encephalopathy. Rifaximin has non-traditional effects on gut microbiota about which a little is known.

Aims & Methods: Aim of our study was to evaluate the effect of rifaximin administration (1200 mg/daily, 10 days) on gut microbiota composition in Caucasian patients with different gastrointestinal diseases (ulcerative colitis, Crohn's disease, irritable bowel syndrome, diverticular disease) and hepatic encephalopathy. Inclusion criteria were no exposure to antibiotics, pre-/probiotics and bowel colonoscopy preparation for at least one month, and omnivore normocaloric diet for at least one year. Fecal samples were collected at baseline (time a), at the end of treatment (time b) and 1 month after the end of treatment (time c). Microbiota composition was assessed by a metagenomic gene-targeted approach (16S rRNA) using the Roche 454 GS Junior, following DNA isolation from stool samples stored at –80°C. Data were analyzed in Qiime. Biostatistic analysis was performed using R-statistics packages.

Results: Nineteen patients were enrolled in the study and all of them completed the follow-up (overall number of faecal samples: 57). No rifaximin-related sides effects were reported. Principal coordinates analysis according to weighted Unifrac distance measure did not show any significant clustering of samples according to rifaximin treatment timepoint ($p = 0.854$; permutational multivariate analysis of variance).Differential abundance analysis computed by allowing for disease effects revealed an increased abundance of Lactobacillaceae at family level (time c vs time a adj.p = <0.0001; time c vs time b adj.p = 0.001) and of Lactobacillus (time c vs time a adj.p = <0.0001; time c vs time b adj.p = 0.001).Notably, rifaximin treatment did not change significantly intra-individual bacterial diversity (alpha-diversity measures: median Chao1 time a/b/c 21/20/22 $p = 0.401$, Shannon time a/b/c 1.45/1.13/1.6 $p = 0.102$).

Conclusion: Rifaximin treatment is able to increase the abundance of the beneficial bacteria Lactobacillus in patients with different gastrointestinal and liver diseases without affecting the overall microbiota composition and intra-individual bacterial diversity.

Disclosure of Interest: None declared

OP431 UTILITY OF ENDOSCOPIC EXAMINATION IN DIAGNOSING ACUTE GRAFT-VERSUS-HOST DISEASE OF THE GASTROINTESTINAL TRACT

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Introduction: Acute graft-versus-host disease (GVHD) occurring within 100 days post-transplant is a critical factor influencing prognosis in transplant recipients. However, because the disease is rare, only a few studies have investigated the endoscopic features of GVHD.
Aims & Methods: In this study, we retrospectively investigated the diagnostic accuracy for acute GVHD in the GI tract and revealed the characteristic endoscopic findings. Between January 2005 and June 2012, 868 patients underwent allogeneic hematopoietic stem cell transplantation at our hospital. Of 377 patients who developed GI symptoms such as diarrhea, nausea, and vomiting, 278 patients were diagnosed based on histopathological assessment of the biopsy specimen taken during upper (GS) or lower (CS) GI endoscopy within 100 days of transplantation. After excluding patients infected with cytomegalovirus, 234 cases (100 GS, 134 CS) were examined to investigate the characteristic endoscopic findings of GVHD and their positive predictive value (PPV).
Results: Biopsy revealed GVHD in 197 (84.2%) patients who had undergone GI endoscopy. The rate of positive biopsy by GI region was 79.2% (76/96) for the stomach, 84.0% (42/50) for the duodenum, 86.5% (83/96) for the terminal ileum, and 88.9% (119/134) for the colon. Frequent endoscopic findings were mucosal change (53.8%) and luster (52.6%) in the stomach; villous atrophy (46.3%) in the terminal ileum; and low vascular permeability (75.6%), edema (68.1%), and tortoiseshell pattern of the mucosa (61.4%) in the colon. No abnormal findings were observed in 65.8% of patients with GVHD in the duodenum. The PPV was 100% for the following findings: mucosal exfoliation in the stomach; villous atrophy, ulcer, and mucosal exfoliation in the terminal ileum; and ulcer and mucosal exfoliation in the colon. It was ≥90% for redness, edema, and erosion in the terminal ileum; and redness, edema, erosion, tortoiseshell pattern, and reduced vascular permeability in the colon. The PPV was ≥80% for mucosal change, luster, redness, and ulcer in the stomach; and edema and erosion in the duodenum. Furthermore, 94.4% (17/18) of patients with mucosal exfoliation throughout the GI tract had Grade 3 or 4 GVHD.
Conclusion: Despite the post-transplantation conditions, the diagnostic accuracy of GI endoscopy for GVHD was 84.2%. Useful endoscopic findings for the diagnosis of GVHD were mucosal change and luster in the stomach; villous atrophy in the terminal ileum; and tortoiseshell pattern, edema, and low vascular permeability in the colon.
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 28, 2015 11:00–12:30
COLORECTAL CANCER: CARCINOGENESIS - DETECTION - PREVENTION – ROOM E5

OP432 COLORECTAL CANCER RISK IN PATIENTS WITH BOTH LYNCH SYNDROME AND INFLAMMATORY BOWEL DISEASE

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Introduction: Lynch Syndrome (LS) and inflammatory bowel disease (IBD) are associated with an increased colorectal cancer (CRC) risk due to genetic (LS) and inflammatory (IBD) factors. Reported lifetime risks of CRC development for patients with LS range from 22 to 74%. IBD patients bear a 1.5 to 2 times greater CRC risk compared to the general population. The increased CRC risk has resulted in recommendations for surveillance and treatment in both patient groups. Although relevant for surveillance and treatment strategies, it is unknown whether CRC risk is further increased in patients that suffer from both LS and IBD. We therefore aimed to establish CRC risk in patients with both LS and IBD.
Aims & Methods: We established a cohort of LS patients assembled from two LS referral centers in The Netherlands (Radboud University Medical Center, Nijmegen; Academic Medical Center, Amsterdam). Patients with confirmed mutations in the mismatch repair genes associated with LS, including MLH1, MSH2 (and EPCAM deletion-mediated MSH2 methylation), MSH6 or PMS2 mutations, were eligible for inclusion. We linked the established LS cohort to PALGA (Dutch Pathology Registry with nationwide coverage) to identify patients with both IBD and LS. Subsequently, we compared patients with both LS and IBD (cases) and LS patients without IBD (controls) by adopting a retrospective cohort study approach in order to establish CRC risk.
Results: 15/1046 (1.4%) LS patients also carried a diagnosis of IBD, including 8 (53.3%) patients with ulcerative colitis (UC), 6 (40.0%) with Crohn's disease (CD) and 1 (6.7%) with indeterminate colitis. Disease extent in UC involved the total colon in 62.5% (5/8) and the left-sided colon in 37.5% (3/8). CD patients had either ileal involvement (50%, 3/6) or ileocolonic involvement (50%, 3/6). Despite a younger age at study inclusion in the case group (median 38.0 y versus 52.0 y, p = 0.001), the rate of CRC development was not significantly different between cases (4/15, 26.7%) and controls (313/1045, 30.4%; Table 1). The 4 cases developed CRC at a younger age compared to controls (median 36.0 y versus 46.0 y, p = 0.042). However, cumulative CRC incidence was similar between both groups (p = 0.124). All CRC patients in the case group concerned UC patients resulting in a higher cumulative CRC incidence for the UC subgroup (4/8, 46.4% at age of 38) compared to controls (313/1031, 7.0% at age of 38, $p < 0.001$).

Variable	Cases(n = 15)	Controls(n = 1031)	p-value
Male sex, n (%)	7 (46.7)	474 (45.3)	0.916
Age at study inclusion, median (range)	38.0 (26-69)	52.0 (18-100)	0.001
Lynch type			0.414
MLH1, n (%)	5 (33.3)	256 (24.8)	
MSH2, n (%)	2 (13.3)	310 (30.1)	
PMS2, n (%)	1 (16.7)	128 (12.4)	
MSH6, n (%)	7 (46.7)	337 (32.7)	
Colorectal cancer, n (%)	4 (26.7)	313 (30.4)	1.000
Age at diagnosis CRC, median (range)	36.0 (34-42)	46.0 (16-86)	0.042

Conclusion: Patients with both IBD and LS developed CRC at a younger age compared to LS patients without IBD, although cumulative CRC incidence was similar. In our unique cohort, CRC only developed in patients with UC and LS. Patients with UC showed a higher cumulative CRC incidence compared to LS patients without IBD.
Disclosure of Interest: None declared

OP433 LIQUID BIOPSY-BASED DETECTION OF COLORECTAL ADENOMA AND CANCER CASES USING FOUR TISSUE-SPECIFIC DNA METHYLATION MARKERS

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Introduction: Investigation of aberrant DNA methylation pattern of several genes may serve as a diagnostic marker for colorectal cancer (CRC) in tissue samples. Cell-free DNA (cfDNA) in the circulatory system can originate from tumor tissue; therefore the evaluation of tumor-related methylated DNA in plasma fraction – as a liquid biopsy - can be a simple and promising method for cancer screening.
Aims & Methods: Our purpose was to identify effective DNA methylation markers in tissue samples of colorectal neoplasia patients. Furthermore, our aims were to compare the cfDNA quantity of patient groups and to analyse the methylation pattern of 4 selected markers in plasma samples. Colon biopsies were collected from healthy (n = 15), adenoma (AD, n = 15) and CRC (n = 15) patients. Pyrosequencing was performed by PyroMark and GS Junior System to define the methylation levels of 19 genes showing decreased mRNA expression on the basis of whole genome gene expression profiling by HGU133 Plus 2.0 microarrays (Affymetrix) (Galamb et al. 2012). Furthermore, EpiTect Methyl qPCR Array (Qiagen) was used to characterize the methylation patterns of 96 genes in healthy (n = 10), low-grade dysplasia (LGD, n = 17), high-grade dysplasia (HGD, n = 6), and CRC (n = 17) samples. After plasma DNA isolation and concentration measurement [normal (n = 20), AD (n = 20) and CRC (n = 20)], bisulfite conversion treatment was performed. 4 potentially hypermethylated markers (SDC2, PRIMA1, SFRP1, SFRP2) were selected for DNA methylation analysis and multiplex preamplification method was developed. Methylation percent of the candidate genes was determined using quantitative methylation-specific PCR and the CT values were compared to a calibration curve based on methylated and non-methylated standard samples.
Results: 6 genes were found to be hypermethylated ($p < 0.05$) in tissue samples of both adenoma and CRC groups (e.g. SDC2, SFRP1) by pyrosequencing. Using qPCR method, we identified 10 candidate genes that were hypermethylated in more than 85% of tumor samples (e.g. SFRP1, SFRP2, SLIT2). Interestingly, the highest mean DNA methylation was measured in HGD, followed by LGD and CRC specimens. In case of plasma samples, the average of total yield (ng) of N, AD and CRC samples was 34 ± 17ng, 63 ± 39ng and 86 ± 23ng, respectively. The methylation of SDC2, PRIMA1, SFRP1, SFRP2 was observed in 95%(19/20), 95%(19/20), 80%(16/20), 80%(16/20) of patients with CRC; 75%(15/20), 80%(16/20), 85%(17/20), 85%(17/20) of adenoma samples; and 20%(4/20), 20%(4/20), 25%(5/20), 30%(7/20) of the healthy controls. Using combined analysis, at least 3 markers were methylated in 95% of CRC, 80% of AD and only 10% of normal samples.
Conclusion: Hypermethylation of tumor-specific genes was detected in tissue samples and 4 selected markers were used as combined epigenetic markers from high-volume plasma samples for CRC screening successfully with high specificity. A two-step amplification procedure was developed to detect adenoma and CRC cases with high sensitivity, despite of the low concentration of cfDNA.

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Disclosure of Interest: None declared

OP434 WHOLE-EXOME SEQUENCING OF SIX AFFECTED INDIVIDUALS IN A FAMILY WITH AN AUTOSOMAL DOMINANT INHERITED SERRATED POLYPOSIS PHENOTYPE

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Introduction: In serrated polyposis syndrome (SPS), characterized by the development of multiple serrated polyps in the colorectum, an association with heritable germline aberrations is suspected. Identification of germline aberrations underlying this clinical phenotype is important for clinical management since SPS patients are at high risk to develop colorectal cancer. We describe a large family with an autosomal dominant inheritance pattern in which we searched for the causative germline mutation.

Aims & Methods: We applied whole-exome sequencing (WES) on germline DNA of six affected family members from two generations. We screened for pathogenic germline variants in genes previously associated with multiple serrated polyps (1). Additionally, we focused on all rare (minor allele frequency (MAF) <0.01) germline variants shared between the six affected family members. Co-segregation analysis was performed for all shared variants. For one remaining variant, RNA expression levels as well as possible allele specific expression bias were determined using EBV-transformed B-lymphocytes derived from affected and unaffected family members.

Results: We encountered truncating variants in two previously described genes (1); one nonsense variant (p.E49*) in *PIF1* and one deletion affecting the canonical splice site of *RBL1*. Both variants did not co-segregate with the development of serrated polyps in the family and the variant in *PIF1* was frequently encountered in our control dataset ($n=2.329$; MAF 0.0167). Thirty variants were shared between all six exomes of which twenty-nine were excluded because of a high MAF (>0.01) in 3 control databases ($n=16$) or because they did not co-segregate with the polyposis phenotype in the family ($n=13$). One missense variant (p.E333K) in the *BCAT1* gene remained, but was predicted to be benign based on five in silico prediction tools. Although we noticed a slightly increased expression of the p.E333K allele, the overall RNA expression levels of the *BCAT1* gene were not elevated in mutation carriers. Also the gene *KRAS,* located 250kb upstream of *BCAT1*, showed normal expression levels in patient-derived EBV cell lines compared to unaffected family members that were wild type for *BCAT1*.

Conclusion: We present a family with autosomal dominant inheritence of SPS. A causative genetic germline aberration was not found using our WES-based approach in this promising family. In our family two truncating variants in previously described *RBL1* and *PIF1* genes are unlikely to explain the serrated polyposis phenotype. We hypothesize that the causative genetic factor might be located outside the regions captured by the whole-exome sequencing approach, and requires whole-genome sequencing to be identified.

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OP435 EPIGENETIC CHANGES OF WNT SIGNALING PATHWAY GENES CONTRIBUTE TO COLORECTAL CARCINOGENESIS AND PROGRESSION TOGETHER WITH MUTATIONS OF APC KEY GENE

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Introduction: The WNT signaling pathway has an essential role in colorectal carcinogenesis and progression which involves a cascade of genetic and epigenetic changes.

Aims & Methods: We aimed to analyze the genetic and epigenetic alterations of WNT pathway genes in parallel during the normal-adenoma-carcinoma sequence using next generation sequencing methods.

Whole-methylome analysis was performed from 30 colorectal tissue samples (9 colorectal carcinoma (CRC), 15 adenoma (AD) and 6 normal adjacent tissue (NAT) samples) by next generation sequencing (Illumina) after enrichment of methylated DNA using MethylCap kit (Diagenode). WNT pathway genes were selected using KEGG pathway database. Differently methylated genes were identified, and promoters regions of these genes were determined according to the 'Integrative annotation of chromatin elements from ENCODE data'. Gene expression was studied using Affymetrix HGU133Plus2.0 microarrays (38 normal, 29 adenoma and 27 CRC biopsy samples). Gene expression data (GSE37364 and in silico using 6 GEO datasets) and promoter methylation results were analyzed to find potentially methylation-regulated genes. For confirmation, data of 5-aza-2'-deoxycytidine-treated colon carcinoma cell lines were also involved. Mutations of WNT genes (APC, CTNNB1) were analyzed by 454 sequencing on GS Junior platform.

Results: The most of the differentially methylated CpG sites were localized in gene body regions. Promoter regions of 32 from the 163 analyzed WNT pathway genes were found to be differentially methylated in CRC samples compared to NAT samples, including hypermethylated AXIN2, CHP1, PRICKLE1, SFRP1, SFRP2, SOX17 and hypomethylated CACYBP, CTNNB1, MYC. In AD vs. NAT comparison, altered promoter methylation of 42 WNT signaling genes was detected including hypermethylated APC, AXIN2, DAAM2, DKK4, PRICKLE1, SOX17, SFRP1,2 and 4 and hypomethylated CACYBP, FZD3. Forty-one genes were identified which showed different promoter methylation between CRC and AD samples. Hypermethylation of AXIN2, DKK1, VANGL1 and WNT5A gene promoters was increased in CRC compared to AD, while promoter methylation of SOX17, PRICKLE1, DAAM2 and MYC genes was found to be higher in AD than in CRC. Inverse expression of 26 genes was observed during the gene expression-methylation comparative analysis. Among others, CACYBP, DAAM2, PRICKLE1, PSEN1, SFRP2 and SFRP1 genes were identified as relevant methylation-regulated WNT pathway genes in colorectal normal-adenoma-carcinoma sequence. APC mutations were detected in 0% of NAT, 27% of adenoma and 29% of CRC samples, while only one AD sample showed CTNNB1 mutation.

Conclusion: Beside the frequent APC mutations, the robust, common epigenetic changes of WNT signaling pathway genes also contribute to the development and progression of CRC. Aberrant DNA methylation also appears in adenomas indicating that DNA methylation is an early event of colorectal carcinogenesis.

Disclosure of Interest: None declared

OP436 COLORECTAL CANCER ALARM SYMPTOM INTERRELATION WITH THE PARTICIPATION IN COLORECTAL CANCER SCREENING AND FAECAL OCCULT BLOOD TEST RESULTS

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Introduction: The purpose of screening programmes is to lower the burden of cancer in the population by discovering disease in its early latent stages before any symptoms appear. The objective of the study was to evaluate if colorectal cancer alarm symptoms correlate to the participation in screening.

Aims & Methods: A self-administered questionnaire was mailed to the colorectal screening target group (50-74 years old) of a randomised faecal occult blood test (FOBT) based pilot-study in Latvia. Questionnaire was sent to all responders and non-responders and it was asked if they had observed any of the listed health problems during the last year (multiple-choice question). Listed symptoms were abdominal pain, stool changes (diarrhoea or obstipation), weakness or fatigue, a lot of mucus in the stool, visible blood on the stool and weight loss.

Results: From 6023 questionnaires delivered to the responders of CRC screening pilot project - 5129 were returned (85.1%). While in non-responder group the response rate was only 14.6% (1195 people). Eligible to analysis were 4930 and 1121 questionnaires respectively.

In the responder group 54.1% had not observed any health changes, 31.8% mentioned one symptom, 10.1% two symptoms, others- more than two symptoms. The most common symptom was stool changes 23.9%, then abdominal pain 14.2% and fatigue 11.2%. The highest rate of the positive FOBT was for responders with visible blood in the stool 26.7%, for other symptoms correlation with positive FOBT was from 12.4-16.2%. In the group that hadn't observed any symptoms FOBT was positive in 10.2% of the cases. Relative risk (RR) of positive tests was significantly higher for patients having symptoms (at least one symptom RR = 1.33, at least two symptoms RR = 1.53, at least three symptoms RR = 1.73 and at least four symptoms 1.96, $p < 0.0001$). In the non-responder group 70.5% (significantly higher than in respondent group $p < 0.0001$) had not observed any health changes. Stool changes were mentioned by 17.8%, other symptoms- by less than 8.8% of non-responder group. At least one symptom was mentioned by 19.8%, at least two by 6.2%, and more symptoms by 3.6% in this group.

At the same time only 1% of responders said that symptoms was the motivator to perform FOBT test, but 35% of non-responders as the reason of non-compliance to screening mentioned feeling heathy.

Conclusion: Health problems related to colorectal cancer alarm symptoms influence the decision to participate in screening program. These symptoms and their quantity correlate with faecal occult blood test positivity.

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Disclosure of Interest: None declared

OP437 GREEN TEA EXTRACTS FOR THE PREVENTION OF COLORECTAL ADENOMA AND COLORECTAL CANCER

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Introduction: Colorectal adenomas are precursors to colorectal cancers, and experimental studies have shown the chemopreventive properties of green tea extract (GTE) on colorectal cancer.

Aims & Methods: The aim of this study was to determine the preventive effect of GTE supplements on metachronous colorectal adenoma and cancer by giving GTE tablets which are equivalent of 9 cup-of-green tea per day (0.9 g/day GTE, 0.6 g/day epigallocatechin gallate [EGCG]). The subjects who had undergone complete removal of colorectal adenomas by endoscopic polypectomy were enrolled. A sample size of 176 patients (88 per each group) considering 20% loss to follow-up was calculated to give the study 80% power to detect a difference, assuming a 2-sided significance test at the 0.05 level. They were then randomized into two groups: supplementation group (0.9 g GTE per day for 12 months) or control group without GTE supplementation. A structured 48-h recall at baseline and the 1-year follow-up was used to assess dietary factors. Follow-up colonoscopy was conducted 12 months later in 140 patients (71 in control group and 69 in the GTE group).
Results: Of the 140 patients completed in the study, the incidences of metachronous polyps at the end-point colonoscopy were 60.6% (43 of 71) in control group and 27.5% (19 of 69) in GTE group (relative risk [RR], 0.25; 95% confidence interval [CI], 0.12 - 0.50). Occurrences of metachronous adenoma showed a decrease in GTE group (24.6%, 17 of 69) compared to control group (42.3%, 30 of 71; RR, 0.45; 95% CI, 0.22 - 0.92); the number of relapsed adenoma was also decreased in the GTE group than in the control group (0.72 ± 1.12 *vs.* 0.33 ± 0.63, $P = 0.014$). There were no significant differences between the 2 groups in terms of body weight, body mass index, waist circumference, serum lipid profiles, fasting serum glucose and serum C-reactive protein levels.
Conclusion: This study of GTE supplement suggests a favorable outcome for the chemoprevention of metachronous colorectal adenomas in Korean patients (ClinicalTrials.gov number, NCT02321969).
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 28, 2015 11:00–12:30

NEW INSIGHTS INTO INFLAMMATION IN THE LOWER GI TRACT – ROOM E6

OP438 LARGE-SCALE DRUG SCREEN REVEALS BENZIMIDAZOLE ANTI-HELMINTHICS AS ANTI-TNF CO-THERAPY

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Introduction: Wound-healing and immunosuppressive macrophages are important players in the regulation of mucosal immunity. Anti-TNF compounds induce this type of macrophages in vitro and in vivo, indicating this as an effector mechanism for mucosal repair in IBD. We have previously shown that the clinical benefit of anti-TNF compounds in IBD patients correlates with their capacity to induce immunosuppressive macrophages in a mixed lymphocyte reaction, indicating this assay as a model system. This was further validated by the fact that addition of azathioprine to the assay resulted in an enhanced induction of regulatory macrophages, again in line with the clinical data showing superior efficacy for thiopurine and anti-TNF combination therapy. Given the relatively high proportion of patients who do not tolerate thiopurine therapy, identification of alternative compounds which can be used as anti-TNF co-medication would be valuable. The aim of this study was to use our culture system in order to screen a library of existing drugs for their potential in anti-TNF combination therapy.
Aims & Methods: A library of 1600 FDA-approved compounds were screened for their capacity to potentiate anti-TNF mediated induction of CD14 + CD206+ regulatory macrophages. For each compound, 4 concentrations were tested. Positive compounds were then selected based on clinical applicability in IBD. Selected drugs were further validated in functional studies including viability, extended dose-response titration and functionality of macrophages.
Results: The initial screen resulted in 154 compounds which potentiated anti-TNF effects in at least 1 concentration tested. Clustering of these compounds revealed significant enrichment in the drug classes of cytostatics (including the positive control thioguanin), steroids and anti-helminthics. In particular the family of benzimidazoles proved effective at inducing regulatory macrophages. This family includes albendazole and mebendazole, both compounds which have been in extensive clinical use with a good safety profile. We further validated these findings and confirmed that albendazole significantly increases the number of macrophages induced by anti-TNF therapy. Although albendazole monotherapy induced macrophages as well, the number of macrophages induced in this case was significantly lower than that seen in combination treatment. The concentrations of albendazole used in these experiment did not affect cell viability. Interestingly, macrophages induced in the presence of albendazole displayed enhanced immunosuppressive capacity compared to anti-TNF monotherapy induced macrophages on a per cell basis, suggesting enhanced functionality. Preliminary in vivo experiments in the T cell transfer model of colitis showed that albendazole and anti-TNF combination therapy resulted in faster endoscopic responses than anti-TNF therapy alone.
Conclusion: The anti-helminthic albendazole has a synergistic effect on anti-TNF in the induction of regulatory macrophages. Given the correlation between induction of these macrophages and clinical response in IBD and the extensive clinical experience with this drug, anti-TNF plus albendazole combination therapy may be a good option for IBD patients who do not tolerate thiopurines.
Disclosure of Interest: M. Wildenberg Lecture fee(s): Takeda, Falck, A. Levin: None declared, A. Ceroni: None declared, Z. Guo: None declared, D. Ebner: None declared, G. van den Brink Financial support for research: PPM services, Crucell and AbbVie, Lecture fee(s): Abbvie, Merck Sharp and Dome, Ferring pharmaceuticals, Consultancy: Abbvie

OP439 EFFECT OF HUMAN AMNION-DERIVED MESENCHYMAL STEM CELL TRANSPLANTATION IN RATS WITH RADIATION PROCTITIS

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Introduction: Mesenchymal stem cells (MSCs) have been reported to be a promising cell source in cell therapy, and large amounts of MSCs can easily be isolated from human amnion. Therapeutic irradiation for intrapelvic cancer often causes radiation proctitis; however, there is currently no effective treatment. We therefore investigated the effect of transplantation of human amnion-derived MSCs (AMSCs) in rats with radiation proctitis.
Aims & Methods: The Medical Ethical Committee of Hokkaido University Graduate School of Medicine, Sapporo, Japan approved this research, and all pregnant women gave written informed consent. Human fetal membranes were obtained during Cesarean deliveries, and amnion was manually separated from the chorion by peeling. AMSCs were isolated and expanded by digestion with collagenase type III. Seven-week-old male Sprague-Dawley rats were γ-irradiated (5 Gy/day) at the rectum for 5 days. Rats were anesthetized and placed in the supine position under a 6-mm thick lead shield with a 3×4-cm opening around the anus. On day 5, AMSCs (1×10^6 cells) were intravenously transplanted. Rats were sacrificed on day 8. Histological analyses were performed, and mRNA expression of inflammatory mediators was measured by quantitative RT-PCR. *In vitro*, after γ-irradiation of rat intestinal epithelial cells (IEC-6), the cells were cultured with AMSC-conditioned medium (CM). The effect of AMSC-CM was evaluated by measuring caspase-3/7 activity, p53 transcription activity, and quantitative RT-PCR for p53-target genes.
Results: Histological examination demonstrated that epithelial injury and infiltration of inflammatory cells in the rectum were significantly suppressed by transplantation of AMSCs. The expression levels of CXCL1, CCL2, TNF-α, and IL-6 were markedly increased by γ-irradiation and they all tended to be decreased by AMSC transplantation. *In vitro,* the cell injury in IEC-6 cells induced by γ-irradiation was inhibited by AMSC-CM, which also inhibited the upregulation of p53 transcription activity, caspase-3/7 activity, and p21 expression by γ-irradiation.
Conclusion: Transplantation of AMSCs improved radiation proctitis, possibly through inhibition of cell injury and inflammatory reactions. AMSC transplantation should be considered as a new treatment for radiation proctitis.

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Disclosure of Interest: None declared

OP440 PRE-CLINICAL PHARMACOLOGY FOR A HUMAN INTERLEUKIN-22 IG FUSION PROTEIN FOR THE POTENTIAL TREATMENT OF INFECTIOUS OR INFLAMMATORY DISEASES

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Introduction: Interleukin 22 (IL-22) belongs to the IL-10 cytokine family (Ouyang et al. 2011) and binds specifically to the IL-22 receptor (IL-22R) heterodimer, which is expressed on a variety of epithelial tissues, including the gastrointestinal (GI) tract epithelium, epidermal keratinocytes, liver hepatocytes, pancreatic epithelium, and renal tubular epithelium (Gurney 2004). IL-22 binding results in activation of the transcription factor STAT3, which further leads to the modulation of innate immunity through multiple different regenerative and protective mechanisms in epithelial tissues, including the GI tract mucosal epithelium (Wolk et al. 2004). Unlike more traditional immunosuppressive biologic therapeutics such as TNF-α inhibitors, IL-22 is not immunosuppressive, but instead has a protective effect in infections and inflammatory disease that has been linked to its ability to meditate innate immunity via multiple mechanisms in epithelial tissues (Wolk et al. 2004). IL-22Fc is a recombinant fusion protein that links the human cytokine IL-22 with the Fc portion of human immunoglobulin.
Aims & Methods: To assess the pharmacological activity of IL-22Fc, STAT3 activation was evaluated in primary hepatocytes isolated from human liver. The *in vitro* activity and potency of IL-22Fc were further evaluated using stably transfected epithelial cells expressing the human IL-22R, and human colonic epithelial cell lines. In vivo studies in the dextran sulfate sodium (DSS) induced mouse colitis model were performed to assess the impact of murine IL-22Fc (muIL22Fc) treatment on histologic colitis scores. Dose ranging *in vivo* efficacy studies were performed in the DSS colitis model and relevant pharmacodynamic (PD) markers were measured including REG3β, an antimicrobial peptide, and serum amyloid protein A (SAA), a STAT3-dependent anti-microbial protein. The pharmacokinetic (PK) and PD relationships of IL-22Fc were also assessed in healthy mice, rats, and cynomolgus monkeys.

Results: In HT29 and Colo205 human colon cell lines, as well as in primary human hepatocytes, IL-22Fc activated STAT3 phosphorylation in a concentration dependent manner with an EC50 of 1.56 ± 0.54 μg/mL for HT29 cells (n = 3), 3.29 ± 2.2 μg/mL for Colo205 cells (n = 3), and 2.89 ± 3.4 μg/mL for primary human hepatocyte from 5 donors. Cell lines also produced PD markers REG3A and SAA after stimulation with IL-22Fc under certain conditions. All muIL-22Fc – treated groups in the DSS colitis model had lower average histologic colitis scores than the control treated group; with the three highest muIL-22Fc dose groups (1.25, 6, and 30 μg) demonstrating a statistically significant decrease in severity of histologic colitis. These results were associated with a dose-dependent induction in PD markers REG3β and SAA in mice; and REG3A, SAA, and LBP in cynomolgus monkeys.
Conclusion: The combined data from the *in vitro* and *in vivo* studies confirm pharmacological activity of IL-22Fc including regenerative and protective mechanisms in epithelial tissues and efficacy in mouse colitis models.
Disclosure of Interest: E. Stefanich Shareholder: Roche, J. Rae Shareholder: Roche, J. Lutman Shareholder: Roche, X. Wang Shareholder: Roche, A. Lekkerkerker Shareholder: Roche, W. Ouyang Shareholder: Roche, J. Qiu Shareholder: Roche, D. Lee Shareholder: Roche, D. Danilenko Shareholder: Roche, K. Loyet Shareholder: Roche, M. Keir Shareholder: Roche, S. Sukumaran Shareholder: Roche, A. Herman Shareholder: Roche

OP441 COMBINATORIAL EFFECTS OF WESTERN DIET AND ADHERENT-INVASIVE E. COLI INFECTION ON INTESTINAL INFLAMMATION

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Introduction: Recent advances have shown that the abnormal inflammatory response observed in Crohn's disease (CD) involves an interplay between intestinal microbiota, host genetics and environmental factors. The escalating consumption of fat and sugar in Western countries parallels an increased incidence of CD during the latter 20th century.
Aims & Methods: The impact of a High-Fat/High-Sugar (HF/HS) diet in mice was evaluated for the (i) gut micro-inflammation (fecal lipocalin-2), (ii) selection of *E. coli* and impact on intestinal microbiota composition, (iii) susceptibility to a DSS-induced colitis, (iv) concentration of short-chain fatty acids (SCFA) and (v) expression and potential protective effect on gut inflammation of their free fatty acid receptor, G-protein-coupled receptor 43 (GPR43).
Results: HF/HS diet increased Lcn-2 level in stools from 5 weeks until 18 weeks of treatment, showing that HF/HS diet creates a specific inflammatory environment in the gut. This was correlated with intestinal mucosa dysbiosis characterized by reduction of bacterial richness, but also by an overgrowth of pro-inflammatory proteobacteria such as *E. coli* and a decrease in protective bacteria. In addition, the fecal transplantation from HF/HS treated mice to germ-free mice increased susceptibility to Adherent-Invasive *Escherichia coli* (AIEC) infection. Interestingly, HF/HS diet led to an exacerbation of gut inflammation following DSS-induced colitis, with an increase of DAI, histological score and release of pro-inflammatory cytokines. Moreover, a significantly decrease of SCFA concentrations in fecal samples from mice fed a HF/HS diet compared with mice fed a conventional diet was observed. The expression of SCFA G-protein coupled receptor 43 (GPR43) was reduced in mice treated with a HF/HS diet and reduced in CD patients compared with controls. Interestingly, mice treated with an agonist of GPR43 were protected against DSS-induced colitis.
Conclusion: Western diet creates a low-grade inflammation in the gut with a decrease of protective SCFA producing bacteria, favoring the overgrowth of opportunistic pathogenic *E. coli* which could aggravate the inflammatory process resulting in chronic inflammation. Moreover, activation of GPR43 receptor pathway could be used as a new strategy to treat CD patients abnormally colonized by AIEC bacteria.
Disclosure of Interest: None declared

OP442 INVOLVEMENT OF FLGM IN THE PATHOGENESIS OF ADHERENT-INVASIVE ESCHERICHIA COLI

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Introduction: AIEC strains (Adherent-Invasive *E. coli*) isolated from ileal lesions of Crohn's disease patients are flagellated bacteria able to invade intestinal epithelial cells and to survive into macrophages. Flagellin, major bacterial flagellum protein, is required for motility but is also recognized by innate immune receptors TLR5 and Naip5-Naip6/NlrC4/Caspase-1 leading to production of pro-inflammatory cytokines. Non-flagellated AIEC mutants presented a reduced ability to adhere to and to invade intestinal epithelial cells and to survive within macrophages. The function of FlgM is to couple flagellar assembly to appropriate temporal flagellar gene transcription.
Aims & Methods: We hypothesized that efficient modulation of flagellin expression is required for mucosa colonization and *in vivo* persistence, and permits AIEC to evade innate immune detection. To test this hypothesis, we constructed AIEC LF82 deficient in the anti-sigma factor *flgM*, which is unable to repress its flagella production and overproduce flagellin. This mutant was tested for its capacity to invade intestinal epithelial cells, to survive into macrophages and to aggravate a DSS induced colitis in a transgenic mouse model expressing human CEACAM6 necessary for AIEC mucosa invasion.
Results: Deletion of *flgM* gene did not alter growth of AIEC LF82 bacteria in Luria Broth (LB). However, this mutant show a decreased of motility and yeast agglutination titer compared to LF82 wild type, indicating that deletion of *flgM* impact type 1 pili and flagella expression. Electron microscopy examination showed a reduction in the number of flagella per bacteria and a shortening of the length of flagella at the surface of LF82-D*flgM* isogenic mutant compared to wild type LF82. This is associated with an increased secretion of flagellin in the culture supernatant of the mutant, suggesting that it could activate innate immunity via the recognition of transmembrane and cytoplasmic receptors. The loss of this anti-sigma factor leads to decrease of AIEC LF82 ability to adhere to and to invade intestinal epithelial TC7 and T84 cells. In addition, LF82-D*flgM* mutant shows reduced ability to survive within THP1 human macrophages. A preliminary study of the behavior of the AIEC-D*flgM* mutant in murine model demonstrate that the regulation of flagella expression and monomeric flagellin subunit released is required for AIEC persistence in the gut of CEABAC10 transgenic mice.
Conclusion: This work aims to better understand the pathogenicity of AIEC strains to develop specific inhibitors interfering with bacteria/cell interaction. Targeting FlgM bacterial factor could be an alternative therapeutic strategy to limit AIEC colonization on the gut mucosa of Crohn's disease patients.
Disclosure of Interest: None declared

OP443 CHROMOGRANIN-A REGULATES P53-UPREGUALTED MODULATOR OF APOPTOSIS (PUMA) AND B-CELL LYMPHOMA-2 (BCL-2) PRO-APOPTOTIC MEDIATORS IN EXPERIMENTAL COLITIS

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Introduction: The pathogenesis of ulcerative colitis (UC) involves increased apoptosis of intestinal epithelial cells. The extrinsic apoptosis pathway is induced by extracellular signals that result in the activation of death receptors and the activation of the TNF-related apoptosis-inducing ligand (TRAIL) / Caspase 8 apoptosis-related cysteine peptidase (CASP8) pathway. The intrinsic pathway is activated in response to stress conditions including DNA damage, oxidative stress through the activation of p53-upregulated modulator of apoptosis (PUMA), Bcl-2 associated X protein (BAX), Bcl-2 associated death promoter (BAD) and Bcl-2 antagonist/killer 1 (BAK1) proteins. Serum chromogranin-A (CgA), released by enterochromaffin cells, is increased in UC patients, and neuroendocrine differentiation represents an early event in the UC-neoplasia pathway in which p53 and CgA are both upregulated and considered as early markers. Therefore, we hypothesized that CgA is involved in the pathogenesis of colitis by mediating cell apoptosis induced through the intrinsic pathway.
Aims & Methods: Using an experimental model of colitis mimicking UC, the aim of this study was to investigate the association between CgA and the apoptotic/cell death markers in colitis.
Colitis was induced in CgA-C57BL/6-deficient ($CgA^{-/-}$) mice and wild type ($CgA^{+/+}$) mice by administration of dextran sulfate sodium (DSS 5%) in drinking water for 5 days. Disease activity index was evaluated daily and mice were sacrificed on day 5 post-DSS induction to assess the extent of colitis. At sacrifice composite macroscopic score were evaluated and tumor necrosis factor (TNF)-α was quantified in colon using ELISA and RT-qPCR. Colonic mRNA levels of TRAIL, CASP8, *PUMA*, *BAX*, *BAD* and *BAK1* were quantified using RT-qPCR.
Results: Delayed onset and reduced severity of clinical disease were observed in $CgA^{-/-}$ mice as compared to $CgA^{+/+}$ mice after induction of colitis. No rectal bleeding and no loose stools were observed in $CgA^{-/-}$ mice and weight loss was significantly decreased. Macroscopic inflammation scores were significantly decreased in $CgA^{-/-}$ mice as compared to $CgA^{+/+}$ mice. Colonic protein and mRNA expression levels of TNF-α were significantly decreased $CgA^{-/-}$ mice. In the colitic condition, *PUMA*, *BAX*, *BAD* and *BAK1* were significantly down-regulated in $CgA^{-/-}$ mice compared to $CgA^{+/+}$ mice. Conversely, the presence or absence of CgA did not affect TRAIL or CASP8 mRNA levels. In control mice groups the deficiency did not affect any inflammatory or apoptotic markers.
Conclusion: These results indicate that a lack of CgA contributes to the improvement of colitis by reducing the disease severity, TNF-α levels and abrogating apoptosis through the intrinsic pathway and not *via* the extrinsic pathway. CgA inhibition may offer a new potential way to protect against apoptosis and might be use as a novel therapeutic strategy in UC.
Disclosure of Interest: None declared

Abstract number: OP444 Table 1: Measurements of the ablated samples

Temperature (°C)	Layer	n	Mean ± SD (μ)	Thickness decrement (percentile)	Layer	n	Mean ± SD (μ)	Thickness decrement (percentile)	Layer	n	Mean ± SD (μ)	Thickness decrement (percentile)
Control	Muscularisthickness	13	177.2 ± 114.7	-	Mucosa (Crypts)thickness	12	338.6 ± 60.8	-	Total thickness	12	990.7 ± 230.5	-
50		29	165.7 ± 110.6	6.5		24	418.9 ± 335.4	-23.7*		24	1135.8 ± 509.1	-14.6*
60		47	123.6 ± 101.3	30.2		42	354.8 ± 177.2	-4.8*		42	924.0 ± 386.0	6.7
90		29	135.0 ± 142.4	23.8		25	314.2 ± 165.1	7.2		25	896.1 ± 521.5	9.5
97	6	108.8 ± 113.8	38.6	6	293.5 ± 105.9	13.3	6	790.5 ± 476.5	20.2			
Control	Submucosathickness	13	137.5 ± 80.3	-	Mucosa (Villi)length	12	295.6 ± 59.9	-				
50		28	146.1 ± 70.6	-6.3*		24	310.9 ± 67.3	-5.2*				
60		47	119.7 ± 78.9	13.0		42	251.9 ± 74.7	14.8				
90		29	130.7 ± 134.1	5.0		25	244.1 ± 96.7	17.4				
97	6	112.0 ± 104.2	18.6	5	186.0 ± 115.5	37.1						

*Increase in thickness

WEDNESDAY, OCTOBER 28, 2015 11:00–12:30

ENDOSCOPIC MANAGEMENT OF BENIGN PANCREATIC LESIONS – ROOM B3

OP444 EX-VIVO CYST ABLATION WITH A NEW EUS-NEEDLE PROTOTYPE DEVICE

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Introduction: Pancreatic cystic lesions (PCLs) are frequently diagnosed in asymptomatic patients. Currently, the only accepted treatment is surgical pancreatectomy which can carry severe complications. Therefore, new treatment strategies are needed.
Aims & Methods: To demonstrate the feasibility and evaluate the efficacy of radiofrequency ablation (RFA) in cystic models with a new EUS needle prototype.
Two centers were involved: Massachusetts General Hospital and Mayo Clinic. To create the cystic models, consecutive 2cm-sections of porcine small intestine were measured, tied off with surgical suture and filled with 2ml of saline. The prototype consisted of a modified EUS 22 gauge monopolar needle with a 1cm length active electrode shaft at the tip and an otherwise insulated needle shaft. The needle was connected to an ERBE Vio300 Electrosurgical unit (ERBE USA, Marietta, GA). Electrosurgical settings were soft coagulation mode with 10 watts and a hemostatic effect of 4. Each ablation was performed until a predetermined temperature was measured by a thermometer with an external sensor in contact with the cyst surface. Immediately after ablation, all samples were processed for histological H&E staining. Each layer was measured in at least two different sites of each sample using a micrometer. All measurements were compared with the corresponding control (unablated) sample.
Results: A total of 32 cystic models were ablated. The maximum temperatures reached were 50, 60, 90 and 97 degrees celsius(°C) in 8, 11, 11 and 2 cysts respectively. The ablation time increased as higher temperatures were reached (range 102-440 sec). The spectrum of macroscopic changes, starting at 60°C, were minimal color change, visible color/texture change, and total dehydration/thinning of the tissue. Overall, a decreased trend in the thickness of all the measured layers was observed as the temperature rose (table 1). However, to reproduce this effect, a temperature over 50°C was required for the muscularis, submucosa and villi of the mucosa, and over 60°C for the crypts of the mucosa.
Conclusion: RFA of a cystic model may be a feasible new management option that can be performed in regular endoscopy labs. The device has the advantage of using currently available needle and electrosurgical instruments. The ablated area appeared to be temperature-dependent with a temperature threshold of at least 60°C and a safe cyst margin below 97°C.
Disclosure of Interest: None declared

OP445 FEASIBILITY AND COMPLICATIONS RATE OF NEEDLE-BASED CONFOCAL LASER ENDOMICROSCOPY (NCLE) IN PANCREATIC CYSTS : PRELIMINARY RESULTS OF A MULTICENTER PROSPECTIVE STUDY

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Introduction: Needle-based confocal laser endomicroscopy (nCLE) is an imaging technique, which enables observation of the inner wall of pancreatic cysts, in vivo and in real-time, during an EUS-FNA procedure.
An international multicentric study (INSPECT) on 66 patients reported a pancreatitis rate of 3%. The rate of technical issues was not mentionned. A prospective multicentric French study (CONTACT) aims at evaluating the accuracy of nCLE for the diagnosis of lonely pancreatic cysts.
Aim: Evaluate the feasibility and the complications rate of nCLE in pancreatic cysts in a multicenter prospective study.
Aims & Methods: Between June 2012 and March 2014, 182 patients have been included, in four French centers.
Following EUS examination, the AQ-flex miniprobe was introduced in a 19G needle and real-time video of the wall was recorded. Procedures were realized with a Cook needle (17% of the cases) or a Boston Flex (83% of the cases). A prophylactic antibiotic therapy was systematically given before each procedure. Causes of technical issues and complications rate were prospectively recorded.
Results: Procedures were technically feasible and satisfactory in 95% of the cases. The locations of the lesions in the pancreas were: uncinate process (n = 6), of the head (n = 94), of the body (n = 63) or of the tail of the pancreas (n = 19). Puncture was done per a transgastric (n = 98) or transduodenal (n = 78) approach, through the second part of the duodenum in 6 patients. Three technical failures of the puncture were reported (2% of the cases). In each of these three cases, puncture was considered only through the second part of the duodenum (one lesion in the uncinate process, two in the head). Cellvizio images have not been acquired due to software issues in seven procedures (4% of the cases). Three minor acute pancreatitis (1, 6%) were reported (48h hospitalization). There was intracystic bleeding without any extravasation in 10% of the cases, without any clinical consequence. No other complication happened.
Conclusion: In a large prospective study of nCLE in pancreatic cysts, the technical sucess rate is 95% and the pancreatitis rate is 1.6%. The main technical limitaion is observed for cysts, which require an approach through the second part of the duodenum (50% failure). The complications rate compares with the complications rate of EUS-FNA.
Disclosure of Interest: None declared

OP446 FEASIBILITY AND SAFETY OF A FULLY COVERED SELF-EXPANDABLE METAL STENT WITH ANTIMIGRATION PROPERTIES FOR EUS-GUIDED PANCREATIC DUCT DRAINAGE: EARLY AND MIDTERM OUTCOMES

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Introduction: Recently, EUS-PD has been used for patients on whom endoscopic retrograde pancreatography (ERP) has failed. Stent-related adverse events such as stent migrations, failures in stent placement, or pancreatic fluid leakages have been of concern in transmural plastic stenting procedures.
Aims & Methods: The aim of this study is to evaluate the feasibility and safety of EUS-PD with a fully covered self-expandable metal stent (FCSEMS) for patients with obstructive pancreatitis who failed ERPs. Twenty five consecutive patients with obstructive pancreatitis underwent EUS-PD with a FCSEMS after failed ERPs. Technical and clinical success, adverse events, and stent patency were assessed.
Results: EUS-PD was successful in all 25 patients (technical success rate, 100%), and symptoms improved in all patients (clinical success rate, 100%). EUS-guided pancreaticogastrostomy (n = 24), pancreaticoduodenostomy (n = 1) and pancreaticojejunostomy (n = 1) were performed. Pain scores improved significantly after FCSEMS placement ($P = 0.001$). Median stent patency duration was 123.5 days (Interquartile range 65.75 – 171.50). Early adverse events occurred in five (20%) patients, including four with self-limited abdominal pain and one with minor bleeding. No other adverse events related to FCSEMS-including stent migration, stent clogging, pancreatic sepsis and stent induced ductal stricture-were observed during follow-up periods.
Conclusion: EUS-PD with an FCSEMS may be technically feasible and relatively safe for patients failed conventional ERPs.
Disclosure of Interest: None declared

OP447 A NOVEL BIODEGRADABLE NON-COVERED SELF-EXPANDABLE STENT TO TREAT PANCREATIC DUCT STRICTURES IN CHRONIC PANCREATITIS; A PILOT STUDY

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Introduction: In chronic pancreatitis (CP), fibrotic pancreatic duct (PD) strictures are a common complication and a therapeutic challenge. Dilatation by

(progressive) plastic stent insertion requires multiple procedures and has limited success. Drainage with self-expandable metal stents seems more effective, but removal and migration problems limit their use. Biodegradable self-expandable stents (BD-SES) might be an attractive alternative, but have never been investigated in humans in this setting.
Aims & Methods: The aim of this prospective pilot study was to evaluate the safety of non-covered BD-SES's (ELLA-CS) in CP patients with a fibrotic PD stricture. Patients were included, in whom treatment with plastic stents for at least 6 months had failed and surgical intervention was considered. Efficacy was a secondary endpoint. The participating centers are university hospitals in Rotterdam, the Netherlands, and Leuven, Belgium. Stents were 6 mm in diameter, 3 or 4 cm in length, with an expected degradation time of 3-6 months. Patients were followed for one year. Stent and stricture resolution were evaluated by ERCP after 6 months.
Results: Stents were placed in 10 patients (median age 56, 6 male, median disease duration 4 years). The median stricture length was 1 cm (IQR 0.5-3.5 cm). All stents were placed successfully, 9 after sphincterotomy and 6 after balloon dilatation. Nine were placed transpapillary, of which two were pulled down with a balloon or forceps after deployment, to achieve an optimal position. One stent was positioned intraductally. No serious peri-procedural complications were encountered, but two patients were admitted shortly because of self-limiting pancreatic pain.
In the eight patients that have completed at least 6-months of follow-up, complete stent degradation was accomplished (stent resolution 100%). In six patients, ERCP demonstrated stricture resolution (technical success rate 75%). In two cases, stent related complications had occurred; ductal hyperplasia and stent migration, both of which were treated with plastic stents and eventually surgery. Two additional patients underwent a Whipple's procedure for other pancreatitis related problems, 9 and 11 months after stent insertion; one because of groove pancreatitis with a gastric outlet obstruction, the other for a CBD stricture and recurrent flares (neither had evidence of a recurrent PD stricture). The remainder four patients are still stricture and pain free after 1 year (clinical success rate 50%).
Conclusion: These preliminary results show that BD-SES's for fibrotic PD strictures in CP are easy and safe to place, degrade completely within 6 months, and may even resolve strictures, resilient to conventional plastic stent treatment. These encouraging results warrant further testing.
Disclosure of Interest: None declared

OP448 LONG-TERM OUTCOME OF ENDOSCOPIC THERAPY FOR CHRONIC PANCREATITIS IN CHILDREN

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Introduction: Chronic pancreatitis (CP) occurs rarely in children and the most frequent presentation is recurrent acute pancreatitis (RAP). Previous publications have shown that endoscopic therapy with ductal drainage, with or without extracorporeal shock wave lithotripsy (ESWL), is safe and efficient. However, long-term results are scarce or inexistant regarding the european population. The aim of this retrospective study was to evaluate the long-term effects of endoscopic therapy on pain relief in children with CP.
Aims & Methods: During a period of 21 years (1991-2012), 41 children with CP had endoscopic therapy. Clinical status was evaluated after therapy, based on the number of hospital admissions (for pain or subsequent endoscopic procedure) during follow-up (FU). Results were considered excellent if no other admission was required, satisfactory if < 5 admissions or ≥ 5 but with no pain or ongoing endoscopic therapy for minimum 12 months at the end of FU, and poor if surgery was required or ≥ 5 admissions were noted with ongoing endoscopic therapy at the end of FU.
Results: 41 patients (female: 25(61%)) were included (median age:10(2-17)). 15 (36.6%) were ≤ 7 years old. Eleven children (26.8%) had hereditary CP associated with cationic trypsinogen mutation. CP was characterized as severe according to the Cambridge classification in 28 (68.3%) children. Duration of disease before treatment was 27 (1-120) months. RAP was seen in 24 (58.5%) patients. Pancreas divisum was seen in 6 patients (14.6%). Endoscopic therapy consisted of pancreatic sphincterotomy of the major ($n = 35$) and/or the minor papilla ($n = 11$) for all patients. ESWL for pancreatic calcifications was required in 9 (22%) patients. Only 2 (4.9%) patients had pancreatic stent insertion during initial therapy. Mild post-ERCP AP occurred in 7 (17.1%) and median length of stay for initial therapy was 3 days (2-8). Median FU of 72 months (7-240) was obtained in 36 children. Subsequent endotherapy during FU was required in 30/36 (85.7%) patients and pancreatic stenting was necessary in 14 (40%), for a median period of 23 (5-148) months. Median frequency of admissions per year (0.66 (0-3.4)) was significantly decreased after therapy as compared to the frequency before therapy (3 (0.6-18))($p = 0.001$). Results were excellent in 5 (13.9%) and satisfactory in 26 (72.2%) patients. Finally, poor results were observed in 5 children (13.9%), who required surgery ($n = 1$) and/or frequent admissions for ongoing endoscopic therapy ($n = 4$).
Conclusion: Therapeutic ERCP in a pediatric population of CP can lead to clinical improvement and can be considered as the initial treatment of choice.
Disclosure of Interest: None declared

OP449 SURVEILLANCE OF LOW-INTERMEDIATE RISK INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

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Introduction: Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are potentially malignant epithelial neoplasms that involve the main duct, branch ducts, or both. Although a great majority of these lesions do not meet consensus criteria for resection and are therefore surveyed regularly, outcomes of long term surveillance are not known. Our goal was to understand the natural history and risk of progression of low-intermediate risk IPMNs that have been surveyed for > 4 years.
Aims & Methods: We conducted a retrospective review of radiology and endoscopy databases between 2001-2013. We included all cystic lesions that (1) met clinical IPMN criteria and, (2) had greater than four year cross sectional imaging (CT/MRI) or EUS follow-up. Data points such as demographics and cyst characteristics were collected. Progression was defined as one of the following: (1) increase in cyst diameter > 2 mm, (2) increase of 20% or more in the cyst's largest dimension, (3) development of such worrisome features as pancreatic duct dilatation, mural nodules, pancreatic atrophy.
Results: We identified a total of 2400 patients with cystic pancreatic lesions of whom 268 patients were followed for > 4 years and 135 met clinical criteria for the diagnosis of IPMN (44% M, 56% F, average age 73). 60 patients (44%) had interval cyst progression of greater than or equal to 20% with an average increase of 69% in the single largest dimension. Of these 60 patients, 15 developed worrisome features. 18 patients (13%) had interval cyst progression less than 20%, of whom two developed worrisome features. 32 patients (23.7%) had cysts with no demonstrable growth in the greatest diameter, however three developed worrisome features. There were no significant differences in age, gender, baseline cyst measurement, CEA or amylase values among progressors and non-progressors.

Table 1: IPMN Characteristics

Baseline Cyst Size	N	No Change	Cyst Size Increase > 2 mm	Cyst Size Increase $> 20\%$	Developed Worrisome Features
< 10 mm	54	20	23	25	6
11-20 mm	58	10	31	27	8
21-30 mm	12	1	9	5	6
> 31 mm	10	0	5	3	3

Conclusion: In a large retrospective cohort of patients with suspected low to intermediate risk IPMNs, nearly half progressed during four-year follow-up as defined by 20% or more growth in the single largest dimension, however only a minority ultimately met resection criteria. There were no significant differences in demographics or baseline cyst characteristics among progressors and non-progressors.
Disclosure of Interest: None declared

WEDNESDAY, OCTOBER 28, 2015 14:00–15:30
COMPLICATIONS OF CROHN'S DISEASE (AV) – ROOM F1

OP450 THE CLINICAL OUTCOMES OF 165 ENDOSCOPIC BALLOON DILATATION FOR ILEOCOLONIC OR CAECAL STRICTURES IN PATIENTS WITH CROHN'S DISEASE

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Introduction: In Japan and most other developed nations, the prevalence of Crohn's disease (CD) is on an increasing trend. CD is characterized by patchy, transmural, progredient inflammation along the intestine with stricture formation in approximately one-third of all CD patients. Strictures are a major cause of morbidity, hospitalisation and surgery. Strictures are caused by transmural inflammation, uncontrolled cell proliferation, tissue remodeling, and have as yet unknown biochemical mediators. Further, while new therapeutic options are aimed at suppressing inflammation, hitherto developed stenotic lesions often require surgical intervention. Endoscopic balloon dilation (EBD) has been expected to be a nonsurgical approach for the management of intestinal strictures.
Aims & Methods: We were interested to assess the true clinical outcome in CD patients who undergo EBD for intestinal strictures; caecal or ileocolonic. Additionally, we wished to identify factors associated with complications, compromising the long-term prognosis after an EBD procedure. From January 2006 to March 2015, 165 EBD sessions for strictures in the lower gastrointestinal tract were undertaken in 71 CD patients. EBD was done in patients who either presented with ileocolonic or caecal stenosis experiencing obstructive symptoms. EBD was carried out by using high-pressure Through-The-Scope Balloons with a diameter of 8-20 mm and a length of 5.5cm, depending on the size of the strictured lumen and the endoscopists' discretion. The primary success was defined as free passage of the scope through the strictured site after the EBD procedure.

Results: The rate of primary success was 79% (130 of 165 EBD procedures). However, during the time course of this study, 47 of the 71 patients (66%) returned for re-EBD or operations due to re-stenosis. Eighteen of the 71 patients (25%) needed surgical intervention for complications related to strictures. The rate of perforation was 1.4% (2 of 165 EBD procedures). We compared demographic features between the operation and the non-operation subgroups including ulcers at the stenotic lesions, duration, and the location of colitis, medications including 5-aminosalicylates anti-tumour necrosis factor (TNF)-α, immunomodulators, nutritional therapy, past surgical interventions, the length of stenosis, and the expansion diameter. In the subgroup who needed surgical interventions, there were significantly higher cases complicated with ulcers at the stenotic lesions ($P = 0.001$). Anti-TNF-α therapy and other medications mentioned above did not influence re-stenosis or the need for operation.
Conclusion: In this study, EBD of intestinal strictures in CD patients was an effective and safe alternative to surgical interventions in the majority of cases. It is believed that long-term anti-TNF-α therapy may promote intestinal strictures, but, anti-TNF-α, immunomodulators or 5-aminosalicylates did not appear to influence re-stenosis or the need for surgical interventions. Likewise, the length of stenosis and the expansion diameter were not associated with complications requiring surgery. Instead, we found that ulcers complicating the stenotic lesions were a significant risk factor for surgery following EBD. Accordingly, we believe that treatment of ulcers at the stenotic lesions prior to an EBD should increase the clinical outcome of EBD in CD.
Disclosure of Interest: None declared

OP451 BIOLOGICAL THERAPY IS ABLE TO MODIFY THE DISEASE PROGRESSION OF CROHN'S DISEASE PREVENTING ITS LONG-TERM ASSOCIATED DISABILITY – A STUDY PERFORMED USING THE LÈMANN SCORE

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Introduction: Crohn's disease (CD) is a chronic inflammatory bowel disorder characterized by an alternation of remission and relapse phases. Even during periods of clinical remission a subclinical inflammation persists, reflecting a progressive, destructive disease course in the later phases of the disease. Surgical resection of the bowel can be considered the ultimate manifestation of bowel damage. Recently a new score, the Lèmann Score (LS), has been proposed in order to assess the cumulative structural damage to the bowel in different CD patients. Limited data are present assessing the value of this instrument in measuring the effect of various medical therapies on the progression of bowel damage.
Aims & Methods: The aim of our study was to evaluate the effect of various medical therapies on the progression of bowel damage using the LS. In this retrospective study we included 87 CD patients who were followed up at our IBD Unit. All patients underwent clinical assessment with measurement of disease status based on HBI index every three months, and bowel magnetic resonance imaging and a colonoscopy every year, or earlier, in case of disease relapse. Patients were divided on the basis of the drug administered during the follow-up: i) biological mono-therapy; ii) azathioprine; iii) mesalazine, and the LS was calculated both at baseline and at the end of follow-up in each group.
Results: We included 87 patients (49 males, mean age 43.5 years, range 19-79) with a median follow-up of 26 months. Among the 35 (40.2%) patients on biological mono-therapy the median LS was 7.1 (range, 2.5-292.3) at baseline and 9.7 (range, 1.3-292.3) at the end of the follow-up ($P = 0.34$). The median LS in azathioprine group (16 patients, 18.4%) was 3.5 (range, 0.6-159.6) and 7.6 (range, 0.6-209.6) at baseline and at the end of follow-up, respectively ($P = 0.0017$). In the mesalazine group (36 patients, 41.4%) the median LS at baseline and at the end of follow-up was 3.2 (range, 0.6-202.6) and 4.3 (range, 1-206.5), respectively ($P < 0.0001$). As far as the proportion of patients who showed a worsening in the LS is concerned, the azathioprine group showed the highest proportion of patients with increased scores (13/16, 81.3%) followed by the group treated with mesalazine (20/36, 55.6%), and patients treated with biological mono-therapy (8/35, 22.9%) ($P = 0.0002$).
Conclusion: Our data suggest that the use of biological therapy rather than azathioprine or mesalazine may change the cumulative structural damage to the bowel and, therefore, is able to modify disease progression in CD patients, preventing its long-term associated disability.
Disclosure of Interest: None declared