Abstracts

investigation in larger more cohorts with more statistical power in order to improve CRC screening.

Abstract PTU-039 Table 1 Diagnostic colonoscopy histopathological and endoscopic characteristics in missed CRC cohort

Anatomical site in colorectum (% total)	
Sigmoid	3 (25%)
Splenic flexure	1 (8.33%)
Transverse	3 (25%)
Hepatic flexure	2 (16.67%)
Ascending	2 (16.67%)
Caecum	1 (8.33%)
Dysplasia (% total)	
Low grade	11 (91.67%)
High grade	1 (8.33%)

Abstract PTU-039 Table 2 CRC misses by endoscopist type

Scope operator	CRC misses (% total)	Endoscopist miss rate (misses/total colonoscopies)
Trainee endoscopist	3/12 (25%)	0.004 (3/750)
Surgical Endoscopist	2/12 (16.67%)	0.008 (2/250)
Physician Endoscopist	7/12 (58.33%)	0.00159 (7/4400)

PTU-040 HMGB1 IN THE PATHOGENESIS OF COLORECTAL CANCER

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Introduction High Mobility Group Box-1 (HMGB1) is a ubiquitous nuclear protein that regulates gene expression. When phosphorylated, it translocates to the cytoplasm and extracellular space to impact immune responses and epithelial cell behaviour. Our previous data revealed that dynamic subcellular localisation of HMGB1 is associated with colorectal neoplastic progression, with cytoplasmic HMGB1 expression a feature of early carcinogenesis. The leading edge of cancer invasion in polyp cancers (CaP) had strong expression in both nuclear and cytoplasmic compartments. Our aim was to define the biological impact of this expression profile.

Methods CD4⁺ helper T cells, CD8⁺ cytotoxic T cells, FOXP3⁺ regulatory T cells, CD20⁺ B cells and CD68⁺ macrophages were assessed by immunohistochemistry on endoscopically retrieved paraffin embedded CaP lesions sourced from the Grampian Tissue Biorepository (n=25). Ethical approval was granted by the Grampian Biorepository Scientific Access Group. The invasive cancer margin was identified by a gastrointestinal pathologist. The immune cell infiltrate was expressed as number of positive cells per high power field (x20) in the adjacent stroma alongside intensity of nuclear and cytoplasmic HMGB1 expression. The impact of HMGB1 on

colonic epithelial cell behaviour was assessed by stimulation of Caco-2 cells (ATCC HTB-37TM) for 48–72 hours with 0, 50 and 100 ng/ml recombinant HMGB1 with (1) analysis of wound healing by scratch assay (images captured at time 0 and 24 hour intervals and analysed with ImageJ), (2) proliferation by incorporation of tritiated thymidine and (3) expression of permeability genes (*CLDN2*, *CLDN4*, *OCN*, *CDH1*, *TJP1*) using TaqMan RT-qPCR, normalised to expression of *GAPDH* and *B2M* and analysed by the Livak method.

Results A robust inflammatory infiltrate was identified adjacent to the invasive cancer margin with a preponderance of CD4⁺ T cells and CD68⁺ macrophages. The subcellular localisation of HMGB1 (nuclear versus cytoplasmic) did not result in phenotypically distinct populations. There was no difference in epithelial restitution in response to HMGB1 over 48 hours, although high concentration at 72 hours was associated with reduced wound healing (p<0.01) and reduced proliferation rate (p<0.01). HMGB1 stimulation significantly decreased the expression of *CLDN4* (p<0.008).

Conclusions Cytoplasmic HMGB1 expression did not impact the phenotype of adjacent immune cell infiltrate at the cancer margin. HMGB1 influences growth dynamics of colonic epithelial cells and reduces the expression of the pore closing tight junction gene, *CLDN4*. Understanding HMGB1 driven biology in CaP could identify an important mechanism for early carcinogenesis.

PTU-041 METHANOGENESIS IN THE GI TRACT – IMPLICATIONS FOR UK BREATH TESTING

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Introduction Methane production from gut microbes has been implicated in clinical constipation and manipulation of the microbiome represents an attractive and alternate therapeutic target. Methane production is not routinely measured during breath testing but the recent North American Consensus (NAC) document has recommended this as standard. To assess prevalence of methanogenesis in patients presenting with bloating symptoms we performed a retrospective analysis of our breath test database from the preceding 6 months.

Methods In total 736 subjects were analysed. The presence of methane levels ≥10 ppm was considered methane-positive. Breath tests for Carbohydrate Malabsorption and Small Intestinal Bacterial Overgrowth (SIBO) were included. Baseline and intra-study bloating was scored on a scale 0–10 with 0 being absent and 10 being extreme. Results were analysed statistically using independent t-tests.

Results 136 subjects (18.5%) had a positive result for excessive methane. Within this group, 129 subjects had a SIBO breath test with 64.3% having a negative result. The remaining 35.7% had excessive methane and SIBO (determined by a rise in hydrogen >10 ppm above baseline within 60 min after ingestion of substrate). There was an overall increase in bloating symptoms for methane-positive compared to methane negative patients (p=0.035) in the absence of SIBO.

Discussion Changes in the microbiome to a methane predominant environment occurs in about 20% of patients presenting with bloating symptoms. This supports the NAC statement that methane should be measured routinely during breath

testing to avoid false negative results. Manipulation of the microbiome to a more hydrogen predominant profile represents an attractive alternative therapeutic objective to conventional laxative therapy.

PTU-042 AN AUDIT TOOL TO EVALUATE POST-COLONOSCOPY COLORECTAL CANCER (PCCRC) RATES IN ENDOSCOPY UNITS

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Introduction Colorectal cancer (CRC) is the third most common cancer globally and the third most common cause of cancer death. Early diagnosis at stages where disease can be treated, significantly improves survival rates justifying the need for CRC screening programs by 'gold standard' colonoscopy. Given the concern for significant numbers of missed lesions, the new JAG Global Rating Scale (GRS) requires all endoscopy units to develop an audit for post-colonoscopy colorectal cancer (PCCRC). Our aim was to provide a template for performing this audit at a major teaching hospital.

Methods We retrospectively reviewed our electronic patient records and collected data on all new CRC diagnoses made over a three-year period (1 st September 2014 – 31 st August 2017). We looked for evidence of colonoscopy performed in the three years prior to diagnosis and applied the following exclusion criteria:

1. No colonoscopy within the 3 years prior to diagnosis
2. Diagnosis of CRC made at different hospital hindering access to patient records
3. Previous flexible sigmoidoscopy only and subsequent CRC diagnosis in transverse/ascending colon
4. Unsatisfactory bowel preparation necessitating repeat endoscopy
5. Alternative investigation/referral arranged by endoscopist (e.g. due to technical difficulty leading to incomplete endoscopy procedure).

PCCRC rate was defined as the proportion of PCCRC diagnoses amongst all CRC cases. For CRC cases, we also analysed patient demographics, timeframe between colonoscopies and individual endoscopist PCCRC rate.

Results Out of a total 944 CRC cases, 691 were eligible for analysis (Figure 1). There were a total of 12 cases of PCCRC, giving our hospital a PCCRC of 1.74%. The average age of patients with a PCCRC diagnosis was 65.25 years (29–80). The average time between initial and diagnostic colonoscopies in PCCRC cases was 14.33% months (range, 1–34) with initial-to-diagnostic colonoscopies separated by <12 months in 5 cases (41.67%), 12–24 months in 5 cases (41.47%) and >24 months in 2 cases (16.67%). Physician endoscopist miss rate ranged from 0.11%–0.21%.

Conclusions Results from our audit show our hospital is within the BSG, JAG and the Association of Coloproctology of Great Britain and Ireland (ACPGBI) quality assurance target of <5% PCCRC at 3 years. Ideally, endoscopy units will use similar methods for the mandatory JAG GRS audit, allowing comparison between different endoscopy units to improve

quality of CRC screening. Our work provides a guidance tool on performing the audit in the hope of achieving this aim.

Abstract PTU-042 Figure 1 Flow chart summarising identification of cases included for analysis.

PTU-043 INTESTINAL DYSBIOSIS OCCURS IN IRON DEFICIENCY AS WELL AS ACTIVE IBD

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Introduction We have previously shown that decreases or increases in dietary iron exacerbate murine models of inflammatory bowel disease (IBD). Active IBD is associated with a dysbiosis typified by a reduction in *Bacteroidetes* and an increase in *Firmicutes*. We have investigated the human intestinal microbiome in relation to luminal iron, by studying patients with iron deficiency anaemia (IDA) and inactive/active IBD. We report results of changes at the phylum level.

Methods Bacterial gDNA was extracted from faeces of patients with IDA (10), Crohn's disease (CD 6 active, 24 inactive), ulcerative colitis (UC 7 active, 13 inactive) and healthy controls (24). Faecal iron and calprotectin were assayed by ELISA. Microbiota composition was determined from the sequence of V4 region of 16S rDNA on the Illumina MiSeq platform. Statistical inferences were made using Welch's t-test with post-hoc analysis (*Bioinformatics* 2010; 26:715–21). Shannon Diversity Index (SDI) and Principal Component Analysis (PCA) were employed to compare population and phylum-level changes among study groups.

Results Faecal iron concentrations were least in IDA (ANOVA, $p=0.001$) and significantly lower in IDA than each other group (post hoc $p<0.05$ for all comparisons). Calprotectin concentrations were increased in association with IBD disease activity.

Faecal phyla changes were seen in IDA as well as in IBD: *Proteobacteria* were markedly reduced in IDA (1.4%) compared to active IBD (15.5%); IBD and IDA were associated with increased proportions of *Firmicutes* ($p=0.01$ and $p=0.05$ respectively).

Conclusion Dysbiosis occurred in IDA as well as in active IBD. *Proteobacteria* are clearly iron-responsive: the increase in luminal iron associated with active IBD appears to promote their growth and might contribute to the excess of this phylum during relapse. The changes in *Bacteroidetes* appear independent of luminal iron, unlike *Firmicutes*. The influence of iron deficiency and supplementation upon the colonic microbiome warrants further investigation.