

BAPEN symposium: “dietary management of GI disorders”

OC-054

IMPACT OF A FERMENTABLE CARBOHYDRATE RESTRICTED DIET ON LUMINAL MICROBIOTA, FERMENTATION, SYMPTOMS AND NUTRIENT INTAKE IN PATIENTS WITH IRRITABLE BOWEL SYNDROME: A RANDOMISED CONTROLLED TRIAL

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^{1,2}H Staudacher,* ^{1,2,3}M C Lomer, ¹J L Anderson, ⁴J S Barrett, ⁴J G Muir, ^{1,3}P M Irving, ¹K Whelan. ¹*Diabetes and Nutritional Sciences, King's College London, London, UK;* ²*Nutrition and Dietetics, London, UK;* ³*Department of Gastroenterology, Guy's and St Thomas' NHS Foundation Trust, London, UK;* ⁴*Eastern Health Clinical School, Monash University, Melbourne, Australia*

Introduction Retrospective studies suggest that dietary restriction of fermentable carbohydrates (Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols, FODMAPs) improves irritable bowel syndrome (IBS) symptoms. Prebiotic fructo-oligosaccharides and galacto-oligosaccharides stimulate colonic bifidobacteria, however the effect of a fermentable carbohydrate restricted diet on the gut microbiota has never been examined. The aim of this randomised controlled trial was to investigate the impact of a fermentable carbohydrate restricted diet on luminal microbiota, fermentation and symptoms in IBS.

Methods Adult patients with IBS were recruited from gastroenterology outpatient clinics. Eligible patients were randomised to the intervention diet or their habitual diet for 4 weeks. A fresh stool sample was collected and analysed for the major bacterial groups using fluorescent in situ hybridisation, short chain fatty acid (SCFA) concentration was analysed using gas liquid chromatography and pH was recorded. The incidence and severity of GI symptoms and stool output were recorded and dietary intake was assessed using food diaries. All outcome measures were recorded at baseline and 4 weeks. Continuous data were compared using an independent samples t-test and categorical data were compared using the χ^2 test.

Results Of 41 patients randomised, six withdrew (five protocol violations, one lost to follow-up). In the intention-to-treat analysis, more patients in the intervention group reported adequate control of symptoms (68%) compared with controls (23%) ($p=0.003$). However, there were strikingly lower concentrations (7.4 vs 8.2 \log_{10} cells/g, $p=0.001$) and proportions (1.2% vs 5.5%, $p=0.002$) of bifidobacteria in the intervention group compared with controls at follow-up. This was not associated with any change in luminal markers of fermentation. There were no differences in energy, protein or fat intake at 4 weeks between groups but total carbohydrate intake was lower in the intervention group.

Conclusion This is the first randomised controlled trial investigating the effect of a fermentable carbohydrate restricted diet, demonstrating significant improvements in symptoms but a dramatic reduction in luminal bifidobacteria, a species that have an important role in colonic health. Significant questions remain; is the shift in bifidobacteria permanent, how might it be prevented and what is the impact of reintroduction of fermentable carbohydrates on the microbiota?

Competing interests None declared.

AUGIS prize papers

OC-055

WHAT IS THE TRUE INCIDENCE OF METACHRONOUS COLORECTAL LIVER METASTASES? EVIDENCE FROM THE UK FACS (FOLLOW-UP AFTER COLORECTAL SURGERY) TRIAL (ISRCTN: 41458548)

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¹S Pugh,* ²A Fuller, ²P Rose, ²R Perera-Salazar, ¹J Mellor, ¹S George, ²D Mant, ¹J Primrose. ¹*University Surgery, University Hospital Southampton NHS*

Foundation Trust, Southampton, UK; ²*Department of Primary Care, University of Oxford, Oxford, UK*

Introduction Detecting patients with resectable metachronous colorectal liver metastases and performing potentially curative surgery is commonly cited as a reason for following up patients with completely resected colorectal cancer. However, the actual incidence of metachronous metastasis in fully staged and optimally treated colorectal cancer patients is not known with certainty. The FACS trial, the UK national trial on colorectal cancer follow-up, provided an opportunity to address this question.

Methods Patients were recruited to the trial following potentially curative resection of the primary colorectal cancer (Dukes' stages A–C, (I–III)). Complete evaluation by CT chest, abdomen and pelvis and a normal CEA (carcinoembryonic antigen) after surgery or adjuvant chemotherapy were prerequisites to trial entry. Patients were randomised in a 2×2 trial design of intensive imaging vs minimal CT imaging and CEA vs no CEA measurement. Follow-up data including site of recurrence and further surgery has been collected prospectively. An observational analysis has been performed on the entire cohort at a median follow-up of 54 months.

Results A total of 1260 patients were recruited of which 22% were in Dukes' stage A (I), 48% stage B (II), and 30% stage C (III) (remainder awaiting data clarification). At follow-up 85.6% of patients were alive without recurrence (stage A 90.9%, stage B 86.7%, stage C 80.4%). Of the 178 recurrences the majority were loco-regional or at multiple sites. Liver metastases were found in 72 (40% of patients with recurrence) and 45 (25%) had liver only disease. A potentially curative liver resection was performed in 35 patients (20%). Thus at a median follow-up of 54 months 5.7% of the study cohort had metachronous metastases in the liver. In 3.6% of the cohort the disease was confined to the liver and 2.8% went on to have a potentially curative liver resection.

Conclusion These preliminary data demonstrate that the incidence of metachronous liver metastasis in fully staged patients with colorectal cancer appears to be low. Furthermore due to the often multi-site nature of the recurrence only a small proportion of patients can be cured. Thus very intensive follow-up strategies to detect colorectal liver metastases are unlikely to be cost effective. These data emphasise the importance of fully staging the liver at the time of treatment of the primary disease.

Competing interests None declared.

OC-056

VIRAL WARFARE: FRONT LINE DEFENCE AND ARMING THE IMMUNE SYSTEM: THE USE OF AN ONCOLYTIC VIRUS AS A VACCINE AGAINST COLORECTAL LIVER METASTASES

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¹R Dave,* ²F Errington-Mais, ³D Kirn, ¹G Toogood, ²A Melcher. ¹*Transplant and HPB Surgery, St James University Hospital, UK;* ²*Section of Oncology & Clinical Research, University of Leeds, Leeds, UK;* ³*Jennerex Biotherapeutics, San Francisco, USA*

Introduction Liver resection for colorectal liver metastases (CRLM) from colorectal cancer (CRC) has a 50% 5-year survival rate. However, recurrence rates are reported as 50% within 2 years. Thus, there is a need for a further treatment modality that may induce long-lasting anti-tumoural activity. Virotherapeutics provides this by directly infecting and lysing tumour cells and inducing immune-mediated tumour cytotoxicity.

Methods Using a double-stranded enveloped pox virus backbone, a Vaccinia virus (VV), termed JX-594, has been genetically manipulated to encode for granulocyte macrophage colony stimulating factor (GM-CSF). Enzyme Linked Immunoabsorbent Assay (ELISA) was used to confirm production of GM-CSF when CRC cell lines and primary CRLM tissue were infected with this VV. ELISA was also

used to measure pro- and anti-inflammatory cytokines. Viral replication was investigated using a plaque assay technique and by directly infecting CRLM tissue with a related GFP-encoding VV. To demonstrate induction of the innate immune response we infected PBMCs with the virus and measured levels of degranulation of Natural Killer (NK) cells, and the cytotoxic ability when activated PBMCs were exposed to CRC targets.

Results JX-594 treatment results in up to 75% lysis of CRC cell lines in 96 h. VV can replicate in CRC cells (250-fold replication in 72 h), thus potentially spreading through a tumour cell population, magnifying its anti-tumour effect. VV is able to produce large quantities of GMSCF. This is a cytokine that can stimulate a variety of immune effector cells including dendritic cells, which can be recruited to the tumour environment. In our study, more than 50% of the NK cells become “armed” in response the viral treatment, with the release of granzymes that can induce apoptosis of target tumour cells. These activated NK cells when exposed to CRC targets, result in a 40%–50% lysis of the tumour cells in 24 h. VV treatment can also cause the up-regulation pro-inflammatory cytokines around the tumour environment, and potentially suppress new vessel formation by inhibiting VEGF.

Conclusion Viral therapeutics holds promise as a novel treatment modality for treatment of disseminated malignancy, providing direct tumour-specific lysis and the induction of tumour-specific innate immunity. It has been shown to be safe for intravenous delivery and early studies show promising results. We propose that VV may provide an adjunct to liver resection for treatment of liver cancer, and we will soon embark on a multi-centre early phase trial, whereby VV will be administered intravenously pre-operatively.

Competing interests None declared.

OC-057 10 YEARS ON FROM THE IMPROVING OUTCOMES GUIDANCE—DEVELOPMENT OF A TERTIARY PANCREATIC CANCER UNIT

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¹M Johnstone,* ^{1,2}C M Halloran, ^{1,2}P Ghaneh, ^{1,2}R Sutton, ^{1,2}J P Neoptolemos, ²M G T Raraty. ¹Liverpool NIHR Pancreas Biomedical Research Unit, University of Liverpool, Liverpool, UK; ²Royal Liverpool University Hospital, Liverpool, UK

Introduction In 2001 the National Institute for Clinical Excellence (NICE) published guidance on best practice for cancer services entitled Improving Outcomes Guidance (IOG). These guidelines specified centralisation, increased patient volume (>200 referrals/year), improved resection rates (>10%–15%) and reduced post-operative mortality rates (<5%). We looked at the development of a regional tertiary pancreatic centre over the 10 years following this, and how practice has changed over this time.

Methods A prospectively maintained database of all referrals with suspected pancreatic cancer to the Supra-Regional Pancreas Centre in Liverpool was interrogated to assess changes in practice and outcome from 2001 to 2010 inclusive. Data were analysed with χ^2 for trend for categorical data and log rank for survival data.

Results 2076 patients with malignancy were referred, rising from 73 in 2001 to 364 in 2010. 511 resections for malignancy were performed (25%), ranging between 21% (42/182) in 2005 and 36% (33/87) in 2003 per year, with no trend over time. 710 patients underwent planned operation for malignancy over the 10-year period ranging from 41 procedures in 2001 and peaking at 97 in 2008, with 94 procedures in 2009 and 88 cases in 2010. The percentage of planned resections that had a successful resection increased from 51% (21/41) in 2001 to 90% (79/88) by 2010 ($p<0.001$). The mortality from resection was 9/567 (2%) and overall was 5% (37/710) including palliative procedures. The 1 year survival rates of patients who underwent a successful resection improved from 65% (13/20) in 2001 to 76% (69/91) by 2009 ($p=0.02$). There

has been a rise in the number of intraductal papillary mucinous neoplasm (IPMN) resected with none in 2001 increasing to 12 resections during 2009, 10 in 2010 and 212 patients currently undergoing surveillance for IPMN. The number of staging laparoscopies has remained fairly constant at around 27 per year, despite the increase in referrals, which reflects more stringent criteria in selecting these patients for laparoscopy.

Conclusion Over the last 10 years we have seen centralisation of services, which was completed in 2007. This has led to an increase in volume of cancer referrals in line with IOG guidance. Although resection rates have stayed constant, this reflects the increasing number of patients referred with irresectable disease for other treatments, including chemotherapy and novel cancer trials. There has been an improvement in case selection as demonstrated by a reduction in the percentage of bypass procedures, reflecting better pre-operative staging of patients. This has also led to an improved 1-year survival in those patients who had a successful resection.

Competing interests None declared.

OC-058 INCREASED MORBIDITY IN OVERWEIGHT AND OBESE LIVER TRANSPLANT RECIPIENTS—A SINGLE CENTRE EXPERIENCE WITH 1325 PATIENTS

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A Hakeem,* A Cockbain, S Raza, S Pollard, G Toogood, M Attia, N Ahmad, E Hidalgo, K R Prasad, K Menon. *Department of HPB and Liver Transplantation, St James's University Hospital NHS Trust, Leeds, UK*

Introduction Obesity levels in the UK have risen over the years. Studies from the US and elsewhere have reported variable outcomes in terms of post liver transplant morbidity, mortality and graft survival in obese liver transplant recipients. There are no such reports from the UK. The aim of this study was to analyse the impact of BMI (Body Mass Index) on outcomes following adult liver transplantation.

Methods Data were retrieved from a prospectively maintained institutional database from 1994 to 2009. Patients were stratified into four BMI categories established by the WHO: underweight (<18.5 kg/m²), normal weight (18.5–<25.0 kg/m²), over weight (>25.0–<30.0 kg/m²) and obese (>30.0 kg/m²). Primary outcome was to evaluate post-operative morbidity and secondary measures were overall patient and graft survival. Categorical variables were analysed by χ^2 , and continuous variables by one-way ANOVA ($p<0.05$ was considered significant). Kaplan–Meier curves were used to study the effect of BMI categories on patient and graft survival.

Results 1400 adult transplants were identified. 1325 patients had height and weight measurements and were included in the study. The overall morbidity was higher in overweight (71.9%, $p<0.001$) and obese patients (69.2%, $p<0.001$) in comparison to normal weight recipients (64.3%). Post-operative septic events were common in overweight (60.6%, $p=0.001$) and obese patients (61.0%, $p=0.007$) in comparison to normal weight patients (50.4%). Post-operative chest infections were much more common in obese (14.2% vs 9.0%, $p=0.038$) and overweight recipients (17.7% vs 9.0%, $p<0.001$) in comparison to normal weight recipients. Obese patients had significantly longer intensive care stay than normal weight patients (mean 4.1 vs 3.2 days, $p=0.043$). The length of post-operative hospital stay was significantly longer in obese (mean 21.5 days, $p=0.009$) and overweight patients (mean 22.4 days, $p=0.000$) in comparison to normal weight patients (mean 18.0 days). Similarly, ascitic or drain fluid sepsis was common in overweight patients in comparison to normal weight recipients (16.5% vs 2.2%, $p<0.001$). There was no difference in overall graft survival ($p=0.222$) and patient survival ($p=0.196$) between the four groups by log-rank test.

Conclusion This is the largest and the only reported UK series on BMI and outcome following liver transplantation. Overweight and