Conclusion Radiation exposure in Crohn's disease appears to be increasing despite new modalities such as ultrasound and MRI. The increase is attributed to the increased use of CT scanning, as availability and accuracy of imaging via CT in Crohn's disease have improved in recent years. With the gradual introduction of low-dose CT scanning, we would hope these levels will fall again in the near future. Furthermore we observed an increase in the use of plain abdominal films of 87.5%. We feel this may be attributable to the shift in attitude towards treating unwell patients with the increasingly effective and available pharmacological therapies, rather than surgical options, although further audit should be carried out to establish if this is indeed the case.
Disclosure of Interest None Declared

Neoplasia and cancer pathogenesis free papers

OC-066 THE CANCER RESEARCH UK (CRUK) FUNDED ICGC OESOPHAGEAL ADENOCARCINOMA PROJECT: MRC RESEARCH CENTRE AND CRUK CAMBRIDGE RESEARCH INSTITUTE

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Introduction Esophageal adenocarcinoma (EAC) has one of the fastest rising incidences of any cancer in the western world. With a 5-year survival below 10% it is one of the most common causes of cancer death in US and UK. Currently little is understood about the genetic alterations that drive the development of OAC. Better understanding of these alterations may allow the development of novel therepeutic approaches
Methods We have performed whole genome sequencing on 22 cases. Targeted amplicon resequencing of 27 recurrently mutated genes was performed on a validation cohort of 100 further oesophageal adenocarcinomas.
Results In the discover set of 22 OACs we identified recurrent mutations (>3 tumours) in 31 genes including several implicated in tumorigenesis; TP53, CDKN2A, ARID1A. Strikingly in the validation cohort we observed that > 30% of EAC samples harbour mutation of one or both of the SWI/SNF complex members ARID1A and SMARCA4. In addition we identified highly recurrent mutations in several additional genes including TRIM58, SSTR4 and MYO18B.
Conclusion Whole genome sequencing provides an unbiased screen of mutational architecture of OAC. This has allowed the identification of several recurrently mutated genes not previously implicated in this disease providing a unique insight to it's pathogenesis
Disclosure of Interest None Declared

OC-067 AN EXPRESSION SIGNATURE OF THE ANGIOGENIC RESPONSE IN GASTROINTESTINAL NEUROENDOCRINE TUMOURS: CORRELATION WITH TUMOUR PHENOTYPE AND SURVIVAL OUTCOMES

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Introduction Gastroenteropancreatic neuroendocrine tumours (GEPNETs) are heterogeneous with respect to biologic behaviour and prognosis. Since angiogenesis is a renowned pathogenic hallmark as well as a therapeutic target, we aimed to investigate the prognostic and clinico-pathological role of tissue markers of hypoxia and angiogenesis in GEPNETs.
Methods Tissue microarray (TMA) blocks were constructed with 86 tumours diagnosed from 1988 to 2010. TMA sections were immunostained for Hypoxia inducible factor 1α (Hif-1α), Vascular Endothelial Growth Factor A (VEGF-A), Carbonic Anhydrase IX (CaIX) and Somatostatin receptors (SSTR) 1 to 3 and Ki-67. Biomarker expression was correlated with clinico-pathological variables and tested for survival prediction using Kaplan-Meier and Cox regression methods.
Results Eighty-six consecutive cases were included: 51% male, median age 51 (range 16–82), 68% presenting with a pancreatic primary, 95% well differentiated. Forty-four cases (51%) had distant metastases (liver 72%, lymph nodes 28%). Median tumour size was 3.0 cm (range 0.6–12.5). Vascular invasion and necrosis were present in 20 (23%) and 18 (21%) of the specimens. Median overall survival (OS) was 8.8 years (range 0.1–13.5). Overexpression of CaIX was observed in 10% of the specimens, VEGF-A in 78%, Hif-1α in 59%, SSTR1 in 17%, SSTR2 in 31% and SSTR3 in 1%. Ki-67 index was obtained in all cases and scored as G1 in 84%, G2 in 13% and G3 in 4%. SSTR2 overexpression was predominant in pancreatic NETs ($p < 0.01$), whilst Hif-1α was predominant in non pancreatic NETs ($p = 0.05$). Higher Ki-67 labelling was associated with larger tumour size ($p < 0.001$) and necrosis ($p = 0.03$). Overexpression of Hif-1α and VEGF-A correlated with the presence of liver metastases ($p < 0.001$). Patients with Ki-67 count > 1% ($p = 0.02$), high Hif-1α and low SSTR2 expression ($p = 0.03$) displayed significantly shorter OS times.
Conclusion We have identified a coherent expression signature by immunohistochemistry that can be used for patient stratification and to optimise treatment decisions in GEPNETs. Tumours with low proliferation index, preserved SSTR2 and low Hif-1α expression have an indolent phenotype and may be offered less aggressive management and less stringent follow up.
Disclosure of Interest None Declared

OC-068 ALGORITHMIC MANAGEMENT OF RADIATION-INDUCED GI SYMPTOMS IS HIGHLY EFFECTIVE: THE ORBIT RANDOMISED CONTROLLED TRIAL

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Introduction Chronic gastrointestinal (GI) symptoms after pelvic radiotherapy are common. Most affected patients never see a GI specialist. We developed a comprehensive algorithm to direct management of new GI symptoms after pelvic radiotherapy. A 3 arm randomised controlled trial was performed to test 2 hypotheses: (1) Algorithm directed intervention is beneficial compared to no intervention (2) outcomes are not worse when patients are managed by a nurse rather than a gastroenterologist.
Methods Patients treated with pelvic radiotherapy > 6 months earlier with persisting GI symptoms were randomised to management according to the algorithm by 1. a GI nurse or 2. gastroenterologist or 3. the self help Macmillan booklet "Pelvic Radiotherapy: Possible Late Effects". After 6 months, booklet arm patients with persisting symptoms could ask to see the gastroenterologist. Patients in the nurse arm were transferred to the gastroenterologist if they had problems beyond the algorithm's scope. The primary end point was change in the modified Inflammatory Bowel Disease Questionnaire – bowel sub score (IBDQ-B) at 6 months. Follow up continued until 12 months. The trial had 80% power to answer the 1st hypothesis after randomising 196 patients and the 2ndafter closing the booklet arm, and randomising 22 more patients to gastroenterologist or nurse.

Results 168 men, median age 70 (range 34 – 83), 50 women median age 61 (29 – 87), 28 treated for GI, 34 gynaecological & 156 urological cancer were randomised to booklet (n = 68), nurse (n = 80) or gastroenterologist (n = 70). 30 (44%) from the booklet and 4 (5%) from the nurse arm crossed to the gastroenterologist. Groups were well balanced for baseline scores and patient characteristics. 66.5% of patients had a baseline IBDQ-B score indicating moderate/severe symptoms. Intention to treat analysis showed a mean improvement in IBDQ-B score in the booklet arm of 4.9 (95% CIs 1.4–8.4), in the nurse arm 8.8 (6.9–11.2) and 10.3 (7.7–13.1) in the gastroenterologist arm. Improvement in IBDQ-B score was both clinically and statistically significant (compared to booklet) in the nurse (p = 0.04), gastroenterologist (p = 0.014) and combined treatment arms (p = 0.006). Outcomes in the nurse treated arm were not worse than those treated by the gastroenterologist (p = 0.428). Improvements were sustained over time.

Conclusion Targeted intervention following a detailed clinical algorithm can significantly ameliorate radiotherapy-induced GI symptoms. Most patients can be managed by a suitably trained and supported nurse. (Funding RfPB, NIHR)

Disclosure of Interest None Declared

OC-069 CONSTITUTIVE ACTIVATION OF THE DNA DAMAGE RESPONSE PATHWAY IN CANCER REPRESENTS A DEREGULATED PATHWAY

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Introduction The DNA damage response (DDR) is an innate cellular response allowing cells to halt the cell cycle and repair DNA damage sustained by activating various mechanisms. The efficacy of conventional cancer treatment modalities is related in their ability to induce DNA damage. Constitutive activation of the ataxia telangectasia mutated (ATM) dependent DDR and repair pathways have been reported in (pre) malignant human tissues and may undermine the efficacy of current cancer therapies. Inhibition of proteins involved in the DDR cascade is an attractive therapeutic concept that may overcome resistance to current cytotoxics and potentiate the effects of radiotherapy.

Methods A tumour microarray was created using 179 sporadic colorectal cancers; 152 were of the microsatellite stable phenotype. The microarray was interrogated using antibodies against proteins of the DDR signalling cascade. A colorectal cancer cell line model was utilised to asses the functionality of the constitutively activated DNA damage pathway. ATM inhibition in combination with ionising irradiation was analysed in the cell line model using radioactive quantification of DNA synthesis, flow cytometric cell separation, clonogenic survival and immunoblotting.

Results Phosphorylated Chk2 threonine-68, a surrogate marker of the DDR, was present in 22% of microsatellite-stable colorectal tumours and 33% of tumours with the microsatellite instability phenotype. High p53 staining was present in 53% of microsatellite stable cancers and 26% microsatellite instable cancers.

P21-null HCT116 cells display constitutive activation of the ATM DDR but display a defect in the ionising radiation induced S-phase checkpoint, termed radioresistant DNA synthesis. This radioresistant phenotype is associated with increased basal levels of Cdc25A protein, deficient DNA damage-induced degradation of Cdc25A and Chk2 mis-localisation. P21-null HCT116 and SW620 cells, which exhibit basal Chk2 threonine-68 phosphorylation, were unable to abrogate the S-phase checkpoint when treated with an ATM inhibitor, suggesting that the ATM–Chk2 arm is non-functional in these cells: inhibition of ATM did not potentiate the efficacy of ionising irradiation.

Conclusion In a colorectal cancer cell line model constitutive activation of the ATM DDR pathway reflected a non-functional pathway and inhibition of ATM in these circumstances was unable to potentiate the efficacy of ionising irradiation. Basal Chk2 threonine-68 phosphorylation in colorectal cancer may reflect a deregulated ATM DDR pathway and/or checkpoint adaption.

A predictive model is proposed that integrates functionality of the ATM-Chk2 axis, p53 mutation status and defects in DNA repair pathways when considering ATM inhibitor therapy.

Disclosure of Interest None Declared

OC-070 PERCEIVED DELAY AMONG PATIENTS WITH COLORECTAL, STOMACH AND OESOPHAGEAL CANCER: ANALYSIS OF DATA FROM A NATIONAL GP AUDIT

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Introduction The UK has significantly poorer cancer survival rates than comparable countries and diagnostic delay is perceived to be a significant contributory factor to this. The RCGP National Audit of Cancer Diagnosis in Primary Care (2009/10) included data on 3655 patients with colorectal and gastro-oesophageal cancer, including free text comments on avoidable delays in diagnosis, as perceived by the participating GPs. The aim of this study was to identify the principal causes of delay, as perceived by GPs, and how they differ by cancer site.

Methods Avoidable delay was reported for 36% of patients with colorectal cancer, 37% gastric cancer and 35% oesophageal cancer. Free text reports of the nature of the delay were available for 753 (28%) colorectal, 87 (28%) gastric and 164 (27%) oesophageal cancer patients. An extended version of The Model of Pathways to Treatment (Walter *et al* 2011) was developed for use as the analytical framework. Comments were categorised by CD with uncertain cases discussed and resolved with GR. In order to validate GP perceptions of diagnostic delay we compared categorised primary care and referral intervals for patients with and without perceived delay.

Results Primary care and referral intervals were significantly longer for patients with a perceived avoidable diagnostic delay (p = <0.0001), for all three cancer sites. The commonest reasons for delay for colorectal, gastric and oesophageal cancer patients were GP appraisal (29%, 14%, 16% respectively), referral delays (e.g. routine rather than 2 week wait) (13%, 23%, 32% respectively) and investigation delays (28%, 34%, 27% respectively). For colorectal cancer patients, help seeking delay was also a significant cause of delay (8%). Because causes of delay were reported by GPs there was a potential reporting bias, with delays occurring prior to first consultation or in secondary care possibly being under-reported.

Conclusion Diagnostic delay for patients with upper and lower GI cancers is multi-faceted, with GP appraisal and type of referral perceived as substantial contributors. Interventions aimed at reducing the time to diagnosis should be targeted at the key causes and settings of delay for different cancer sites.

Disclosure of Interest None Declared

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OC-071 COMPARISON OF FAECAL M2-PK AND FIT IN SCREENING FOR COLONIC POLYPS IN AN AVERAGE RISK POPULATION

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