Constitutive Activation of the DNA Damage Response Pathway in Cancer Represents a Deregulated Pathway

**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 involved in the DDR cascade an attractive therapeutic concept that may overcome resistance to current cytotoxics and potentiate the effects of radiotherapy.

**Results**
Phosphorylated Chk2 threonine-68, a surrogate marker of the DDR signalling cascade. A colorectal cancer cell line model was utilised to assess the functionality of the constitutively activated DNA damage pathway. ATM inhibition in combination with ionising irradiation was analysed in the cell line model using radioimmunoblotting.

**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.

**Disclosure of Interest**
None Declared

**OC-068**
A Predictive Model of Total Patient Delay in Cancer Diagnosis and Treatment

**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 3665 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 56% 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

**OC-069**
A Comparison of Faecal M2-PK and FIT in Screening for Colonic Polyps in an Average Risk Population

**Introduction**
The Andersen Model of total patient delay: A systematic review of its application in cancer diagnosis.' Journal of Health Services Research and Policy Vol 17, No 2, pp110–118

**Conclusion**
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

**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 3665 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 56% 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

**OC-071**
Comparison of Faecal M2-PK and FIT in Screening for Colonic Polyps in an Average Risk Population

**Introduction**
The Andersen Model of total patient delay: A systematic review of its application in cancer diagnosis.' Journal of Health Services Research and Policy Vol 17, No 2, pp110–118

**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.

**Disclosure of Interest**
None Declared