0–10 scale) and 76% had no CSBMs (mean rate 0.2/wk). Significant improvements in linaclotide-treated patients were seen for both co-primary and all 12 secondary parameters. For the first co-primary parameter (≥30% reduction from baseline in mean abdominal pain or discomfort score with neither score worsening for ≥6 of the first 12 wks), 54.1% of linaclotide-treated patients and 38.5% of placebo-treated patients were responders (p<0.0001). For the second co-primary parameter ("considerably relieved" or "completely relieved" on the weekly degree-of-relief of IBS symptoms question for ≥6 of the first 12 wks), 39.4% of linaclotide-treated patients and 16.6% of placebo-treated patients were responders (p<0.0001). Similar improvements in both co-primary endpoints were seen at 26 wks (53.6% vs 36.0%, 37.2% vs 16.9%; both p<0.0001). Also, rates for sustained abdominal pain/discomfort response and sustained IBS degree-of-relief response at 12 and 26 wks were significantly greater in linaclotide-treated vs placebo-treated patients (all p<0.0001). Linaclotide significantly improved CSBMs, stool consistency, straining, bloating, SBMs, abdominal pain and abdominal discomfort vs placebo over 12 and 26 wks (p<0.0001). The most common adverse event (AE) was diarrhoea, causing discontinuation in 4.0% of linaclotide-treated and 0.2% of placebo-treated patients.

Conclusion Treatment of IBS-C with linaclotide produced statistically significant improvements in abdominal and bowel symptoms at 12 wks and were sustained over 26 wks. Diarrhoea was the most common AE.

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OC-083 OPTIMISING RADIATION BOWEL INJURY THERAPY, THE ORBIT STUDY, A RANDOMISED CONTROLLED TRIAL

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Introduction Chronic gastrointestinal (GI) symptoms after radical pelvic radiotherapy are common. There is no evidence whether medical intervention helps. Most affected patients are never referred to specialists. We developed a comprehensive, peer-reviewed management algorithm for patients with new onset GI symptoms after pelvic radiotherapy. A prospective three arm randomised controlled trial was performed to test two hypotheses: (1) intervention using our algorithm provides benefit at 6 months after randomisation compared to no intervention; (2) outcomes do not differ when patients are managed by nurse or doctor. Other end points include: cost-effectiveness of intervention; effect on non-GI symptoms; outcomes after 12 months.

Methods Consenting people who had completed pelvic radiotherapy >6 months previously with persisting GI symptoms were randomised to see a GI nurse or gastroenterologist, both following our algorithm, or to receive the MacMillan booklet "Pelvic radiotherapy: possible late effects". After 6 months patients in the booklet arm with persisting symptoms could 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). The trial was designed with 80% power to answer the 1st hypothesis after randomising 196 patients and the 2nd after closing the booklet arm, and randomising 22 more patients to gastroenterologist or nurse.

Results This 1st analysis includes 152 men, 44 women randomised to the three arms and followed for 6 months: booklet (n=68) vs combined treatment arms (66 nurse, 62 gastroenterologist). Median age was similar in both groups (69 years range 29–87); 25 patients had radiotherapy for GI, 30 gynaecological, 141 urological cancer. 18 (9%) withdrew/were withdrawn from the trial; 26 (38%) from the booklet group and 5 (8%) from the nurse arm crossed to the gastroenterologist. Intention to treat analysis showed a non-significant (p=0.056) improvement in IBDQ-B score of 2.8 points (95% CI 6.5 to −0.1). Planned per protocol analysis in 158 patients with complete data sets showed significant (p=0.041) improvement in IBDQ-B between treated and non-treated arms of 3.4 points (95% CIs 6.7 to 0.1).

Conclusion Medical intervention can ameliorate radiotherapy-induced GI symptoms. A 2nd analysis in December 2012 will address the other end points and the 2nd hypothesis. This study was funded by RFPB, NIHR.

Competing interests None declared.

Oesophageal free papers

OC-084 THE CLONAL PROGRESSION OF BARRETT'S OESOPHAGUS TO OESOPHAGEAL ADENOCARCINOMA

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Introduction Barrett's oesophagus (BO) is a common premalignant condition, wherein the normal squamous oesophageal epithelium is replaced by a columnar, intestinal phenotype. It is the predominant risk factor for the development of oesophageal adenocarcinoma (OA)[1] which develops through a metaplasia: dysplasia: carcinoma sequence. Initial studies suggested that BO lesions were genetically clonal.[2] However; our group has shown, by gland micro-dissection, that multiple clones are present within BO and it is therefore a genetically heterotypic disease.[3] Furthermore, Maley *et al*[4] have shown that genetic diversity increases the risk of BO progressing to cancer. Here, we demonstrate that although Barrett's dysplasia is polyclonal, oesophageal adenocarcinomas arising from Barrett's are typically clonal.

Methods DNA was macro-dissected from dysplastic and cancerous regions of endoscopic mucosal resection (EMR) and oesophagectomy specimens and screened for mutations in p16*INK4A*, *TP53* and *K-RAS*. Mutated specimens were serially sectioned; crypts and carcinomas were histologically graded and then micro-dissected using a P.A.L.M. laser capture microscope. DNA was extracted from dissected material and was sequenced for the point mutations identified in the initial screen.

Results Individual glands from 10 specimens (EMRs and oesophagectomies) were laser captured and sequenced for mutations identified as per above. Seven specimens contained *TP53* mutations and the three remaining specimens were mutated for p16*INK4A*.

Overall, seven of these specimens contained both mutated and wild type dysplastic glands, with a further one specimen containing three distinct p16*INK4A*mutation. However, the related cancers from these specimens were monoclonal for a mutated genotype found in the dysplasia. These data show that Barrett's dysplasia is polyclonal but Barrett's adenocarcinoma is monoclonal, suggesting that a cellular competition may be involved in the evolution of Barrett's adenocarcinoma from its surrounding dysplasia.

Conclusion

1. Barrett's dysplasia exhibits a mosaic pattern of clones, indicating genetic diversity in Barrett's dysplasia.
2. Oesophageal adenocarcinomas were monoclonal outgrowths from polyclonal Barrett's dysplasia.

Competing interests None declared.

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OC-085 CIRCULATING TUMOUR MARKERS CAN DISCRIMINATE BETWEEN PATIENTS WITH AND WITHOUT OESOPHAGEAL NEOPLASIA

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Introduction Oesophageal cancer is the fastest rising cause of gastrointestinal cancer in the UK, and associated with a poor prognosis. Early diagnosis represents the best opportunity for cure, but early disease is often asymptomatic. Current surveillance programs improve outcome, but rely on two yearly endoscopic screening of previously identified Barrett's oesophagus patients. This has limited sensitivity and acceptability to patients. New endoscopic treatments for oesophageal dysplasia can avoid major surgery, but discriminating between patients with and without invasive disease can be challenging. A discriminating diagnostic blood test may offer improved patient outcome.

Methods In this study, we optimised a series of promising diagnostic markers utilising circulating free DNA (cfDNA), with a preparation method allowing small DNA fragments to be purified. cfDNA was isolated from 115 patients including a "normal" population of 44 patients (Barrett's oesophagus or normal endoscopic findings). Twenty-five patients had high grade dysplasia (HGD) or intramucosal cancer (IMC), and 46 patients had invasive cancer. In each case real time quantitative polymerase chain reaction (RT-PCR) was performed for Line 1 79 bp (quantitative total DNA marker), Line 1 300 bp, Alu 115 bp, Alu 247 bp and mitochondrial primers. Each marker was analysed for differences between normal, HGD and IMC, and invasive cancer populations using Mann–Whitney U tests and ROC curves. The best performing were analysed in combination by logistic regression. A Bonferroni correction was applied.

Results The average age of the normal population group was 56.1 years, the HGD and IMC population group 70.0 years, and the cancer population group 68.9 years. The mean total DNA (ng/ml) was 10.8, 14.1, and 19.2 respectively. Mean DNA marker levels ng/ml. Analysing total DNA, mitochondrial DNA and Line 1 300bp fragment DNA levels, there were highly significant differences between the normal group vs all dysplastic and cancerous patients ($p \leq 0.003$).

Conclusion The combination DNA marker was able to discriminate the normal population from all dysplasia and cancer patients with a ROC curve of 0.778. This may offer the prospect of a simple blood test to stratify patients and improve surveillance for dysplasia and early cancer. The same model was able to discriminate the normal population from invasive cancer patients with a ROC curve of 0.847. This may help in the rapid identification of patients who require surgery.

Abstract OC-085 Table 1

Mean DNA	Total	Mito	115	300	247	79/300	115/247
"Normal"	10.8	1.1	35.6	1.8	3.1	6.3	11.0
HGD + IMC	14.1	4.2	42.6	3.2	4.6	6.1	10.3
Inv. cancer	19.2	6.2	76.9	5.3	4.9	8.8	16.3

Competing interests None declared.

OC-086 SURGERY ALONE VS CHEMORADIOTHERAPY FOLLOWED BY SURGERY FOR STAGE I AND II OESOPHAGEAL CANCER: FINAL ANALYSIS OF A RANDOMISED CONTROLLED PHASE III TRIAL—FFCD 9901

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Introduction Resection remains the best treatment for local control of oesophageal carcinoma (OC), but local recurrence, distant metastasis and poor survival remain an issue after surgery. Often investigated in locally advanced OC, the impact of neoadjuvant chemoradiotherapy (NCRT) is unknown in patients with stage I or II OC. The aim of this multicentre randomised controlled phase III trial was to assess whether NCRT improves outcomes for patients with stage I or II OC.

Methods 195 patients were randomly assigned to surgery alone (S group, n=98) or to NCRT group (NCRT group, n=97; 45Gy given in 25 fractions over 5 weeks with two courses of concomitant chemotherapy by 5-Fluorouracil 800 mg/m^2 on days 1–4 and cisplatin 75 mg/m^2 on day 1 or 2). The primary endpoint was overall survival. Secondary endpoints were progression free survival, postoperative morbidity and 30-day mortality, R0 resection rate and prognostic factor identification. Analysis was done by intention to treat.

Results Patient and tumour characteristics were well-balanced between the two groups. Patients were preoperatively staged I in 18%, IIA in 49.7%, IIB in 31.8%, unknown in 0.5%. Postoperative morbidity and 30-day mortality rates were 49.5% vs 43.9% (p=0.17) and 1.1% vs 7.3% (p=0.054) in the S group and NCRT group, respectively. After a median follow-up of 5.7 years, 106 deaths were observed. Median survivals were 43.8 vs 31.8 months, respectively (HR 0.92, 95% CI 0.63 to 1.34, p=0.66). The trial was stopped due to futility.