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Introduction EMR is an established treatment for large colorectal polyps, yet the data regarding efficacy and outcome are principally limited to single centre experience. We present a multicentre study to determine prognostic factors of short-term (3 month) and long-term (1 year) outcomes following an index (intention to treat (ITT)) EMR for large sessile colorectal polyps.

Methods Endoscopy databases & hospital coding records identified patients that had an ITT EMR for colonic polyps 2 cm or greater between 2005 and 2010 in five North-West teaching hospitals. Patients were audited longitudinally for 1 year. Multivariate analysis (Logistic Regression Model) determined significant prognostic factors (OR [95% CI]; p<0.05 as significant).

Results Demographics: 313 patients (mean [SD] age 69.7[10.4] years, 65.5% male, 86% ASA grade 1–2) underwent EMR for mean polyp size of 33.5 [11.5] mm. Morphologically; 63.8% were flat lesions and 21.7% were located in the right colon. Procedure: 26% were performed by inexperienced endoscopists (Outcomes: Cancer diagnosis was in 9.5% (6.3% invasive & 3.2% intra-mucosal). Complications; Perforation rate 0.5%, bleeding rate 0.5% & all cause 30-day mortality 0.6 %, with no procedure related mortality. Recurrence rate was 26% & treated endoscopically in 64.6%, & surgically in 8.5%. Overall, surgery was required in 7.3%, of which 8.7% were emergencies (to treat perforation) and 56% was for cancer. ITT short-term success rate was 68% and 1-year success rate was 82.4%, with an adjusted rate of 87.2%. Prognostic Factors: Predictors of recurrence were cancer histology (OR 9 [95% CI 4 to 22]=<0.05), piecemeal resection (OR 4 [95% CI 1.5 to 11] p<0.005) and EMR session >1 (OR 22 [95% CI 10 to 50] p<0.005). Poor prognostic indicators for long-term success were cancer (OR 11 [95% CI 4.5 to 28] p<0.005) and EMR session >1 (OR 3.6 [95% CI 1.5 to 8.4] p=0.003). While endoscopist inexperience, increasing polyp size, no adjuvant APC were poor prognostic factors univariately, on multivariate analysis they were insignificant. Gender, age, ASA, Training, site, morphology and complications were not significant factors.

Conclusion While recurrence rates in EMR for large colonic lesions were high (>1/4), long-term outcomes were good (cure rate 87.2%) with complications similar to previous series. Most important poor prognostic factors were cancer histology and requirement of more than 1 session.

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OC-016 | **HUMAN COLORECTAL ADENOMA GROWTH IS CHARACTERISED BY PERIODS OF QUIESCENCE AND RAPID CLONAL EXPANSION**

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Introduction Very little is known about the dynamics and rates of adenoma growth in the human colon. Longitudinal barium and endoscopic studies demonstrate most smaller adenomas to be static over many years, with a significant proportion even regressing.[1][2] We have recently shown that methylation patterns at CpG loci within non-expressed genes can be used to infer the dynamics of clonal expansion in the normal human colon.[3] By combining clonal mutational analysis with sampling of these methylation patterns for crypts within human adenomas, we aimed to learn more about how these important pre-malignant epithelial lesions grow.

Methods Fresh frozen human adenomas were screened for common tumourigenic mutations known to occur in adenoma progression. Multiple individual crypts spaced across the whole lesion were then laser-capture micro-dissected, the mutation(s) detected at screening confirmed and methylation tags at CpG islands of non-expressed genes sampled in order to infer dynamics and patterns of growth.

Results Crypts within adenomas clonal for APC and KRAS mutations demonstrated significantly less methylation pattern diversity than those from adenomas that were clonal for an APC mutation only, suggesting there had been a recent, rapid clonal expansion in the APC/KRAS mutated lesions. Genetically distinct sub-clones could be identified within adenomas, and analysis of methylation patterns showed them to be expanding rapidly. There was no correlation between the spatial separation of crypts and their respective epigenetic distances—as measured by comparisons of crypt methylation patterns—within the adenomas studied. Therefore, in those lesions that had not undergone a recent clonal expansion, there had been a sufficient time period of little or no growth to allow the methylation patterns of neighbouring crypts to diverge.

Conclusion The data collected here suggests that human adenomas display punctuated growth, characterised by periods of relative quiescence and rapid clonal expansion. Further data collection and analysis should allow the relative growth rates of genetically distinct lesions and sub-clones within adenomas to be estimated, and may help better inform our management and follow-up of patients with these lesions.
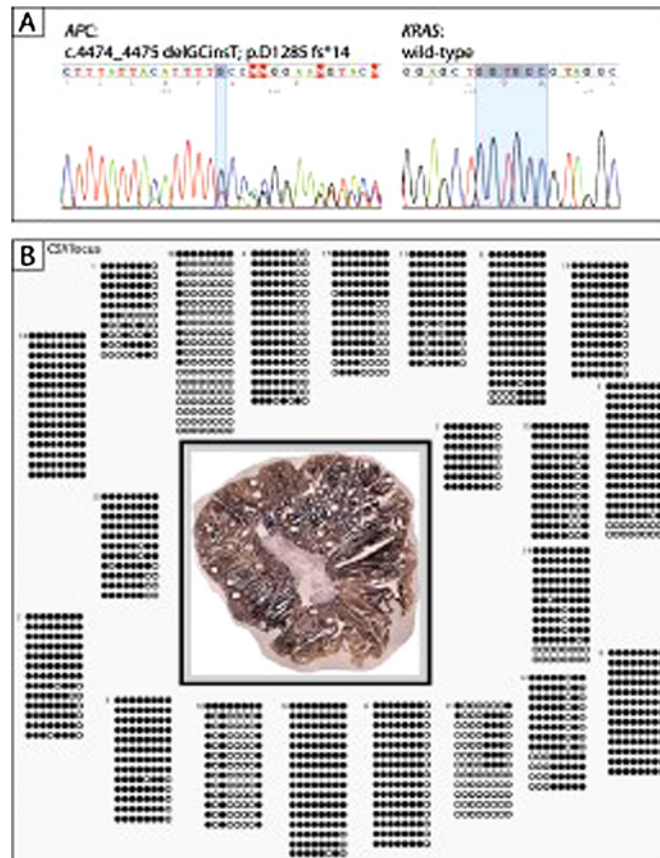
Abstract OC-016 Figure 1

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OC-017 | ### TRIM44: FROM PROGNOSIS TO THERAPY IN OESOPHAGEAL ADENOCARCINOMA AND BREAST CANCER

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Introduction The incidence of oesophageal adenocarcinoma (EA) has quadrupled in the last 30 years and outcomes remain poor. Unlike other epithelial cancers, targeted therapies for EA are at an early stage. Using gene expression profiling, we have previously identified TRIM44 as an independent prognostic gene in EA.

Methods The aims of this project were to (1) Explore the mechanism of dysregulation of TRIM44 and association with prognosis. (2) Examine the oncogenic potential of TRIM44 in EA and other epithelial cancers (3) Identify therapeutic options exploiting TRIM44 dysregulation.

Results Analysis of our EA expression microarray data (n=75), an independent matched aCGH and expression microarray of 997 breast cancers (BC) and an online database (Tumourscape n=1932, various epithelial tumours) revealed focal amplification of TRIM44 in 8% of EA, 6% of BC and 4% of epithelial tumours. Amplification in EA was validated using FISH on tissue microarrays (n=164). Expression of TRIM44 was copy number driven in both EA and BC and amplification conferred a poor prognosis in BC (p=0.037). Functional work demonstrated oncogenic addiction to TRIM44 in cell line models harbouring amplifications; siRNA knockdown in HSC39 (amplifications) and JIMT-1 (high expression) decreased proliferation of cells by twofold (p<0.05) and increased subG0 fraction on FACS (2.5-fold, p<0.05). In contrast, knockdown in OE19 (low expression) had no observed effect. Overexpression of TRIM44 in Hela cells using a Tet-inducible system increased proliferation (2.5-fold, p=0.0038) and invasiveness (twofold, p<0.05). Analysis of the microarray data (EA and breast) identified a potential link between TRIM44 and the mTOR pathway, and suggested sirolimus (mTOR inhibitor) as a therapeutic option. Validation of these findings were performed by IHC of amplified EA samples and showed exact co-localisation of TRIM44 and p-mTOR staining. In addition, treatment of HSC39 and JIMT-1 with RAD001 (mTOR inhibitor) showed that they were highly sensitive (IC50 <30 nm).

Conclusion TRIM44 is amplified in >5% of EA leading to increased proliferation and invasion in vitro. Our data suggest a mode of action of TRIM44 via the mTOR pathway. Evaluation of mTOR inhibitors in EA tumours is worthy of consideration and these are currently being evaluated in phase I/II oncology clinical trials in other epithelial cancers such as renal cell and lung cancer). Assessment of TRIM44 amplification status may allow selection of patients who are more likely to respond.

Competing interests None declared.

OC-018 | ### VALIDATION OF TWO APC-DEPENDENT POTENTIAL BIOMARKERS OF COLORECTAL CARCINOGENESIS

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Introduction Most cases of sporadic colorectal cancer develop via the adenoma carcinoma sequence and APC mutation is a key early molecular event. APC regulates B-catenin function and the WNT signalling pathway to control intestinal homeostasis. However, mutation or loss of APC gene results in translocation of B-catenin into the nucleus, where it forms a heterodimeric transcriptional factor complex with TCF and results in altered cell fate. We have previously performed a proteomic analysis of changes which occur in murine intestinal epithelium following acute b-napthoflavone-induced deletion of Apc expression (Apc$^{fl/fl}$ mice). Several proteins showed increased abundance following intestinal Apc deletion and we hypothesised that some of these may represent potential biomarkers for the serological detection of the early stages of human colorectal cancer.

Aims To investigate whether two proteins which were demonstrated to be upregulated in Apc$^{fl/fl}$ intestinal epithelium by proteomic analysis, namely serine/arginine-rich splicing factor 2 (SRSF2) and ribosomal protein L6 (RPL6) show altered expression in murine and human intestinal tumours.

Methods The expression patterns of SRSF2 and RPL6 were assessed by immunohistochemistry and RTqPCR in intestinal and colonic tumour samples obtained from Apc$^{Min/+}$ mice aged 1, 3 and 6 months and 15 human subjects with colorectal cancer.

Results RTqPCR demonstrated a 3.0-fold increase in SFRS2 expression and a 2.8-fold increase in RPL6 expression in colonic polyp tissue from 6-month old Apc$^{Min/+}$ mice relative to colonic tissue from Apc$^{+/+}$ wild-type mice of the same age. Immunohistochemistry showed nuclear rather than cytoplasmic localisation of both SFRS2 and RPL6 in intestinal and colonic polyps from Apc$^{Min/+}$ mice aged 3 months and 6 months. The alteration in subcellular localisation of SFRS2 and RPL6 appeared to occur in adenomatous cells which also displayed nuclear translocation of B-catenin. Statistically significant increases in the relative expressions of SFRS2 (1.2-fold) and RPL6 (1.9-fold) mRNAs were also observed in human colorectal cancer tissue samples relative to adjacent unaffected colonic tissue from the same patients.

Conclusion RPL6 and SFRS2 both showed altered expression in murine and human intestinal/colonic tumours. Both these proteins are involved in regulating cell cycle progression—RPL6 regulates the G1-S transition via cyclin E and SFRS2 affects the G2/M transition via CDC5, possibly through alternative splicing. The altered expressions of PRL6 and SFRS2 may therefore deregulate cell cycle control and promote cellular proliferation, a characteristic phenotype of the intestinal epithelium of Apc$^{fl/fl}$ mice as well as intestinal tumours.

Competing interests None declared.

OC-019 | ### ALTERED TRAIL, CASPASE12, BAK AND FAS-L EXPRESSIONS ARE ASSOCIATED WITH INCREASED SUSCEPTIBILITY TO RADIATION INDUCED INTESTINAL EPITHELIAL APOPTOSIS IN NF-κ B1-NULL AND NF-κ B2-NULL MICE

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Introduction The Nuclear Factor κ B (NFκB) family is composed of five members, RelA, c-Rel, NFκB1, RelB and NFκB2. The first three members signal via the classical pathway and the last two via the alternative pathway to regulate several cellular processes including apoptosis. NFκB1 has previously been shown to regulate radiation-induced apoptosis in the murine small intestine, but the underlying mechanisms have not been defined. The roles of other family members, particularly those involved in alternative pathway