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Session theme:

Gastrointestinal Oncology

Biomarkers for Detection, Treatment, and Prognosis of GI Cancers

Abstract title:

Quantifying evolution of early dysplastic lesions in ulcerative colitis predict future colorectal cancer risk

Background: Ulcerative colitis (UC) increases the risk of colorectal cancer (CRC). Colitis-associated CRCs (CA-CRCs) bear a unique pattern of genomic alterations that begin to accrue prior to tumour growth (Baker et al. *Gut* 2018). We hypothesised that detection of such colitis-associated genomic alterations would predict subsequent cancer risk. Specifically, chromosomal copy number alterations (CNAs) occur in colonic epithelial cells and subsequently evolve, clonally expand, and reveal signatures indicative of future malignant CRC phenotype. Low-pass whole-genome sequencing (lpWGS) is a cost-effective technique for high-resolution CNA assessment in formalin-fixed, paraffin-embedded tissue that can detect predictive biomarkers of early cancer changes in UC.

Methods: We selected 67 patients with LGD, 22 of who subsequently progressed to HGD/CRC a median 427 days later (IQR 218–907). Progressor patients were matched for age, gender, disease duration, and LGD location with 45 controls who remained HGD/CRC-free >5 years later. Two blinded pathologists confirmed histological diagnoses. Low-pass WGS (0.1x) was performed using a standardised next-generation sequencing pipeline and genomic data was analysed along with clinical/endoscopic features in subsequent multivariate and survival analyses. Predictive values and sensitivity/specificity of models were calculated at the end of follow-up, with censoring occurring at 5 years.

Results: In UC, the number of early CNA events is greater in LGD of progressors than in LGD of non-progressors ($p < 0.0001$). Using multivariate Cox proportional hazards models that include clinical/endoscopic and genomic variables for LGD lesions, only CNAs were found to be statistically significant in determining risk of neoplastic progression. Kaplan–Meier analysis estimated that patients in this cohort bearing the greatest number of abnormal segments in LGD were significantly more likely to develop future CRC/HGD than the lower three quartiles (HR 7.5, $p < 0.0001$, negative predictive value = 84%, sensitivity = 64%, and specificity = 93%).

Conclusions: CNA burden predicts cancer risk with high specificity. LGD lesions demonstrate a surprising diversity in CNA burden, and high-risk LGD lesions typically bear CNA signatures indistinguishable from those measured in HGD/CRC. With further validation in progress, lpWGS has the promising potential for translational utility in early detection by stratifying patients with LGD according to risk of progression to HGD/CRC. Such genomic evolutionary biomarkers could be integrated into web-based risk prediction tools that we have developed for shared decision-making using published cancer risk estimates to help clinicians and patients alike better understand cancer risk in early UC dysplasia (www.uc-care.uk).

Figure 1

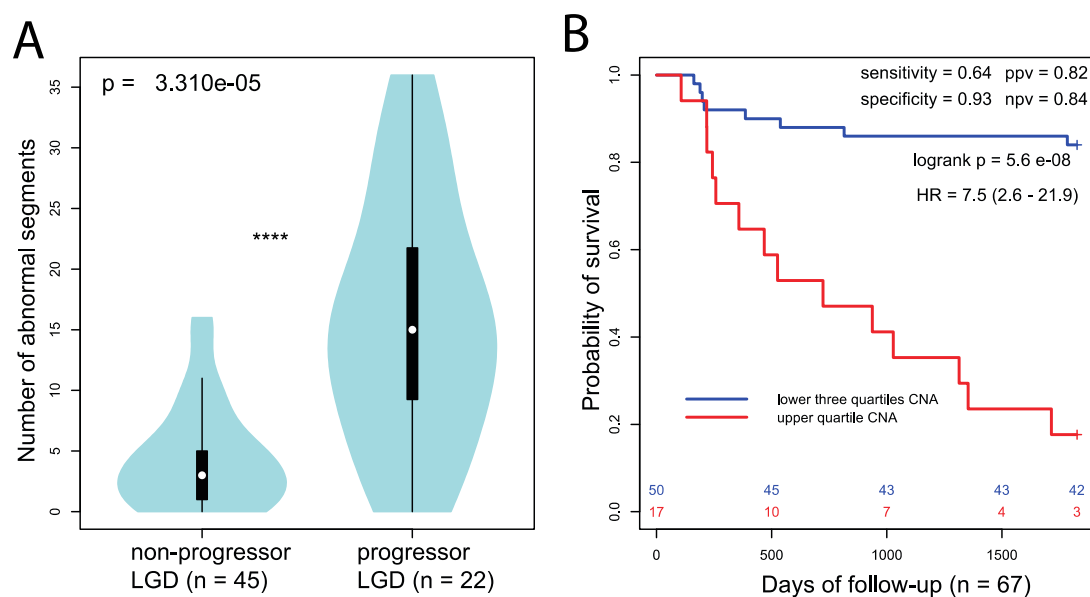


Figure 2

UC-CaRE : Ulcerative Colitis - Cancer Risk Estimator

A visual tool for patient-specific risk management

Physician Name:

Date:

Please answer the following for the ulcerative colitis patient with low grade dysplasia.

Low grade dysplasia (LGD) lesion shape:

☐ Polypoid

☒ Nonpolypoid

☐ Invisible

Is the LGD lesion large (≥ 1 cm)?

☒ No

☐ Yes

Is there a stricture?

☐ No

☒ Yes

Is the LGD metachronous?

☐ No

☐ Yes

Did the patient have a previous diagnosis of colitis for dysplasia?

☐ No

☐ Yes

Is the LGD multifocal?

☐ No

☐ Yes

Was chromoendoscopy performed?

☐ No

☐ Yes

Predicted Risk of High Grade Dysplasia and/or Colorectal Cancer

Probability of recidiva

Time since LGD diagnosis (years)

0 0.2 0.4 0.6 0.8 1.0

0 2 4 6 8 10

Your risk of developing high grade dysplasia (HGD) and/or colorectal cancer (CRC) after 1 year is: 17.5 %

