Digest

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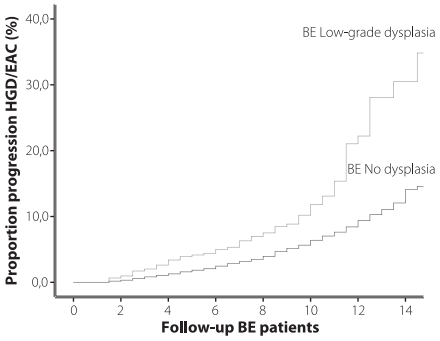
Risk of malignant progression of Barrett's oesophagus

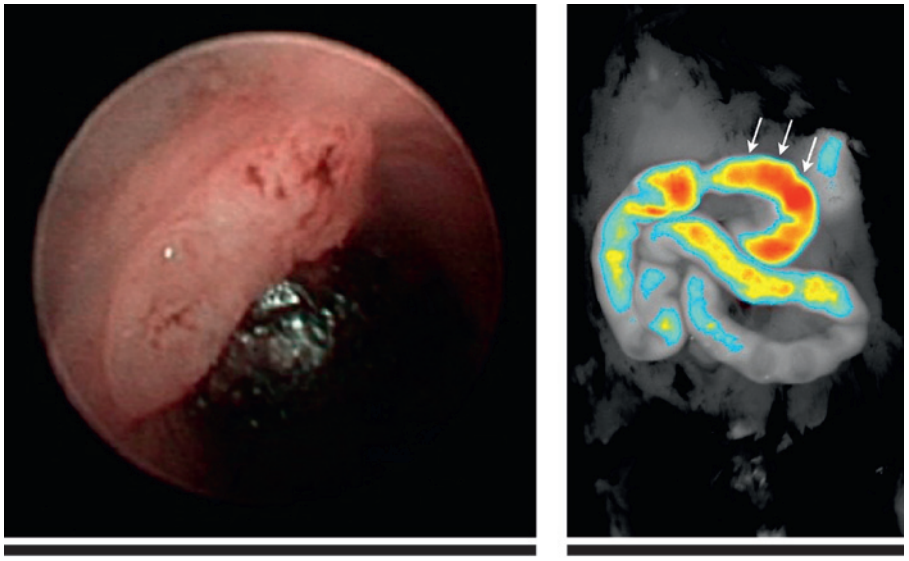
Published estimates of the annual risk of cancer in patients with Barrett's oesophagus (BO) vary widely and range from 0% to 2.9% per annum. The variation may be partly explained by publication bias favouring small studies with high cancer incidence rates. In this study, De Jonge *et al* estimated the progression rate of BO to high-grade dysplasia (HGD) and oesophageal adenocarcinoma (OAC) in a nationwide cohort of patients with BO in The Netherlands, and assessed the value of the factors age, sex and initial histology as predictors of malignant progression in BO. A total of 42 207 patients with BO were included; 4132 (8%) of them had low-grade dysplasia. Patients were followed-up for a total of 78 131 person-years. Incidence rates per 1000 person-years were 4.3 (95% CI 3.4 to 5.5) for OAC and 5.8 (95% CI 4.6 to 7.0) for HGD/OAC combined. Risk factors for HGD/OAC were increased age, male gender and presence of low-grade dysplasia at baseline. This is the largest cohort of unselected patients with BO and the estimates reported should enable an improved risk assessment in BO (see figure). ***See page 1030***



Progression rate to high-grade dysplasia (HGD)/oesophageal adenocarcinoma (OAC) in 16 333 patients with Barrett's oesophagus.

Molecular imaging of VEGF using confocal laser endomicroscopy

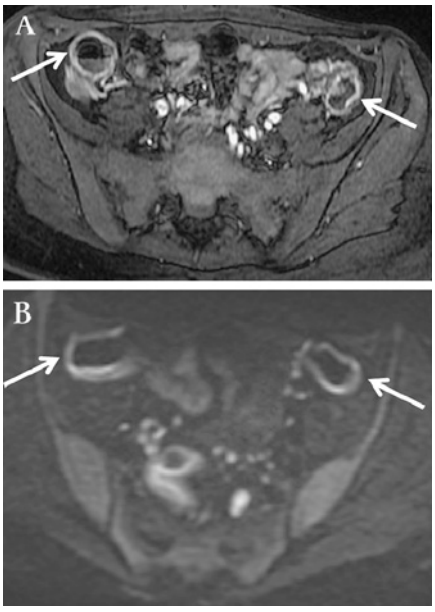
Confocal laser endomicroscopy (CLE) allows in vivo histological examination of the gastrointestinal tract in real time during endoscopy, but the feasibility of 'in vivo immunohistochemistry' using fluorescence labelled monoclonal antibodies remains unanswered. Vascular endothelial growth factor (VEGF) plays an important role in angiogenesis of healthy and malignant tissue. In this study, Foersch *et al* evaluated CLE for in vivo molecular imaging of VEGF in gastrointestinal cancers. Molecular imaging of tumours in APCmin mice (see figure), in xenograft models and in surgical specimens of patients with colorectal cancer was achieved after application of labelled antibodies. From all tumour sites examined with CLE in vivo, targeted specimens were obtained for histology, immunohistochemistry and fluorescence microscopy. A VEGF-specific signal was visualised in vivo in almost all APCmin mice and xenograft tumours. In human tissue, a VEGF-specific signal was observed in 12/13 malignant specimens and in 10/11 samples from healthy mucosa from the patients. CLE findings correlated well with ex vivo microscopy. The study proves the feasibility of this approach and offers exciting prospects for early detection of lesions at risk and stratification, and surveillance of targeted treatments. ***See page 1046***



CLE setting in APCmin mice. Tumors (arrow) in the ileum and colon are exposed and can be examined with CLE system while blood flow is preserved. APCmin tumor in the colon during NBI colonoscopy. In vivo macroscopic imaging of angiogenesis (VEGFR-2) in an APCmin mouse tumors (arrows) using MAESTRO imaging system.

Detection of colonic inflammation in IBD using magnetic resonance without bowel preparation

In this cohort study, the accuracy of MRI in combination with diffusion-weighted imaging (DWI-MRI) without oral or rectal preparation in assessing colonic inflammation in inflammatory bowel disease was evaluated. A total of 96 consecutive patients who underwent DWI-MRI-colonography without bowel preparation were studied (ulcerative colitis (UC)=35; Crohn's disease (CD)=61, and 68 also had concomitant endoscopy). In UC, a segmental magnetic resonance score (MR-score-S) >1 detected endoscopic inflammation with a sensitivity and specificity of 89.47% and 86.67%, respectively (p=0.0001). The technique performed less well in CD, where an MR-score-S >2 had a sensitivity and specificity of 58.33% and 84.48%, respectively, for detecting inflammation in the colon. In UC the total magnetic resonance score (MR-score-T) correlated with the total modified Baron score (r=0.813, p=0.0001), and in CD the MR-score-T correlated with the Simplified Endoscopic Activity Score for Crohn's Disease (r=0.539, p=0.001). The DWI

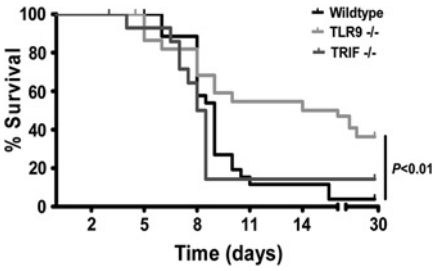


A 22-year-old woman with a severe attack of ulcerative colitis (pancolitis); (A) Rapid gadolinium enhancement in the right and left colons (full arrows). (B) Diffusion-weighted hyperintensity in the right and the left colons (full arrows).

hyperintensity was a predictor of colonic endoscopic inflammation and, again, its accuracy for detecting colonic inflammation was greater in UC than in CD (p=0.004). The authors conclude that DWI-MRI-colonography without bowel preparation is a reliable tool for detecting colonic inflammation in UC. ***See page 1056***

MyD88/TLR9-mediated immunopathology and gut microbiota dynamics in intestinal graft-versus-host disease

The microbiota is known to aggravate graft-versus-host disease (GvHD) after allogeneic stem cell transplantation, but the underlying mechanisms of intestinal GvHD (iGvHD) remain poorly understood. The authors in this study analysed the composition of the microbiota (via culture and molecular methods) and the impact of bacterial sensing via Toll like-receptors (TLRs) in iGvHD in a new irradiation-independent, treosulfan- and cyclophosphamide-based murine allogeneic transplantation model. They found that the inflammatory responses in iGvHD were accompanied by shifts in the composition of the microbiota towards enterobacteria, enterococci and *Bacteroides/Prevotella* spp. Analysis of iGvHD in MyD88−/−, TRIF−/−, TLR2/4−/− and TLR9−/− recipient mice showed that bacterial sensing via TLRs was essential for iGvHD development. However, only TLR9−/− mice showed increased survival rates. The important role of TLR9-mediated immunopathology was confirmed by reduced macroscopic disease and colonic apoptosis, and by reduced T cell and neutrophil numbers within the colon after treatment with a TLR9 inhibitory oligonucleotide. The results therefore show the critical role of gut microbiota, innate immunity and TLR9 in iGvHD, and anti-TLR9 strategies may be seen as novel therapeutic strategies. ***See page 1079***

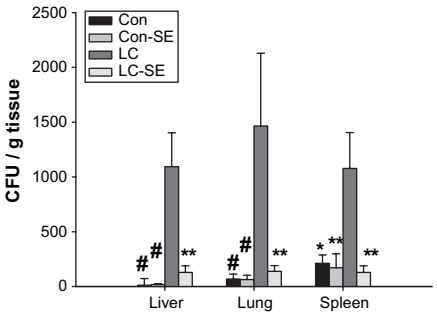


Survival of wild-type (n=30), TRIF−/− (TRIF, n=24) and TLR9−/− (TLR9, n=27) mice.

Improving defence against Gram-negative sepsis in cirrhosis

Spontaneous bacterial peritonitis is a dangerous complication of liver cirrhosis. Bacterial translocation of enteric Gram-negative bacteria, mainly of *Escherichia coli*, is the major cause of spontaneous bacterial peritonitis. R Wiest and his group describe an interesting and novel feature of Gram-negative infection in cirrhosis, namely a role for the sympathetic nervous system.

It is well known that the sympathetic nervous activity is increased in advanced cirrhosis, presumably as a consequence of reduced centrally effective blood volume. Using a rat model of cirrhosis, the authors show that chemical splanchnic sympathectomy prevents bacteraemia following intraperitoneal *E coli* administration, but has no effect on *Staphylococcus aureus* translocation. These data demonstrate an important role for the adrenergic system in the regulation of host defence against Gram-negative bacteria. Moreover, they support the contention that a decrease of

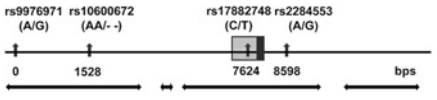


Organ-specific reduction in bacterial tissue burden by *E coli* after sympathectomy in cirrhotic rats.

mortality by non-selective β-blockade in cirrhosis is related to prevention of bacterial infections, in particular of spontaneous bacterial peritonitis. ***See page 1127***

HCV progression to severe fibrosis—is it in the IFNGR2 gene?

Progression of hepatitis C virus (HCV) infection is highly variable, with some patients developing cirrhosis in <20 years. Whereas viral load or genotype seem not to be important, age at infection, alcohol intake and obesity are considered relevant risk factors for fibrosis. Recently, research has focused on the impact of genetic factors. In the present study almost 400 very well characterised patients with HCV were investigated. The authors selected a substantial panel of 36 genes encoding enzymes relevant for extracellular matrix turnover, profibrogenic or antifibrogenic cytokines and their receptors. Investigation of 384 single nucleotide polymorphisms led to the identification of four interferon γ receptor 2 variants which were strongly associated with fibrosis progression. These exciting findings will be supplemented by investigations on the biology of these gene variations. ***See page 1120***



Schematic representation of the chromosome 21 region ranging from 33 689 800 to 33 702 200 bp, and including the 5′ region, exon 1 and part of intron 1 of *IFNGR2*.