6110 POSTER

Influence of smoking on the clinico-pathological features of colorectal cancer: review of a prospective database

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Background: Smoking is a risk factor for colorectal cancer (CRC) development. The impact of smoking on clinico-pathological features of CRC is not well defined. A prospective cancer database was used to review the effect of smoking status on the clinico-pathological features of CRC.
Material and Methods: Data from 5 hospitals in Victoria, Australia, was collected prospectively between January 2003 and December 2008. All stages of CRC were included. Patients were classified as never smokers, ex-smokers (no cigarettes for at least one month) or current smokers. Demographic factors, histopathology and post-surgical complications were compared when stratified by smoking status. Data was analysed using a repository (BioGrid Australia) allowing linkage of de-identified data across institutions.
Results: In total 1805 patients were identified with known smoking status and CRC. 13.7% (n = 245) were current smokers, 30% (n = 541) ex-smokers and 56.5% (n = 1019) never smokers. The median age of current smokers was significantly younger (61) than for ex-smokers (70.7) and never smokers (68.6), p < 0.0001. 20% (n = 49) of current smokers with CRC were under 50 years old, vs 10.2% (n = 104) of never smokers (p < 0.0001). Less women were current or ex-smokers (29%, n = 236) than men (67%, n = 550) (p < 0.0001).
Current smokers had significantly less screen-detected CRC: 4.5% (n = 11), compared with never smokers, 8.8% (n = 90, p = 0.02). Smokers were more likely to be diagnosed with rectal cancer (38%, n = 93) than ex- or never smokers (31%, n = 487) (p = 0.04). Smokers presented with fewer stage III cancers than never smokers (20.8%vs29.2%, p = 0.009). Median body mass index (BMI) was lower for current smokers (25.4kg/m^2) than ex- or never smokers (26.75kg/m^2, p = 0.0009). There were no significant differences for diabetes status or lymph node yield.
Despite being younger, significantly more post-surgical medical and surgical complications occurred in current smokers. Return to theatre occurred in 8.2% of current smokers (n = 20) vs 2.2% of never smokers (n = 22), p < 0.0001. Post-operative inpatient death occurred in 3.7% (n = 9) of current smokers vs 1.8% (n = 18) of never smokers (p = 0.08).
Conclusions: Smokers present with CRC at a younger age; are less likely to be screen-detected; have lower BMI; have more rectal rather than colon cancer; and have more post-surgical complications despite being younger. An independent association for CRC and BMI will be presented in multivariate analysis. Given that 20% of smokers were diagnosed under 50 years of age, screening for smokers from a younger age than current guidelines, may be appropriate.

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Calcium/magnesium (CaMg) reduces grade 2+ oxaliplatin-induced neurotoxicity in patients with glutathione S-transferase pi 1 (GSTP1) I105V polymorphism

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Background: FOLFOX has emerged as a standard therapy in colorectal cancer. Oxaliplatin's dose-limiting toxicity is a cumulative sensory neurotoxicity (sNT) which commonly requires stop of therapy before tumor progression. Polymorphisms in GSTP1 have been implicated in susceptibility for early onset of sNT on FOLFOX. We analyzed GSTP1 in patients (pts) enrolled in N04C7, a phase III trial to evaluate IV CaMg vs placebo as neuroprotectant for adjuvant FOLFOX in colorectal cancer.
Materials and Methods: Of 102 pts enrolled, 98 evaluable pts provided blood for DNA extraction. TaqMan was used for GSTP1 I105V genotyping. Primary endpoint of N04C7 was to compare grade 2+ chronic sNT during or after therapy between CaMg and placebo. Secondary endpoints were to compare among GSTP1 subgroups (A/A wildtype, A/G heterozygous, G/G I105V polymorphism): overall grade 2+ sNT, time to grade 2+ sNT, and time to grade 2+ sNT before reaching cumulative oxaliplatin dose of 800 mg/m^2.
Results: No difference was found (Chi-square, p = 0.8) in grade 2+ NT among the GSTP1 subgroups: A/A (14/44), A/G (11/38), G/G (6/16). Interestingly, in GSTP1 I105V pts (i.e., G/G, n = 16), 0/6 pts treated with CaMg experienced grade 2+ NT compared to 6/10 pts treated with placebo (Fisher's Exact Test, p = 0.03). In contrast, in GSTP1 A/A or A/G pts (n = 82), 11/42 pts treated with CaMg experienced grade 2+ NT compared to 14/40 pts treated with placebo (Chi-square, p = 0.4). Finally, we observed no association between GSTP1 subgroups and time to grade 2+ sNT or time to grade 2+ sNT before reaching cumulative oxaliplatin dose of 800 mg/m^2 (Kaplan-Meier, all p > 0.5).
Conclusions: This study provides preliminary evidence that pts with the GSTP1 I105V polymorphism could benefit from CaMg as neuroprotectant against oxaliplatin-induced sNT. Further prospective validation of GSTP1 I105V and its association with the effectiveness of CaMg is warranted.

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Heterogeneous expression of cyclooxygenase-2 and inducible nitric oxide synthase within colorectal tumors: correlation with tumor angiogenesis

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Background: Recent studies have shown that the cyclooxygenase (COX) and the inducible nitric oxide synthase (iNOS) pathways are involved in the development of tumor angiogenesis in human cancers. We aimed at investigating whether a different pattern of COX-2 and iNOS expression/activity exists within different areas of colorectal tumors and to analyze the relationship between these two enzymes and tumor angiogenesis.
Methods: Microvessel density (MVD) and COX-2, iNOS, vascular endothelial growth factor (VEGF) and VEGF receptor-2 (VEGFR-2) protein expression were evaluated at both the invasive front (IF) and the tumor center (TC) in 46 human colorectal cancer specimens. We also investigated the concentration of PGE_2 and NO at the same sites.
Results: COX-2 and iNOS protein expression and activity were significantly higher within the IF than the TC of the tumor specimens. Similarly, MVD and VEGF/VEGFR-2 expression significantly increased from the TC to the IF. Only COX-2 expression was significantly correlated with MVD and VEGF/VEGFR-2 expression at both the TC and IF.
Conclusion: Our study shows a heterogeneous expression of COX-2 and iNOS in colorectal cancer. The up-regulation of COX-2 at the IF parallels an increase in vessel density and VEGF/VEGFR-2 expression, thus supporting the hypothesis that the tumor periphery is the most aggressive portion of a colorectal tumor.

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BRAF V600E mutation and Amphiregulin (AR) immunohistochemical expression in the prediction of benefit from cetuximab plus irinotecan in KRAS wild-type metastatic colorectal cancer (mCRC) patients

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Background: *BRAF* V600E mutation is suggested to predict resistance to anti-EGFR monoclonal antibodies, in *KRAS* wild-type (wt) mCRC patients. Also the expression of the endogenous EGFR ligand AR might play a predictive/prognostic role.
Materials and Methods: We retrospectively assessed *KRAS* codon 12−13, *BRAF* V600E mutations and AR expression at immunohistochemistry (IHC) in 86 mCRC patients treated with cetuximab plus irinotecan. *KRAS* and *BRAF* mutations were detected by PCR and sequencing and AR-IHC was performed on tissue sections from paraffin-embedded tumors.
The correlation among *BRAF* mutations, AR expression (as a continuous variable) and clinical outcome was investigated in the subgroup of *KRAS* wt patients.