Mini International Session 1: ‘Colorectal cancer’

**LYMPHOVASCULAR INVASION IS A SIGNIFICANT PROGNOSTICATOR IN RECTAL CANCER PATIENTS WHO RECEIVE PREOPERATIVE CHEMORADIOThERAPY FOLLOWED BY TOTAL MESORECTAL EXCISION**

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Background: This study was designed to identify the significance of lymphovascular invasion as a prognosticator for tumor recurrence and survival in rectal cancer patients treated with preoperative chemoradiotherapy (CRT) and total mesorectal excision (TME).

Methods: Between January 2003 and October 2010, the study included 328 patients with primary rectal cancer who had received preoperative CRT followed by TME. We analyzed the clinicopathologic factors that may be associated with survival, such as age, gender, carcinoembryonic antigen (CEA) value, pathologic T and N stage, tumor response, histologic grade, lymphovascular invasion (LVI), and perineural invasion.

Results: Higher pathologic T and N stage, poor tumor response, high-grade histology, and positive LVI were adverse prognostic factors for both disease-free survival (DFS) and overall survival (OS) on the multivariate analysis. Perineural invasion was a significant adverse prognostic factor affecting DFS (P = 0.046) but not OS (P = 0.68). Increased T and N stage and distant recurrence, but not local recurrence, were significant factors associated with LVI. The LVI-negative group had a higher DFS (71.4 versus 56.2%, P = 0.012) and OS rate (86.7 versus 63.4%, P = 0.020) at 5 years than the LVI-positive group did.

Conclusions: Positive LVI had a negative impact on survival patients with rectal cancer who received preoperative CRT and TME and is significantly associated with an increased chance of distant recurrence. Based on this finding, more tailored adjuvant chemotherapy is warranted for advanced rectal cancer patients with LVI to reduce the distant dissemination of tumor.

**PROGNOSTIC IMPACT OF miR-146 POLYMORPHISM IN PATIENTS WITH RESECTED COLORECTAL CANCER**

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Background: MicroRNAs (miRNAs) are small noncoding RNAs with regulatory functions as tumor suppressors and oncogenes. The rs2910164 is a C to G polymorphism located within the sequence of miR-164a precursor, which leads to a change from a C:U pair to a G:U mismatch in its stem region. Recent evidence suggested that the rs2910164 SNP in miR-164a was associated with development of familial breast and ovarian cancers, and prostatic cancer. The aim of this study was to investigate the association between this genetic variant and prognosis of colorectal cancer (CRC) operated curatively.

Methods: A total of 349 CRC patients who underwent curative surgery between March 2003 and August 2006 were consecutively enrolled. DNA was extracted from fresh frozen normal tissue and each polymorphism (PPP1R13L rs1005165 and rs967591; ERCC1 rs11615 and rs735482) was genotyped by polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP).

Results: No statistical significance between these four variants and survival in a multivariate analysis for all CRC patients. However, the CC genotype of the PPP1R13L rs1005165 was significantly associated with worse survival in 164 patients with rectal cancer (HR = 2.10 and P = 0.037 for RFS; HR = 2.27 and P = 0.039 for DSS, respectively) as a recessive model of the C allele in a multivariate analysis. Meanwhile, no statistical differences in clinicopathologic characteristics were observed according to the rs1005165 genotype in rectal cancer patients.

Conclusions: Our results suggest that PPP1R13L variant is possible prognostic marker in Korean patients with rectal cancer.

**EGFR-MEDIATED RE-ACTIVATION OF MAPK SIGNALING CONTRIBUTES TO INSENSITIVITY OF BRAF MUTANT COLORECTAL CANCERS TO RAF INHIBITION**

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BRAF mutations occur in 10–15% of colorectal cancers (CRCs) and confer adverse outcomes. Whereas RAF inhibitors such as vemurafenib (PLX4032) have shown effectiveness in melanoma patients with BRAF mutation, they are surprisingly ineffective in BRAF mutant CRCs, and the reason for this disparity remains unclear. Here, we identified a potential mechanism of de novo resistance in CRC tumors by utilizing biochemical and pathological analyses. Compared with BRAF mutant melanoma cells, BRAF mutant CRC cells were less sensitive to vemurafenib, and P-ERK suppression was not sustained in response to treatment. Although transient inhibition of phospho-ERK by vemurafenib was observed in CRC, rapid ERK re-activation occurred through EGFR-mediated activation of RAS and BRAF. BRAF mutant CRCs shown remarkably higher expression of phospho-EGFR compared with BRAF mutant melanomas, suggesting that CRCs are specifically poised for EGFR-mediated resistance. Combined RAF and EGFR inhibition blocked reactivation of MAPK signaling in BRAF mutant CRC cells and markedly improved efficacy in vitro and in vivo. These findings support to start a clinical trial of combined RAF and EGFR inhibition for the treatment of BRAF mutant CRC patients.

**PPPI1R13L VARIANT AS A PROGNOSTIC FACTOR IN PATIENTS WITH RECTAL CANCER**

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Background: Genetic variants related with apoptosis and DNA repair pathways may play a meaningful role in cancer progression as well as carcinogenesis. Among them, PPP1R13L and ERCC1 polymorphisms was found to synergistically affect these pathways. The aim of this study was to investigate the association between these genetic variants and prognosis of colorectal cancer (CRC) operated curatively.

Methods: A total of 349 CRC patients underwent curative surgery between March 2003 and August 2006 were consecutively enrolled. DNA was extracted from fresh frozen normal tissue and each polymorphism (PPP1R13L rs1005165 and rs967591; ERCC1 rs11615 and rs735482) was genotyped by polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP).

Results: No statistical significance between these four variants and survival in a multivariate analysis for all CRC patients. However, the CC genotype of the PPP1R13L rs1005165 was significantly associated with worse survival in 164 patients with rectal cancer (HR = 2.10 and P = 0.037 for RFS; HR = 2.27 and P = 0.039 for DSS, respectively) as a recessive model of the C allele in a multivariate analysis. Meanwhile, no statistical differences in clinicopathologic characteristics were observed according to the rs1005165 genotype in rectal cancer patients.

Conclusions: Our results suggest that PPP1R13L variant is possible prognostic marker in Korean patients with rectal cancer.

**ASSOCIATION BETWEEN CpG ISLAND METHYLATOR PHENOTYPE (CIMP) AND TREATMENT RESPONSE OF FOLFIri WITH GETUXIMAB IN PATIENTS WITH METASTATIC COLORECTAL CANCER (mCRC)**

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Background: CpG island methylator phenotype (CIMP) is a subset of colorectal cancers characterized by promoter CpG island hypermethylation in multiple genes.
CIMP-positive patients have a higher rate of KRAS mutation than CIMP-negative patients. While the KRAS mutation status has a predictive role in predicting response to anti-EGFR antibodies, the predictive role of CIMP has not been established. PI6 (CDKN2A) is one of the CIMP markers and p16 hypermethylation also has been reported as a marker of fluorouracil and irinotecan resistance.

Methods: We retrospectively collected tumors from 49 patients with metastatic colorectal cancer (mCRC) who were treated with 5-fluorouracil, leucovorin, irinotecan (FOLFIRI) and cetuximab. Pyrosequencing was used to examine the methylation of six CpG island loci (p16, p14, MINT1, MINT2, MINT31, hMLH1) in DNA extracted from formalin-fixed paraffin-embedded specimens. To analyze the relation between CIMP markers and clinical outcome, logistic regression and Cox regression were carried out. KRAS mutation was available in 36 patients and is currently analyzing in 15 patients.

Results: There was a trend toward higher frequency of KRAS mutation in CIMP + tumors (3/14, 21.4%) than CIMP tumors (2 of 35, 5.7%). The disease control rate (DCR, CR + PR + SD) was 64.3% (9/14 patients) in CIMP+ and 94.4% (32 of 35 patients) in CIMP− (Fisher’s exact, P = 0.03). Although a trend toward shorter progression-free survival (PFS) and overall survival (OS) was seen in CIMP +, this was not statistically significant. Among our six CIMP genes, p16 methylation was strongly associated with lower DCR (Fisher’s exact, P = 0.01). In multivariate analysis, KRAS mutation and p16 methylation were associated with shorter PFS and OS.

Conclusions: Promoter CpG island hypermethylation of p16 was predictive of clinical outcomes in mCRC patients treated with cetuximab and FOLFIRI.

FIRST-LINE CHEMOTHERAPY PLUS CETUXIMAB IN PATIENTS GROUPED ACCORDING TO PROGNOSTIC RISK FACTORS: ANALYSIS OF THE CRYSTAL AND OPUS STUDIES

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Background: Analysis of randomized trials has shown that mCRC patients can be divided into prognostic risk groups according to baseline clinical parameters including ECOG performance status, white blood cell count (WBC), alkaline phosphatase (ALP) and number of metastatic (met) sites (Köhne C, et al. Ann Oncol 2002; 13: 308–317). The effect of adding cetuximab to first-line chemotherapy (CT) on overall survival (OS) in these groups of KRAS wild-type mCRC patients was investigated in the CRYSTAL and OPUS studies.

Methods: Patient risk groups were: low-risk (LRG= ECOG 0/1, 1 met site), intermediate-risk (IRG= ECOG <1, >1 met site, ALP <300 U/L or, ECOG >1, low WBC, 1 met site) and high-risk (HRG= ECOG <1, >1 met site, ALP >300 U/L or ECOG >1, high WBC, or ECOG >1, low WBC and >2 met sites). Exploratory analyses comprised estimates of effects using Cox’s proportional hazards model for OS on individual patient data and comparison of treatment arms by log-rank test.

Results: In the pooled analyses, in both treatment arms, OS was longest in LRG patients (median 27.0 months, 95% CI 24.8-29.5 for the CT + cetuximab group [n = 173] and 25.7 months, 95% CI 21.9-8.7 for the CT group [n = 164]), and shortest in HRG patients (median 17.7 months, 95% CI 13.1-19.3 for the CT + cetuximab group [n = 46]; 12.6 months, 95% CI 9.2-14.4 for the CT group [n = 99]). In IRG patients median OS was 16.4 (95% CI 14.9-20.0) and 22.2 months (95% CI 19.5-25.7) in the CT (n = 213) and CT + cetuximab (n = 166) arms, respectively. Adding cetuximab to CT led to marked improvements in OS in the HRG (hazard ratio [HR] 0.675, 95% CI 0.506–1.157; P = 0.203) and IRG (HR 0.781, 95% CI 0.622–0.981, P = 0.033), while improvements in LRG patients (HR 0.869, 95% CI 0.672–1.124, P = 0.287) were observed only after prolonged follow-up. Data were similar in the separate CRYSTAL and OPUS studies.

Conclusions: The analysis confirms the concept of prognostic risk groups for OS based on baseline clinical parameters in patients with KRAS wild-type mCRC. Benefit from the addition of cetuximab to first-line CT in terms of OS appears to be more pronounced in the IRG and HRG.

CHEMOTHERAPY PLUS CETUXIMAB IN PATIENTS WITH COLORECTAL METASTASES GROUPED BY SITE: A POOLED ANALYSIS OF THE CRYSTAL AND OPUS STUDIES

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Background: In the CRYSTAL and OPUS studies, adding cetuximab to first-line chemotherapy (CT) improved clinical benefit in patients with KRAS wild-type (wt) metastatic colorectal cancer. In a pooled analysis of these trials, the benefit of treatment according to whether patients had liver-limited disease (LLD) or non-LLD was analyzed.

Methods: Cox’s proportional hazards model for overall survival (OS) and progression-free survival (PFS) or logistic regression model for best overall response and R0 resection were used on individual patient data, stratified by study. Likelihood ratio tests were used to explore interactions.

Results: Adding cetuximab to CT significantly improved PFS (median 11.9 versus 9.2 months, hazard ratio [HR] 0.53, P = 0.0095) and overall response rate (ORR, 72.0 versus 43.2%, odds ratio 3.51, P = 0.0001) in LLD patients, and OS (median 22.0 versus 17.3 months, HR 0.76, P = 0.0023), PFS (median 9.4 versus 7.4 months, HR 0.68, P = 0.0004) and ORR (52.8 versus 37.2%, odds ratio 1.88, P < 0.0001) in non-LLD patients. An increase in R0 resection rates for both patients with LLD (11.8 versus 5.3%, odds ratio 2.38, P = 0.0112) and non-LLD (3.3 versus 1.7%, odds ratio 1.97, P = 0.1870) was also observed. No treatment-by-study interactions were found. Treatment effects did not vary significantly by the LLD status (PFS: P = 0.68, OS: P = 0.68; ORR: P = 0.0737; R0 resection: P = 0.71). However, LLD versus non-LLD patients had improved outcomes in each treatment arm: PFS, CT HR 0.74, P = 0.0910; CT + cetuximab HR 0.66, P = 0.0309; OS, CT HR 0.70, P = 0.0091; CT + cetuximab HR 0.74, P = 0.0388; ORR, CT odds ratio 1.20, P = 0.47; CT + cetuximab odds ratio 2.32, P = 0.0015; R0 resection, CT odds ratio 3.15, P = 0.0496; CT + cetuximab odds ratio 3.82, P = 0.0018.

Conclusions: The OS benefit from adding cetuximab to CT is more pronounced in non-LLD patients, thus strengthening the value of cetuximab in palliative treatment. The LLD status is associated with improved prognosis and may be predictive for response in patients receiving CT + cetuximab, facilitating potentially curative resection. More patients (with R0 resection and longer follow-up) may be needed to confirm an OS benefit from CT + cetuximab in LLD patients.