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Relative risk according to the DNMT3B C → T promotor polymorphism in gastric cancer

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Background: As the recent research about methylation is gone, the methylation of CpGisland was reported to important pathway of tumorigenesis as another epigenetic modification. This methylation process is mediated by DNA-methyltransferase (DNMTs) and DNMT1, DNMT3B was confirmed as active subtypes. It was reported that the activity of DNMT3B increased in bladder, colorectal, renal and pancreas cancer. DNMT3B genc increases activity of promotor about 30% in cases of C → T promotor polymorphism in vitro. Exact pathway of promotor polymorphism is undefined, but Tvariant increases translation of DNMT3B and derives hypermethylation of tumor suppressor gene and cause functional inactivity in human. In this study we recognize about correlation between the rate of C → T promotor polymorphism of DNMT3B gene and susceptibility in gastric cancer.
Materials and methods: 176 patients who was diagnosed of gastric cancer was case group and control group was 70 patients woho was identitied H.pylori infection in gastrofiberoscopic examination. All patient group and control groups picked 10cc blood sample and extracted DNA and performed PCR, we extracted 380 bp target DNA and performed restriction reaction rsing Avrll enzyme (New England Biolab, Inc). In case there is T variant, we could confirm two bands that have 207 bp and 173 bp. We analysed data using SPSS statistically.
Results: In case there is T variant, it is 150 cases (85.2%) – CT (71.6%), TT (13.6%), CT+TT (85.2%) in cancer group and is significantly higher in the cancer group than the control group (42 cases (60.0%) – CT (42.9%), TT (17.1%), CT+TT (60.0%) ($p < 0.05$). In multivariant analysis, relative risk in CT (heterozygote type) was high 4.523 times than cc (wild type), and it was high 2.154 times in TT (homozygote type), and increased 3.846 time in case is CT+TT (T variant) ($p < 0.05$). However, If there was T variant, we can assume that the relative risk of gastric cancer increases 3.846 times. But, there was no significance correlation with stage, differentiation and Lauren's classification by T variant. The infection rate of H. pylori was 34.6%, the rate of gastric cancer is higher in H. pylori positive groups (87.1%) than negative groups (63.4%). In case of T variant, H. pylori infection rate was increased about 1.19 times, but there was no statistical significance.
Conclusions: In these results, we can conclude that T variant of CNMT3B promotor gene shows about 1.42 times higher than normal and the relative risk increase 3.846 times if there is the T variant of DNMT3B promotor gene in gastric cancer. However, there is no relation between T variant and pathologic status and H.pylori infection rate.

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Duplex RT-PCR improves accuracy in detecting lymph node micrometastasis in early gastric cancer

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Background: We previously reported that MUC2 is a useful marker in the detection of lymph node micrometastasis (LMM) in gastric cancer *(J surg oncol. 2004; 88: 63–70)*. However, MUC2 is rarely expressed in early poorly-differentiated adenocarcinoma. To improve accuracy in detection of LMM in gastric cancer, we paid attention to a novel gene, *TFF1*, which is preferentially expressed in diffuse-type gastric cancer cells. We have examined its potential as a novel marker for the detection of lymph node micrometastasis in gastric cancer, and investigated a novel method for LMM detection in gastric cancer.
Material and methods: We selected 33 histologically node negative (pN0) early gastric cancer patients who underwent curative surgery in our surgery department between July 2002 and June 2004. This study group consisted of 22 mucosal cancer and 11 submucosal cancer patients. Each lymph node was dissected into two pieces. One piece was formalin fixed and paraffin embedded for histological examination. The other was used for duplex (MUC2 and TFF1) reverse transcriptase-polymerase chain reaction (RT-PCR) assay.
Results: MUC2 and TFF1 were expressed in 22 of 33 (66.7%) and 30 of 33 (90.9%) of the gastric carcinoma specimens. MUC2 and TFF1 were expressed in 5 of 13 (38.5%) and 13 of 13 (100%) undifferentiated carcinoma specimens. The positive rate of TFF1 was significantly higher than that of MUC2 in the undifferentiated carcinoma specimens ($P = 0.002$). All carcinoma specimens were positive for MUC2 and/or TFF1. MUC2 was expressed in 15 of 310 lymph nodes (4.8%) from 6 patients (18.2%). TFF1 was expressed in 9 of 310 lymph nodes (2.9%) from 6 patients (18.2%). The detection rate of LMMs was raised until 6.8% (21 lymph nodes) and 33% (11 patients) by using duplex RT-PCR assay. We were able to detect LMMs in 7 of 22 patients (31.8%), especially in mucosal cancer. In the 7 cases, 3 cases were MUC2 positive/TFF1 negative and the other 4 cases were MUC2 negative/TFF1 positive. Duplex assay revealed no false positive results in the control specimens.
Conclusions: Duplex RT-PCR assay provides higher accuracy than either MUC2 or TFF1 alone to detect LMM in early gastric cancer.

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Gastric cancer susceptibility in the P53 codon 72 polymorphism

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Background: The P53 codon 72 polymorphism results in either arginine or proline, there are many studies to clear the relationship between P53 codon 72 genotypes and specific cancer risk and susceptibility. Recently, the P53 codon 72 polymorphism has been extensively studied to determine the risk factors responsible for carcinogenesis. The purpose of this study was to investigate the association of the genotype distribution of the P53 codon 72 polymorphism and gasric cancer susceptibility via in comparison of gastric cancer group and normal control genotypes. We also studied the relation between the distribution of P53 codon 72 genotypes and the state of P53 immunohistochemical staining, infectivity of Helicobacter pylori and the clinicopathologic findings in gastric cancer patients.
Materials and methods: In our study, the samples consisted of 145 gastric cancer patients and 77 normal controls. The analysis was performed by polymerase chain reaction (PCR), restriction fragment length polymorphism (RFLP) method using DNA extracted from gastric cancer patients blood and normal controls blood.
Results: The frequency of three genotypes arg/arg, arg/pro and pro/pro in gastric cancer patients was 41.1%, 38.6% and 20.0%. In controls, it was 36.3%, 53.2% and 10.3%. There was no statistical significance ($p = 0.312$, 0.665). There was no correlation between the frequency of the three genotypes and the state of P53 immunohistochemical staining infectivity of H. pylori. The pro/pro homozygote was more frequent in lymph node metastasis (25.6% vs 7.3%, $p = 0.026$).
Conclusions: The P53 codon 72 polymorphism does not contribute to gastric cancer susceptibility. The P53 codon 72 polymorphism is not associated with the state of P53 immunohistochemical staining and the infectivity of H. pylori but pro/pro genotype is associated with the lymph node metastasis in gastric cancer patients.

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Value of elevated Ki67 index (>10%) and p53 protein expression as prognostic factors in GIST

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Background: Gastrointestinal stromal tumors are the most common mesenchymal tumors and express CD117. But the prediction of the malignant potential of GISTs is still difficult. The aim of this study is to evaluate the prognostic accuracy of elevated Ki67 index and p53 overexpression in combination with classical prognostic factors(tumor size and mitotic index.
Material and Methods: A retrospective study was conducted of 84 patients who had re-evaluated to confirm diagnosis based on immunohistochemical analysis with CD117 expression, between Jan 1991 and Dec 2001. Cases were classified and very low, low, intermediate and high risk group according to 2001 NIH consensus symposium. Elevated Ki67 index was assign to the lesion that displayed 10% or more of immunoreactive cells. And p53 expression is assign to the area with 5% or more of eosinophilic nucleus.
Results: The elevated Ki67 was noted in 37 (44.0%) out of 84 cases. High risk patients showed elevated Ki67 index frequently ($P < 0.0001$) and there was significant difference between elevated Ki67 and survival rate ($P = 0.0417$). The p53 expression was noted in 32 (38.1%) out of 84 cases. p53 expression was significantly higher in high risk patients ($P = 0.0081$). But, there was no significant difference between p53 expression and survival rate. As a result of multivariable analysis, tumor size ($P = 0.0059$), mitotic rate ($P = 0.0016$) and elevated Ki67 index ($P = 0.0384$) were proved as significant independent prognostic factors.

Conclusions: Judging from the results of our retrospective study, p53 is related to disease progression but is uncertain as prognostic factor in GISTs. We think that tumor size, mitotic rate and elevated Ki67 index is the helpful prognostic factors in GISTs.

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Prediction of chemosensitivity to 5-FU in gastric cancer by gene polymorphism

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Background: Fluorouracil is widely used in the treatment of gastric cancer. Thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD) and methylenetetrahydrofolate reductase (MTHFR) relate with the action of 5-FU. The aim of this study was to evaluate the predictive value of gene polymorphism of these enzymes to the effect of 5-FU in patients with gastric cancer by HDRA (histoculture drug response assay).
Material and methods: From August 2004 to April 2005 we examined eighty-seven histologically proven gastric carcinoma tissue specimens with HDRA to 5-FU. Patients were categorized into a chemosensitive (>30% inhibition) or chemoresistant (30% inhibition >) group. All patients were received postoperative adjuvant immunochemotherapy with mitomycin, 5-FU and OK-432. Genomic DNA was extracted from blood and genotypes were determined.
Results: There were no significant relationships between chemosensitivity and gene polymorphisms (TYMS gene polymorphisms (double (2R) or tri-tandem (3R) repeats of a 28-bp sequence in the promoter region ($p = 0.34$) and a 6-bp variation in the 3'-untranslated region ($p = 0.15$)) and MTHFR C677T polymorphism ($p = 0.18$)). IVS14 + 1G>A mutation in the dihydropyrimidine dehydrogenase gene was not noted in all patients.
Conclusions: Our data did not provide evidence that gene polymorphism of these enzymes influence the effect of 5-FU in patients with gastric cancer. But the observation of these patients can provide additional information of relationships between clinical data and gene polymorphisms.

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A novel mode of antitumor activity for imatinib mesylate: consequences for the design of surrogate markers of efficacy and combination therapies

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We have recently reported that STI571 has not only a tumor cell autonomous effect but also acts on host dendritic cells (DC) to promote natural killer (NK) cell activation and NK cell-dependent antitumor effects in mice (Borg C. et al, J Clin Invest, 2004).
Moreover, about 50% of gastrointestinal sarcoma (GIST) bearing patients undergoing therapy with STI571 acquire NK cell activation correlating with clinical outcome. The study of the Time To Progression (TTP) for 43 patients that benefited from a median follow up of 13.2 months in both cohorts of GIST, those exhibited enhanced NK cell functions ($n = 22$) at 2 months of Gleevec versus those who did not ($n = 21$) revealed that TTP is significantly longer in patients with NK cell activation (Log Rank Test, $p = 0.03$).
The potential associated prognostic factors: type of c-kit mutation, extra-gastric primary tumor, haemoglobin level <7 g/dL, performance status over 2 and pulmonary metastases at entry, were all comparable in these two cohorts.
The lack of STI571-mediated NK cell induction found in the other 50% of cases could be assigned to the presence of high numbers of $CD4^+CD25^{high}$ regulatory T cells (Treg) in blood at entry, which were shown, by us, to inhibit NK cell effector functions in human ex-vivo and in-vitro. The mean percentages of Treg among $CD3^+CD4^+$ T cells in GIST patients displaying NK cell induction were not elevated compared with normal volunteers (mean 1.1 ± 0.3 GIST, mean 1.2 ± 0.4 in NV, $p = 0.5$) whereas these yields were increased by three fold in the group of patients with no NK cell induction (mean 3.2 ± 0.8E in GIST, $p = 0.02$). We finally found that the combination of immunopotentiating dosages of cyclophosphamide (aimed at reducing Treg function) with STI571 had synergistic anti-tumor effects in a mouse model of lung melanoma metastases. Altogether, NK cell activation is a novel surrogate marker of efficacy of STI571 which is critical for TTP and could be enhanced by pre-treatment of GIST patients with Treg inhibitors.

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Influence of hepatic dysfunction on safety, tolerability, and pharmacokinetics of PTK/ZK in patients with unresectable hepatocellular carcinoma

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Background: Vascular endothelial growth factors (VEGFs) and VEGF receptors (VEGFRs) are important mediators of tumor growth and metastasis, and their expression is associated with poor prognosis in patients (pts) with hepatocellular carcinoma (HCC). PTK/ZK is a novel, oral, angiogenesis and lymphangiogenesis inhibitor that blocks tyrosine kinase signaling from all known VEGFRs.
Methods: This was an open-label, multi-center, phase I study to characterize the safety, tolerability, and pharmacokinetic (PK) profile of PTK/ZK, administered once daily at a dose of 750 mg, 1,000 mg, or 1250 mg in adults with unresectable HCC. Pts previously treated with surgery, chemotherapy, or radiotherapy were eligible. Pts were stratified into 3 groups based on total bilirubin and AST/ALT levels. Pts in groups 1–3 had mild, moderate, and severe hepatic dysfunction, respectively. PK data were collected from all pts on days 1, 28, and 56. The primary endpoints were safety, tolerability of PTK/ZK, and the effects of hepatic dysfunction on the PK of PTK/ZK.
Results: 34 pts were enrolled, 21 in group 1; 8 in group 2; and 5 in group 3. In all groups, the most frequently reported adverse events (AEs) were nausea, vomiting, anorexia, fatigue, diarrhea, and dizziness. A correlation between these AEs and the study drug dose was not observed. In group 1, 2 of 4 pts who received the 1,250 mg/d dose experienced unacceptable AEs (Common Toxicity Criteria [CTC] grade 3 fatigue and CTC grade 4 elevation of AST). 2 of the 6 pts who received the 1,000 mg/d dose experienced unacceptable AEs (ALT over 1.5 x baseline and fatal hepatic tumor hemorrhage). No unacceptable AEs were observed at the 750 mg/d dose, defined as the maximum tolerated dose in pts who have mild hepatic impairment. PK analysis indicated that there was no accumulation of PTK/ZK. Patients' time on PTK/ZK treatment ranged from 5 to 415 days. The best response based on modified RECIST criteria was stable disease. There were no partial responses or complete responses.
Conclusion: PTK/ZK is generally well tolerated in most pts with mild and moderate degrees of HCC-related hepatic impairment at the dose of 750 mg/day.

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Prominent tumour-infiltrating lymphocites improved disease free survival in early stage gastric carcinoma

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Introduction: The degree of lymphocytes infiltration is a significant determinant of outcome for a variety of malignancies including non Hodgkin's lymphoma, oesophageal carcinoma, malignant melanoma, colorectal carcinoma and breast cancer. Pathologists have for a long time recognised that tumour prognosis is closely correlated with several morphological features including histological type, TILs, tumour associated eosinophils and mast cell. Gastric cancer could be associated with lymphocytic infiltrate, although the functional role and prognostic significance of this infiltrate is unknown.
Materials and methods: Patients: Between 1993 and 2004, 204 patients underwent a R0 gastric resection for T1-T2 N0. 55 of these patients (31 men and 24 women with a mean age of 62.82 ± 11.8) were analysed. Correlation between free disease survival and clinical (age, sex), and pathological features (tumour site and diameter, Laurén, Bormann and WHO classification, vascular and lymphatic invasion, pTNM) were analysed.
Histopathological examinations: All surgical specimens stained with haematoxylin and eosin (H&E). Microscopic examination included histological differentiation of tumour, assessment of invasion, identification of presence of cancer cells at the surgical margin and IEL, PLT and CRL (Figure 1) infiltrating lymphocytes.
Statistical analysis: Software SPSS 11.0 was used for statistical analysis (SPSS Inc., Chicago, IL, USA). Correlations of clinic pathological features and molecular alterations gastric and disease free survival cancers were analysed using the Cox regression. Overall disease free survival was