After initial studies, we used DLD-1 cells as the *in vitro* model system. First, we revealed that oxaliplatin and 5-FU act synergistically on DLD-1 cells by MTT assay and median effect analysis. Second, we treated the cells with a serial concentration of oxaliplatin, such as 2-10 μ M, and the treatment resulted in down-regulation of TS protein expression by Western blotting. Further, we treated the cells with a serial concentration of oxaliplatin, such as 2 to10 μ M, and the oxaliplatin pre-treatment resulted in down-regulation of TS mRNA level up to 40% (mean ± S.D. of ratio to reference control = 0.60 ± 0.21, range: 0.42 0.84) by real-time PCR assay using the Lightcycler (*Roche Molecular Biochemicals*).

In this study, our data provide important information explaining the reason why combination of oxaliplatin and 5-FU results in better objective response in 5-FU-resistant patients than oxaliplatin alone does. Our data also suggest that TS down-regulation happens at the transcriptional level. TS modulation and down-regulation had shed light on the useful potential strategy to achieve objective response in 5-FU-resistant colorectal cancer patients.

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Preoperative chemoradiation with oral Tegafur for locally advanced rectal cancer: intermediate results.

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Background: a phase II oriented study has evaluated tolerance and efficacy (downstaging, characteristics of residual tumor and patient outcome) of neoadjuvant chemoradiation using concurrent daily high-dose Tegafur for rectal cancer.

Material and methods: from 5/98 to 5/01 62 consecutive patients with cT_{3-4} and/or cN_+ rectal cancer were treated with 45-50.4 Gy (1.8 Gy/day; 25-28 fractions), and oral Tegafur 1200 mg/day (400 mg every 8 hours, including weekends). Surgery was performed 6 weeks after the completion of chemoradiation. All patients received a presacral boost with intraoperative electron radiation (10-12.5 Gy). Adjuvant chemotherapy was recommended (5FU-LV, 4-6 cycles).

Results: there were 43 males and 19 females, 25 patients (40%) were >70 years old. Severe co-morbidity was present in 43% of patients. In the neoadjuvant treatment segment 13 patients (21%) had grade 3 dermatitis, 16 (26%) grade 3 and 2 (3%) grade 4 diarrhea, and 1 patient had grade 3 anemia. The median dose of radiotherapy was 50.4 Gy. Surgery consisted on anterior resection in 38 patients (61%) and abdomino-perineal amputation in 24 (39%). Adjuvant chemotherapy was given to 67% of patients. Thirty-four patients (55%) had minimal microscopic residual tumor in the surgical specimen (*mic* category). The total T downstaging rate was 58% (N downstaging 31%). With a median follow-up of +29 months, the pelvic control rate was 97%, disease free survival 79% and overall survival 86%.

Conclusions: neoadjuvant chemoradiation with oral Tegafur is feasible, acceptably tolerated and active, with the advantages of oral fluoropirimidin potentiation during protracted preoperative radiation therapy programs.

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The potential role of erbb-2 and cyclooxygenase-2 expression in human colon carcinoma and risk conditions

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Background: ERBB2/Neu receptor tyrosine kinase and cyclooxygenase-2 (COX-2) represent promising molecular targets for cancer therapy and/or prevention. This study investigates the relation between ERBB2 and MET expression and COX-2 presence in human colon carcinomas.

Design: Immunohistochemistry was performed on paraffin sections from 124 primary human colon carcinomas (CC), 10 cases of ulcerative colitis and 20 villous colonic adenomas (risk conditions for human CC). Membranous stain for ERBB2/MET and cytoplasmic stain for COX-2 were evaluated in neoplastic tissue, non-neoplastic dysplastic tissue (NNDT) surrounding the tumor, and normal mucosa (NM).

Results: The table shows the results. ERBB2, COX-2 and MET expression was higher in well differentiated tumors ($p \leq 0.001$). Strong MET expression was also present in the NNDT. Increased ERBB-2, COX-2 and MET expression was recorded in 7/10 cases of ulcerative colitis and 18/20 adenomas. Linear regression revealed a strong positive correlation between membranous CERBB2 and cytoplasmic COX-2 staining ($r=0.83$, $p \leq 0.0001$) in neoplastic and NNDT epithelial populations. Thus, ERBB2 may play a key role in regulating COX-2 expression in neoplastic and putative precancerous colon epithelial cells.

Table: ERBB2, COX-2 and MET expression

Condition	# cases	ERBB2*	COX-2*	MET*
NM	6	6.9±1.2	2.6±1.2	60.6±7.3
NNDT	62	12.7 ± 2.4^{a}	8.9 ± 1.5^{a}	96.3±11.9
WDCC	40	$97.3\pm18.2^{a,b,c}$	$98.3\pm17.3^{a,b,c}$	$95.1\pm12.8^{a,c}$
MDCC	64	$23.7\pm4.6^{b,d}$	$41.3\pm7.3^{b,d}$	$42.1\pm3.8^{a,b}$
PDCC	20	$8.6\pm2.6^{d,c}$	$9.1\pm3.2^{d,c}$	$19.8\pm3.9^{b,c}$

*M±SM, WD: well differentiated, MD: moderately differentiated, PD: poorly differentiated, $^{a,b,c}p \leq 0.001$, $^{d}p \leq 0.05$

Conclusions: This study shows that overexpression of ERBB2 and COX-2 may represent an early dysfunctional event of human colon carcinogenesis. These markers may be important targets relevant to chemoprevention or adjunct therapy of well-differentiated colon carcinoma. However more direct studies are needed to clearly establish these observations.

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Radiotherapy for rectal cancer causes acute and prolonged impairment of cobalamin status.

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Background: Radiotherapy for rectal cancer may induce acute or late injury to the intestine. The terminal ileum may be prone to damage since it may be included in the radiation volume, and its position is relatively fixed. The terminal ileum is the only site for receptor mediated absorption of vitamin B12. The aim of the study was to investigate whether (neo-)adjuvant radiotherapy for rectal cancer may have negative impact on cobalamin status.

Method: Consecutive patients with rectal cancer receiving pelvic radiotherapy with curative intent (50 Gy in daily fractions of 2 Gy, during 5 weeks) were evaluated prospectively. Serum cobalamin, serum methylmalonic acid (MMA) and serum total homocysteine (tHcy) were measured in 54 patients at start and end of radiotherapy, at follow-up 4-6 weeks after completed radiotherapy, and in 23 patients 1 year after radiotherapy.

Results: Mean serum cobalamin decreased from 306 pmol/L pretreatment to 267 pmol/L ($p<0.0005$) at the end of radiotherapy, and further to 247 pmol/L ($p<0.0005$) at follow-up after 4-6 weeks. Mean serum MMA was 0.16 μmol/L at start of treatment, 0.17 at the end of radiotherapy (n.s.), and had increased to 0.19 ($p=0.007$) 4-6 weeks after radiotherapy. There was also a significant reduction in serum and erythrocyte folate 4-6 weeks after radiotherapy, as compared to baseline. However, there was no change in serum tHcy levels. One year after radiotherapy, mean cobalamin was 249 (lower than baseline, $p=0.023$), and mean MMA was 0.21 (higher than baseline, $p<0.0005$).

Conclusion: Our data show biochemical evidence of early impairment of cobalamin status during and in the weeks after radiotherapy for rectal cancer, as reflected by a reduction of serum cobalamin combined with an increase of serum MMA. At follow-up 1 year after radiotherapy, there was evidence of persistently impaired cobalamin status. This observation may motivate routine monitoring of cobalamin status during follow-up of patients after radiotherapy.