colorectal cancer treated with CPT-11 were included in our retrospective study. The expression of hMLH1, hMSH2, and Bax was analyzed all tumors by immunohistochemistry. The MSI phenotype could be determined in 44 tumors through the analysis of the mononucleotide tracts located in the coding regions of RII-TGFb, BAX, hMSH3 and hMSH6 genes, and that of BAT26. A partial or minor response to chemotherapy with CPT-11 was observed in 11 patients, disease stabilization in 19 patients and progression in 20 patients. Staining of hMLH1 was undetectable in 3 of the 50 tumors, whereas only 1 tumor lacked hMSH2 expression. We found no association between a defect in hMLH1 staining and the response to CPT-11. Among the five tumors that displayed a MSI+ phenotype, four had frameshift mutations within TGFb-RII, BAX or hMSH3 genes. Among these, 3 tumors displayed mutations in BAX and showed a markedly reduced staining with the anti-Bax antibody. A decrease in Bax expression was associated with a better response to CPT-11 ($p<0.001$). We also found a significant correlation between the MSI+ phenotype and the umor responsiveness to CPT-11 ($p<0.001$). Our preliminary results indicate that MSI screening could help to select patients who would benefit from chemotherapy with CPT-11.

1107 POSTER

## Randomized study of postoperative chemotherapy (CT) after preoperative chemoradiation (CTRT) in locally advanced rectal cancer (LARC). Preliminary results

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**Purpose:** to assess the value of concomitant CTRT as preoperative treatment and of postoperative CT in LARC. Study design: multicentric randomized 9/93-2/01. Random arms: preop. CTRT all cases; Arm A: surgery + observation; Arm B: surgery + postop CT. Endpoints: preop. CTRT: compliance, toxicity and tumor downstaging; postop. CT: freedom from loc. and dist. recurrences, survival.

**Matherials and methods:** 635 pts. (Arm A 309, Arm B 326). Inclusion criteria: tumor invading the perirectal fat at DRE (fixed or tethered) or at intrarectal US; age below 76; tumor origin lower 2/3; adenocarcinoma. Pts characteristics: males 419, females 216; median age 62 yrs; fixed 109, tethered 425, perirectal fat at US only 95. Preop. CTRT: 45 Gy (180 cGy x 5 weekly); 5-FU 350 mg/mq and Folinic Acid 10 mg/mq days 1 to 5 and 29 to 33, of the RT course. Postop. CT (Arm B): 5-FU 350 mg/mq and Folinic Acid 100 mg/mq days 1 to 5, six cycles, 3 weeks apart.

Results (to be considered preliminary as the data collection is still ongoing): Compliance to preop. CTRT: full treatment 584 (92%); RT only 3; 1 CT course 44; no CT and RT 7. Surgery: inoperable 15; refusal 4; died before surgery for intercurrent death 7; for disease 2; for toxicity 3; missing data 42; undergoing surgery 562 (88.5%%). Type of surgery: APR 188 (33.5%), LAR 340, TEM 24, palliative 10. Perioperative morbidity: anastomotic deiescence 44, perineal abscess 12, intestinal occlusion requiring surgery 12. Clinical downsizing (surgical evaluation): Tumor size reduction > 50% 353 (64.2%). Downstaging (pathological examination): T0 96 (17.4%), T1-T2 201(36.5%), T3 253; N+ 122(22.2%); positive margins 16(2.9%). Compliance to postop. CT: randomised Arm B 326; receiving 6 cycles 149, < 6 cycles 37, refusal 54, missing data 66. Follow-up: data available 536; median length 24.8 months; local recurrence only 28 (5.2%); local and distant 19 (3.5%); distant only 114 (21.3%). OS 5 yrs 67.3%. Prognostic factors: initial T extent $p<0.02$; APR $p< 0.05$; downstaging $p<0.05$; pN+ $p<0.05$. Treatment arms: distribution of prognostic factors well balanced; no difference neither in recurrence rate (n° of events: Arm A 71, Arm B 71) nor in survival (Arm A 63.5%, Arm B 67.5%).

**Conclusion:** concomitant CTRT was proved feasible as preop. treatment in LARC and resulted in a high downsizing/downstaging and in a low local recurrence rate. Postop. CT had a low compliance and did not result at the moment in any advantage on relapse rate or OS.

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## Evaluation of the clinical impact of serum tumor markers in colorectal cancer. A prospective longitudinal study

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**Purpose:** A controlled prospective study was designed to establish the efficacy of CEA, CA 19-9, and CA 72-4 serum markers as "decision making" clinical parameters when used in combination with the accepted diagnostic procedures in colorectal cancer, and to determine whether or not early treatment will have an impact on patient survival.

**Methods:** 315 consecutive patients with pathologically confirmed adenocarcinoma of the colorectal tract were assigned to a Study (n=220) or Control Arm (n=95), and followed for at least 3 years after surgery, or until the time of diagnosis of recurrence. Blood was taken for tumor marker estimation at each follow-up. An increase in serum marker levels was considered significant either when negative serum levels became positive or when an increase of greater than 50% of the mean of two previous positive levels was detected.

**Results:** The three serum markers paralleled the status of the disease in approximately 70% of the cases. No false positive were observed. The time interval between tumor marker increase and clinical diagnosis of recurrence was significantly shortened in Study compared to Control Arm, allowing an earlier diagnosis and treatment of recurrence ($p<0.0001$). For all markers the majority of the patients in the control arm had times to restaging greater than 150 days. As a result, radical surgery for recurrence increased from 28.1% (Control Arm) to 40.3% (Study Arm). Moreover, when the two arms were compared, an increased survival time for patients undergoing radical surgery for recurrent disease (Log Rank= 11.3, $p< 0.001$) was observed in the Study Arm. Patients in the Study Arm who received chemotherapy had a median survival time longer than patients in the Control Arm (Log Rank= 8.53, $p= 0.0035$). A significant improvement of the overall survival rate of colorectal cancer patients was observed in the Study Arm (log Rank= 16.7, $p< 0.0001$).

**Conclusions:** We can conclude that serum tumor markers can be used in combination to "guide" the timing for diagnostic imaging procedures during post-surgical follow-up of colorectal cancer patients. The adjunct of serum tumor markers in the post-surgical follow-up of colorectal cancer patients will allow an early diagnosis of recurrent disease, which may still be treatable by radical surgery, thus significantly increasing the overall survival.

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## Thymidylate synthase and dihydropyrimidine dehydroge-nase expression in stage II and III colorectal cancer patients receiving adjuvant 5-fluorouracil

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**Purpose:** To investigate the importance of thymidylate synthase (TS) and dihydropyrimidine dehydrogenase (DPD) expression for the disease specific survival of patients with colorectal cancer (CRC) receiving adjuvant 5-FU chemotherapy.

**Methods:** In paraffin-embedded primary tumor sections of 309 patients which participated in our adjuvant studies of colon (FOGT-1) or rectum (FOGT-2) cancer TS and DPD gene expression analysis could be successfully performed. mRNA quantitation was performed using a reverse transcription polymerase chain reaction technique with b-actin as internal standard.

**Results:** The median TS level was 0.75 (range: 0.21 - 7.21) and the median DPD levels was 0.28 (range: 0.01 - 1.62). The effect of TS and DPD on survival was analyzed in 295 patients. Univariate analysis revealed that only nodal stage, UICC stage, and TS were associated with disease specific survival, while DPD showed a slight tendency. Thus, patients with lower nodal stage, lower tumor stage, or higher TS (> 0.6) survived longer and patients with lower DPD levels (£ 0.4) tended to survive longer. Multiple Cox regression analysis showed that besides tumor stage only the combination of TS and DPD expression turned out to be a prognostic factor for disease specific survival.

**Conclusions:** Among patients receiving 5-FU therapy these with high TS and low DPD levels have longer survival than those with low TS and high