1103 POSTER

Impact of multimodality approach to patients with colorectal cancer. The experience of a hospital registry of tumors

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Introduction: Colorectal cancer (CRC) is the third tumor in relevance in our area. The high incidence of this tumor makes mandatory an accurate analysis of the impact of multidmodality treatment in the survival of affected patients (pts).

Objective: To determine the relative survival of pts afected by CRC diagnosed and/or treated in our sanitary area analysed by age, sex and tumoral stage since 1993, date of implementation of a systematic, multimodality treatment of CRC.

Patients and methods: From 1993 to 1997, 1528 pts affected of CRC were registred in our Hospital Registry of Tumors (HRT). We crossed our data with data from Regional Registry of mortality in order to know the vital state and reason of death. The observed survival rate was determined by Kaplan-Meier method, the expected survival rate by Cox model using the Regional population death tables. Relative survival rate was calculated as the quocient between observed and expected survival rate. We compared our results with other results reported from USA, Surveillance Epidemiology and End Results Registry (SEER) and Europe, EUROCARE.

Results: Relative survival in women with CRC was 0.59 (0.54-0.66) and in men 0.57 (0.52-0.62). In Europe, five years survival was: women 0.41-0.56 and men 0.40-0.56. Survival analysis by stage in our HRT was for women Stage (E) I 0.96 (0.83-1), EII 0.82 (0.71-0.81), EIII 0.60 (0.51-0.71), EIV 0.09 (0.06.0.23), unknown E 0.34 (0.20-0.57). And for men EI 0.86 (0.73-1), EII 0.74 (0.65-0.85), EIII 0.5 (0.40-0.62), EIV 0.17 (0.10-0.19), unknown E 0.36 (0.25-0.53).The existence of a "hospital byass" can be observed when focusing differences in distribution by stages between HRT and SEER (HRT: I 11.4%, II 28.9%, III 33.2%, IV 15.6%, Unknown 10.8%; SEER: I 17.1%, II 28.1%, III 21.1%, IV 17.1%, unknown 16.6%). Five years relative survival in HRT/SEER were: I 0.90/0.90, II-III 0.66/0.65, IV 0.14/0.08, unknown 0.35/0.34.

Comclusions: These results show that survival in CRC in our HRT is better than the one observed in Europe and similar to SEER. Although we cannot apply these results to a general population we can conclude that a multimodality approach to these pts with a good oncologic surgery with high index of salvage resections and a correct coordination with chemo-radiotherapy treatments leads to an improvement in survival. Using hospital survival analysis we will be able to evaluate further therapeutic approaches in oncology.

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Preoperative (chemo)radiotherapy for rectal cancer: Influence of treatment schedule on locoregional control

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Purpose: To assess the influence of two different preoperative schedules on down staging and local control.

Material & Methods: 118 patients with adenocarcinoma of the rectum were referred for preoperative radiation between 1995 and 2000. Local tumour extension was assessed by clinical examination, echoendoscopy and CT scan of the pelvis. There were 7 Stage I tumours, 39 stage II and 72 stage III. In 72 patients the tumour was located ≤6 cm from the anal margin. Two different preoperative schedules were used: 54 patients were treated with 10 times 3 Gy followed by surgery 38 days (14–58 days) later, the other group of 64 patients were treated with 25 times 1.8 Gy combined with 5-FU, LV during the first and last 5 days of irradiation. The interval between the last day of irradiation and surgery was 41 days (14–111 days) in these patients. In 55% of the cases postoperative adjuvant chemotherapy was given.

Results: Local control at 1, 2 and 3 years was 100%, 96%, 90% respectively, disease free survival was 97% at 1 year, 87% at 2 years and 77% at 3 years. There was no statistically significant difference in T-stage ($X^2 = 4.98$, $p > 0.05$) or distance of the tumour from the anal margin ($X^2 = 0.77$, $p > 0.05$) between the two patient groups; the number of patients with clinically positive nodes was higher in the group treated with preoperative combined modality treatment ($X^2 = 9.44$, $p \leq 0.025$). The anal sphincter was preserved in 82 patients (69%); in 60 patients a TME with construction of a colo-anal J-pouch was performed. Sixty three percent of these patients had a temporary protective ileostoma. Down staging, defined as a reduction in the pathological stage compared to the clinical stage, was obtained in 60 patients (51%), 26 of these patients were treated with the short schedule. In 15 patients (13%) there was no residual tumour left in the resection specimen. Only 4 of these patients were treated with 30 Gy in 10 fractions. Seven patients developed a local recurrence, 3 of these were irradiated to a total dose of 30 Gy. Distant me-tastasis were detected in 18 patients, 10 of them were treated with the short schedule.

Conclusion: There was no significant difference in down staging or local control between the short and the long irradiation schedule. The anal sphincter could be preserved in 73% of the patients. The upfront use of chemotherapy had no statistical significant influence on sphincter preservation or down staging, although more complete regressions were obtained in the patients treated with the combined modality.

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BAX protein expression (BAX-E) correlates with local invasiveness in primary colon cancer (CC)

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Purpose: The existing multimodal treatment options for CC require better prognostic markers to adapt treatment strategies to the individual patients' tumour biology. An imbalance between apoptosis and proliferation is believed to influence the course of malignancies. Recent work has shown that pro-apoptotic Bax-E. in liver metastasis is of prognostic significance in stage IV CC. We sought to test the prognostic role of Bax-E. in primary CC.

Methods: Archival tumour specimens of 371 pats. with Dukes A, B or C CC were retrieved. All pats. underwent R0-surgery in one singular institution and did not receive adjuvant chemotherapy. Follow up was performed in accordance to a standardized protocol (median follow-up 31.6 months). Bax-E. was determined by semi-quantitative immunohistochemical assessment (AB N20, Santa Cruz, USA).

Results: Bax-E. was detected in 353 of the samples (95.1%). Overall staining of 100% of the tumor cells was detected in 141 samples (38.0%). 18 (4,9%) showed no staining at all. The mean percentage of Bax expressing cells was 91.5%. Evaluation of the percentage of positive cells, the staining intensity and the Bax index involving both intensity and percentage of Bax positive cells failed to show a significant influence on overall survival (OS), Nor did disease free survival (DFS) correlate to Bax staining properties. OS was rather influenced by the UICC stage,disease relapse and age. Interestingly Bax staining intensity and the Bax index correlated to the invasion stages of the tumor (p=0.015 and 0.013 respectively) and the grade of differentiation (G category p=0.001).

Conclusion: Neither the percentage of bax positive tumour cells nor the intensity of bax expression proved to have a prognostic significance in regard to OS or DFS. However, a decrease of Bax-E. showed a significant correlation with higher depth of tumour invasion (T category) and the differentiation grade. It is concluded, that bax contributes to the local aggressiveness and invasion but that overall prognosis in CC, which most often is determined by the development of distant metastasis, is most certainly influenced by other factors.

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Role of the DNA mismatch repair system in the responsiveness of metastatic colorectal cancers to chemotherapy with CPT-11 (Irinotecan)

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The aim of our study was to assess the potential relationship between the microsatellite instability (MSI), a feature of tumors with DNA mismatch repair defect, and the response to CPT-11 treatment. Fifty patients with metastatic

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.

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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