1118 POSTER

Neoadjuvant radiotherapy for locally advanced rectal carcinoma: results of two treatment schedules

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Objective: To evaluate the outcome of pre-op accelerated-hyperfractionated RT and RT plus simultaneous chemotherapy (CTX) for advanced rectal cancer.

Patients and methods: From 5/95 to 12/99 a total of 55 pts (median age 64y) were treated pre-op. Group 1 (n=35): RT alone (TD 25Gy, SD 2,5Gy bid) for pts with primarily resectable cT2-4cN0-2M0 adenoca. Group 2 (n=20): RT (minimal TD 45Gy/SD 1,8Gy/25Fx/5 weeks) plus 2 cycles of simultaneous 5-FU (1g/m2 PVI d1-5 and d29-33) for pts with primarily unresectable cT3-4cN0-2M0. In node positive patients post-op 5-FU/Leucovin was administered. Median follow-up was 23 months.

Results: All pts of group 1 underwent surgery (R0: 89%) with sphincter sparing procedure (SSP) in 22/35 pts; resection rate in group 2 was 80% (R0: 88%, SSP 8/16 pts). LRFS, DFS, CSS and OS at 36 months were 93%, 87%, 91%, 87% (group 1) and 83%, 55%, 62% and 54% (group 2) respectively. Negative prognostic factors for outcome were positive margins (p=0,009), T4 vs T2/3 (p=0,045), low tumour site (p<0,1) and N2 (p<0,1). 4 pts with histologically proven complete remission (pCR) following combined treatment were NED after a median follow-up of 38 months.

Conclusions: The goal of complete resection can be achieved in the majority after pre-op RT or RT+CTX with promising results regarding local control and survival. Pts with pCR following RCT carry a favourable prognosis.

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Preoperative chemoradiotherapy improves downstaging and survival in advanced rectal cancer

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Objective: Locally advanced tumors of the rectum show a high incidence of local recurrence and can often not be operated by sphincter sparing procedures. The impact of preoperative chemoradiation on resectability, local control and survival rates is analysed.

Methods and materials: In the years 1994 to 2000 51 patients (35 men, 16 women) with a median age of 62 years (range 24-83) were treated with preoperative chemoradiation. The tumorstages were uT3 (N=36), uT4 (N=15), cN1 (N=18) and cN2 (N=1). Distribution according to histological grade was G1 5, G2 32, G3 5 and Gx 9 cases. 61% (31/51) of the patients had a tumor located closer than 6cm to the anus and were considered critical for sphincter sparing surgery. Almost all patients (47/51) received a simultaneous chemotherapy with 5-FU which was administered in 8 different oncology centers. A continuous 5-FU infusion with a dose of 200 or 225 mg/m²/day over 5 weeks was applied in 82% of cases. Radiation was administered with a 3 field technique encompassing the whole pelvis with the patient lying prone on a belly board. All patients received a total dose of 45Gy in 1,8Gy daily fractions. Surgery was carried out 13-74 days (median 31 days) after the end of chemoradiation.

Results: All patients finished chemoradiation as planned in a median time of 35 days (range 31-39 days). All patients except for 2 (1 refused, 1 lost to follow-up) were operated. In 30 cases a sphincter sparing resection was possible, among those were 12 patients with a tumor closer than 6cm to the anus. 19 patients anderwent abdominoperineal resection. The resection was R1 in 3 and showed close margins in 4 cases. Pathological downstaging was achieved in 59%for T stage and in 24% for N+ stage. Downstaging of the primary to pT0 was found in 20% of cases. Upstaging occurred in 7 cN0 cases to pN1 and in 2 patients to pM1 (liver). Estimated 5 year overall-survival (according to Kaplan-Meier) was 90% and disease-free survival 70%. In 9 patients local and/or distant recurrence was documented.

Conclusion: Simultaneous radiation and 5-FU is well tolerated and allows for significant downstaging in rectal cancer resulting in excellent survival rates. It furthermore enables sphincter sparing surgery in distal tumors. Close or positive margins are found to be a negative prognostic factor.

1120 POSTER

Tumor suppressor gene nm23-H1 in sporadic colon adenocarcinoma

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The discovery of genetic alterations in oncogenes and tumor-suppressor genes, which accompany tumor formation in a wide variety of human tumor types, has encouraged the search for genes that may promote or suppress tumor spread and metastasis. Nm23 gene was originally identified by differential hybridisation of K-1735 melanoma cell line clones of varying metastatic potential. A tumor metastases-suppressor function was implicated by the reduced expression of nm23 in highly metastatic sublines compared with non-metastatic sublines derived from the same K-1735 clone.

Nm23 expression has been shown to be higher in several different tumors of lower metastatic potential than in the corresponding tumors of higher metastatic potential, including breast, hepatocellular, ovarian and gastric carcinomas and melanoma. In other tumors, such as neuroblastoma, pancreatic carcinoma and head and neck carcinomas, surprisingly, the opposite trend has been reported.

The purpose of this study was to evaluate whether the expression of the nm23-H1 protein or loss of heterozygosity (LOH) of the nm23-H1 gene is associated with tumor stage and grade of tumor differentiation. In addition, we also investigated the correlation of nm23-H1 expression with 5-year survival.

Paraffin tissue sections were analyzed immunohistochemically using monoclonal antibody NM301 to human nm23-H1 protein. DNAs (normal and tumor) isolated from microdissections of parafin sections were used for LOH analysis.

Of 102 adenocarcinomas that were examined, 41% showed a weak positive immunostaining for nm23-H1 protein.The most nm23-H1 positive tumors were in Dukes' B (67%) and in the well differentiated tumors (65%). Statistical analysis showed that there was no statistically significant difference in survival between the patients with nm23-H1 positive tumors and patients with tumors that were not stained for nm23-H1 protein.

To analyze LOH at the nm23-H1 gene we used VNTR marker located in untranslated 5' region of the nm23-H1 gene. At this nm23-H1 locus 60% of samples were informative and 33% of them demonstrated LOH. The nm23-H1 LOH was more frequent in tumors that were larger than 5 cm than in smaller ones. Positive correlation was found between the nm23-H1 LOH and histological grade of tumors. Positive correlation was also found between the nm23-H1 LOH and Dukes' stage of tumor samples.

1121 POSTER

Expression of tumour associated antigens in colorectal cancer

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Purpose: The relationship of tumour-associated antigens with colorectal carcinoma was studied by immunohistochemistry with a panel of monoclonal antibodies (MAbs).

Materials and Method: Tumour tissue samples were obtained from 24 patients with colorectal cancer (Duke's stages B, C and D) and five patients with benign colorectal conditions. Immunohistochemistry was performed following standard procedures; the tumour associated antigens included: carcinoembryonic antigen (CEA, C365 MAb), colonic glycolipid (C505 MAb), normal colorectal antigen (NCA, C198 MAb), Lewis x (KM380 MAb), sialyl Lewis x (KM93 MAb), Lewis y (C14 MAb), Tn hapten (83D4 MAb) and MUC1 (C595 MAb). Immune reaction was graded according to positive staining, intensity and distribution; staining intensity was scored in grades: negative, low, moderate and strong.

Results: In colorectal cancer tissue sections, a high expression of tumour antigens was found being colonic glycolipid the most frequently observed (79% positive sections/total); NCA reacted in 76%; CEA in 75%. MUC1 was positive in 67% while sialyl Lewis x was detected in 53%; Lewis x and Lewis y in 44% and Tn in 30%. Some samples showed a remarkable positive expression of glycolipid antigen, NCA, CEA and Lewis x; Lewis y showed a moderate staining; an interesting feature was the expression of MUC1 in invasive areas of several specimens. The other antigens showed a weak and restricted reaction. Tissue samples from benign colorectal conditions reacted weakly although occasionally a strong immune staining was observed; the pattern of reaction was always restricted to some areas of the section.