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Preoperative chemoradiation for T3-T4 rectal cancer acute toxicity and tumor response our experience

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Purpose: To define acute toxicity and down-staging of rectal cancer patients who received chemo-radiation followed by curative surgery

Methods: From May 1993 to December 1998, 66 pts (median age 61 years, M/F 41/25) underwent preoperative chemo-radiation. Selection criteria were: biopsy proven adenocarcinoma; age < 75 years; ECOG performance status 0–2 and clinical preoperative stage T3–4 and/or lymphnode positive. In 52 pts, Radiotherapy (RT) was delivered to a total dose of 45 Gy in 25 fractions; FU (350 mg/m^2/day) and LV (10 mg/m^2/day) were administered on day 1 to 5 and 29 to 33 during RT. 14 pts received a total dose of 50.4 Gy in 28 fractions as well as continuous infusions (300 mg/m^2/day) of FU and a weekly bolus of Carboplatin (70 mg/m^2).

Results: All pts completed RT. Chemotherapy was withdrawn in 8 pts due to toxicity. Surgery was performed in all pts (56 low anterior resection, 10 abdominoperineal resection). Acute toxicity was scored according to the RTOG morbidity scale. 34 pts developed gastrointestinal toxicity: 22 Grade 1–2, 13 Grade 3, 22 pts had hematological toxicity: 12 Grade 1–2; 8 Grade 3; 2 Grade 4. Down-staging was obtained in 42 pts. (63.6%); complete pathological response was found in 10 pts (15.1%). The pathological TNM stage was: stage 0 9 cases, I:27, II:18, III:10 and IV:2. After a median follow-up of 29 months, no local recurrences were observed.

Conclusions: Our data confirm hat acute toxicity of combined chemo-radiotherapy is acceptable; down-staging is obtainable in a good number of pts. In 84.4% of our pts, sphincter preservation was maintained.

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Phase I/II study of oxaliplatin (L-OHP) plus 5-Fluorouracil concurrent with external beam radiotherapy (EBRT) in rectosigmoid carcinoma

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Purpose: To evaluate the tolerance and pathological response of a combined program using L-OHP plus EBRT in rectosigmoid carcinoma.

Material and Methods: From 6/97 to 2/99 a total of 32 patients (p) were enrolled on the trial: 26 p primary tumors (T2: 1 p, T3:19 p and T4:6 p), 3 p had liver metastases and 3 p with local recurrences. Two cycles of L-OHP 100 mg/m^2 plus 5-Fu 1 g/m^2 (max. dose: 1.5 g) was administered for 3–4 days during the first and last week of EBRT (45–54 Gy). Preoperative chemoradiation was given to 28 p (25 assessable for response).

Results: Complete pathological response was found in 20% (5/25) and postradiation stages were: T1–2 (24%), T3–4 (24%) and N+ (32%). Surgery performed included a low anterior resection in 18 p (72%) and 61% for those located at <6 cm. In 16 p (64%) the pathological report described important changes (wall confined or scattered residual tumor foci) after combined modality. Toxicity was considered mild in 16 p, moderate in 7 p and severe in 9 p (28%). Adverse side effects observed (grade III–IV) were: acute enteritis in 10 p, cutaneous 4 p, hemathologic in 3 p and urinary in 1 p.

Conclusions: This combined approach induces important downstaging (64%) leading to considerable number of sphincter preserving surgeries. L-OHP plus Fluororuracil seems to be an important rediosensitizer of normal tissues with important short-term toxicity. A dose modification of L-OHP to 80 mg/m^2 in this concurrent program is recommended.

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Expression of the erbB family in colorectal adenocarcinoma

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Purpose: The most frequently implicated receptors in human cancers are members of the EGF receptor (erbB) subfamily. In addition to EGFR, it includes erbB-2, erbB-3, and the recently discovered erbB-4. Transforming activity of different erbB genes by overexpression have been observed in a variety of tumors. Gene amplification and/or an icrease in transcription are the most common cause of erbB protein overexpression in tumors. The present study investigates expression of the different erbB proteins in colon cancers and its correlation with patient's survival.

Methods: The expression of erbB proteins was examined by immunohistochemistry using specific antibody and immunoperoxidase reaction. The results were analyzed semiquantitatively and correlated with patient's survival.

Results: In the present study we found expresion of the EGFR and erbB-2 protein in all tumor specimens investigated. The erbB-3 protein was expressed in 78% colorectal adenocarcinomas. EGFR was overexpressed in 51% of colorectal adenocarcinomas, but there was no correlation between EGFR overexpresion and patient's survival. The level of erbB-2 protein varies between tumors and elevated expression correlates strongly with survival ($p < 0.001$). The patients with tumors that were immunohistochemicaly positive to erbB-3 protein had significantly shorter survival ($p < 0.01$). In a multivariante analysis of clinico-pathological factors and erbB proteins expression, age, Dukes' stage, erbB-2 and erbB-3 protein were found to be independent prognostic markers.

Conclusion: This findings indicate that assessement of erbB-2 and erbB-3 overexpression can be useful indicator in prognosis of colorectal adenocarcinoma.

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Radioimmunoguided surgery for recurrent colorectal cancer manifested by isolated CEA elevation

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Purpose: Surgeons are hesitant to operate only on the basis of increasing CEA. We investigated the use of radioimmunoguided surgery (RIGS$^{©}$) in enhancing the surgeon's capability in detecting intraabdominal disease.

Methods: 19 pts. who underwent RIGS for suspected tumor recurrence based solely on elevated CEA were included in the study. They had colonoscopy and CT of the abdomen and chest, all of which were negative. All pts. underwent scintigraphy scan with an anti-CEA monoclonal antibody (MoAb) labeled with ^{99m}Tc or indium I-111. Prior to injection, human anti-mouse antibody (HAMA) levels were measured. Pts. were injected with the CC49 MoAb (an anti-TAG-72 tumor-associated glycoprotein) labeled with ^{125}I. In surgery, pts. had traditional exploration followed by survey with the gamma-detecting probe.

Results: Traditional exploration identified 26 recurrent tumors, 7 hepatic, 8 pelvic, 6 retroperitoneal, 3 colonic, 1 splenic and 1 anastomotic. RIGS exploration confirmed all these and identified additional tumor sites in 7 pts. resulting in changed surgical plan. CEA scan correlated with intraabdominal findings in 6 pts., additional findings not detected by the scan in 8 pts. Abdominal pathology did not correlate with the scan in 3 pts. and CEA scan results were undetermined in 2 pts.

Conclusion: Pts. with elevated CEA and no other findings should be operated using RIGS as this can provide the surgeon with more accurate knowledge of the extent of disease.

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Mutations in repeated sequences within cancer genes in sporadic replication error positive colorectal cancers

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Purpose: Up to 15% of colorectal cancers are characterized by DNA microsatellite instability (MIN), a mutator phenotype of mismatch repair genes, characterized by replication errors in neutral microsatellite sequences and in repeated sequences within cancer genes. In this study we investigated mutations in three putative cancer genes in 14 Replication ERror positive (RER+) tumors derived from the analysis of 150 sporadic colorectal cancers.

Methods: Fragments containing two (A)6 traits in PTEN gene, a (A)8 trait in hMSH3 and a (C)8 in hMSH6 were amplified from 14 RER+ tumor DNA and directly sequenced.

Results: Among the 14 RER+ tumors tested hMSH3, hMSH6 and PTEN mutations were detected in 7 (50%), 6 (42.8%) and 3 (27.4%) tumors, respectively.

Conclusion: Our data confirm the role of hMSH3, hMSH6 and PTEN as important mutational targets in RER+ colorectal tumors.