725 POSTER

Differing percentages of p53 gene mutations, correlation of p53 protein with point mutations and genetic instability in right and left colon cancer

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Purpose: Right and left-side colon carcinomas (CC) can display different pathologic and oncogenic characteristics.

Methods: 111 cases of CC (63 in left colon and 48 in right) were analyzed. p53 mutations (mp53) were studied by PCR at exons 5–8. PCR products were analyzed by SSCP and direct DNA sequencing. Immunohistochemical studies were also performed. Genetic instability (GI) was assessed according to 5 microsatellite markers at chromosome 18 near the DCC gene.

Results: The incidence of mp53 was 43.7% and 34.9% in right and left colon, respectively. In right CC, there was a marked correlation between mp53 and lymph node metastasis that was not observed in left colon ($p = 0.05$). The rate of coexistence of mp53 and GI was similar in the two groups of tumors. We observed significant differences in the correlation of these two variables with the presence of lymph node metastasis. The correlation between mp53 according to SSCP and immunohistochemical findings was poor, especially in left CC. The rate of GI was 27.07% and 15.87% in right and left colon, respectively; in right colon, its presence was directly associated with tumor size.

Conclusions: The findings suggest that GI is prone to occur in right CC during tumor growth and that it can be detected in sporadic right CC. The association of GI and mp53 in right CC with lymph node metastasis may mean that these alterations are indicative of a subgroup with a worse prognosis. These data suggest that left and right CC have differing oncogenic alterations with distinct prognostic implications.

726 POSTER

Long-term weekly treatment of advanced colorectal cancer (CRC) with fluorouracil (5-FU) and leucovorin (LV): 5 year-results of a multicentric phase II trial of 5-FU pharmacokinetic monitoring in 152 patients

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In a previous study with a 5-FU stepwise dose escalation and a pharmacokinetic monitoring in a weekly regimen, we found a relationship between 5-FU plasma levels and response in advanced CRC. We defined a therapeutic 5-FU plasma range: 2–3 mg/l (Proc. AACR 92). We investigated presently 5-FU intensification with an individual dose-adjustment, based on pharmacokinetic monitoring.

Methods: 5-FU was administered by 8-hour weekly infusion, plus 400 mg/m^2 LV. The initial dose of 5-FU (1.3 g/m^2) was adapted weekly, according to 5-FU plasma levels to reach the therapeutic range.

Results: 152 patients entered the study from 12/1991 to 12/1994. Toxicity was mainly diarrhea (39%; 5% grade III) and hand-foot syndrome (30%; 2% grade III). There were 17% complete, 42% partial, 30% minor responses and stable disease, and 11% progressive disease. Median overall survival was 19 months. **Pharmacokinetic Study:** the 5-FU dose necessary to reach this plasma range varied widely: mean: 1803 ± 386 mg/m^2/wk (950 – 3396). 13 patients were immediately in the toxic zone with 1300 mg/m^2/wk. 51 patients required at least 50% increase of the 5-FU dose. Variations in 5-FU pharmacokinetics were observed throughout the treatment.

Conclusion: Individual 5-FU dose adjustment with pharmacokinetic monitoring provided a high percentage of responses and a good survival with a very low incidence of toxicity.

727 POSTER

The influence of surgery on metachronous distant metastases and survival in rectal cancer

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The present study examines the effects of the quality of surgery, as reflected by local recurrence rate, on survival and incidence of initial distant metastases.

1581 consecutive patients undergoing curative resection for rectal carcinoma were prospectively recruited to this cohort study between 1974 and 1991. Total mesorectal excision was introduced in 1986. No patient received adjuvant radiotherapy or chemotherapy. The median follow-up period was more than 13 years.

1285 patients had no local recurrence, but 275 of them developed distant metastases (UICC I: 8%, UICC II: 16%, UICC III. 40%). 306 patients with local recurrence had a significantly lower observed 5-year survival rate ($p < 0.0001$). The local recurrence rate decreased from 39 to 9% ($p < 0.001$). The observed five-year survival rate improved from 50 to 71% ($p < 0.001$). There was no change in the incidence of distant metastases ($p = 0.70$).

Quality of surgery is an independent prognostic factor for survival in rectal cancer, but has no influence on the initial occurrence of distant metastases. Local recurrence cannot be considered an outcome criterion of adjuvant treatment without consideration of the surgeon as a risk factor.

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Serum CEA indicates presence of lymph node metastases and response to preoperative radio-chemo-thermotherapy in locally advanced rectal cancer

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We investigated whether CEA serum level may indicate response to preoperative regional radio-chemo-thermotherapy (RCTT) in locally advanced rectal cancer. 55 pts with primary (n = 37) and recurrent rectal cancer (n = 18) entered a phase II trial. Preoperative treatment consisted of radio-chemotherapy (45 Gy/5-FU and LV). Regional hyperthermia was carried out once a week prior to radiotherapy. Six weeks after completion of RCTT, patients underwent resection of their tumor. CEA serum levels were determined before and after RCTT and postoperatively. The mean CEA value was significantly lower after RCTT (26.1 ± 110 μg/l) than prior to RCTT (30.3 ± 81.6 μg/l, $p = 0.015$). After tumor resection a further decrease of CEA was observed (2.1 ± 3.7 μg/l; $p < 0.000$). There was no significant difference between primary and recurrent tumors. However, in patients with histologically proven lymph node metastases. mean CEA values pre- and post-therapy were higher (38.1 ± 95 and 29.1 ± 64 μg/l) than in node negative patients (7.3 ± 20.5 and 1.7 ± 1.6 μg/l; $p = 0.009$). Responding patients had significantly lower CEA levels after completing RCTT than non-responders (2.5 ± 4.2 vs 5.5 ± 62.6 μg/l; $p = 0.0008$).

Serum CEA determinations prior and after preoperative radio-chemo-thermotherapy for locally advanced rectal cancer indicate response to treatment and the presence of lymph node metastases. This might be helpful to decide on further treatment planning.

729 POSTER

Venous invasion as a prognostic factor in colorectal carcinoma

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Purpose: The putative prognostic value of venous invasion was evaluated in a series of 414 patients submitted to surgical resection for colorectal carcinoma.

Methods: There were 181 women and 233 men. The mean age ± SD was 62.9 ± 12.9 y (median: 65.0 y). Follow-up information was obtained in 87% of the patients. The following parameters were evaluated: site, macroscopic type, degree of differentiation, staging according to Dukes and venous invasion (searched in orcein stained slides). Survival curves were calculated following Berkson's actuarial method. Chi square after the Yates correction, Wilcoxon, and Kaplan-Meier method were used in the statistical analysis of the data.

Results: There were significant correlations between venous invasion and macroscopic type ($p = 0.005$), degree of differentiation ($p = 0.0005$), staging ($p = 0.0001$) and survival ($p = 0.01$). Venous invasion kept its prognostic significance when the influence of staging was controlled.

Conclusions: The search for venous invasion in surgical specimens of colorectal carcinoma provides useful prognostic information and should therefore be always performed. This holds particularly true whenever dealing

with B Dukes cases since it contributes to identify a subset of patients that may benefit from adjuvant therapy.

730 POSTER

Anal carcinoma: Regional recurrences dependent on target volume of sphincter-sparing radio-/chemotherapy

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Purpose: Different volumes are published for radical RT of anal ca. Including only the small pelvis into the ref vol., we examined whether this PTV is sufficient enough for the prevention of pelvic recurrences (REC).

Patients: From 1979-Oct 1996, 80 pts (56 f, 24 m, median age 66 yrs) with anal ca were treated for sphincter sparing with RT (80 pts) and ChT (52/80): T1 19 pts, T2 34 pts, T3 21 pts, T4 5 pts, N1-3 14 pts; 55 with biopsy, 21 with excision and 4 with LN-excision. RT was mostly given with two parallel opposed fields, SD 1.8 Gy, TD 45 Gy, with concomitant ChT in week 1 (5-FU 1000 mg/m^2, d 1–5; Mito-mycin-C 10 mg/m^2, d 1) and 5 (5-FU 1000 mg/,m^2, d 29–34). For 48 pts, interstitial LDR-brachytherapy (BT) was used as a boost, but replaced 1995 by endocavitary HDR-BT (14 pts). 15 pts had an e$^-$ boost. The time gap of 6 wks between RT and boost was changed to two wks after 1990.

Results: 17 out of 80 pts developed a loco-regional REC. 11/17 pts had a local REC, 5/53 T1/2 tumours (9.4%) and 6/26 T3/4 tumours (23%). Shortening the treatment time reduced the REC-rate, p = 0.06. 11/17 pts had a regional REC (5x with local REC). Two inguinal and one presacral REC were not covered by the PTV. All pelvic RECs developed inside the PTV, i.e. inside the small pelvis, below the iliacal bifurcation.

Conclusions: The PTV, covering only the small pelvis, has proved to be sufficient in preventing pelvic regional recurrences. There was no pelvic recurrence outside this volume.

731 POSTER

Immuno-chemoembolisation in the treatment of colorectal livermetastasis

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Introduction: Intra-arterial chemotherapy of colorectal livermetastasis leads to an elevation in cytostatic drug concentrations and higher remission rates. The aim of this study was to evaluate the efficiency of a combination of intra-arterial immunotherapy and chemotherapy. In order to activate the hepatic immunsystem we used Granulocyt-Macrophages Stimulating Factor (GM-CSF) intra-arterially.

Methods: Up to now we treated 34 patients (28 male/6 female) with isolated colorectal livermetastasis by two cycles of intra-arterial immuno-chemoembolisation. 12 out of 34 patients were previously treated by systemic chemotherapy and two patients by regional chemotherapy. Treatment consisted of 150 mcg GM-CSF applicated at day one and two, 1000 mg 5FU applicated on day three and four and 40 mg melphalan as embolisation in combination with lipiodol and gel-foam via an angiographicly placed hepatic-artery system. Treatment free interval was 28 days, re-evaluation for remission was done four weeks after the second cycle according to WHO-criteria.

Results: In 34 patients we saw 5 complete remissions, 5 CR after downstaging and resection and 20 PR In two cases there was a stable disease leading to an overall remission rate of 89%. Sideeffects were usually low and acceptable mostly correlated to chemoembolisation with vomiting 13.5%, abdominal pain 17.3% and transient elevation of the liver enzymes 13.5%. Interestingly there was a very low rate of leucopenia not exceeding WHO-grade II of 3.9%. One year survival rate is 92%.

Conclusion: The intra-arterial application of GM-CSF in combination with cytostatic chemotherapy is possible without any strong local or systemic side effects. This method leads to a high local remission rate. Further studies have to evaluate the efficiency of intra-arterially applicated GM-CSF for the hepatic immunsystem leading to a higher level of cytocines in the hepatic tissue.

732 POSTER

Peritoneal carcinomatosis treatment with curative: Institut Gustave-Roussy experience

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Purpose: The aim of this study is to report the results of a phase II study in which the PC was treated with complete cytoreductive surgery associated with the treatment of the residual microscopic disease by immediate intraperitoneal postoperative chemotherapy (IIPC) for five days (Mitomycin®, Fluorouracil®, Adriamycin®, and Platinol®).

Methods: Fifty-four patients with a PC from miscellaneous origins were treated between January 1993, and April 1996. The PC was important (clinically evident), but extraperitoneal localization free, in 29 cases. The PC was fortuitously discovered during a laparotomy for extraperitoneal cancer localization in 25 cases. Operative time was 7:21 hours, associated with extensive peritonectomies, and resection of invaded organs (4 organs per patient). IIPC was complete (5 days) in 91% of patients.

Results: Three postoperative deaths (5.5%) were reported. Morbidity was present in 61% of patients, and was related to surgical extension ($p < 0.001$). Two-years survival of 50% was correlated with the importance of the PC ($p < 0.01$), and was the same for both groups of patients (isolated PC *vs.* moderate PC associated with extraperitoneal localization). PC recurrence rates were 30% at two years.

Conclusion: Complete cytoreductive surgery associated with IIPC is a logical and promising treatment of PC. However, it appears that: it is a heavy treatment for patients (and physicians), and its lawfulness will be proved only after a randomized study (currently going).

733 POSTER

Intraoperative radiotherapy (IORT) for recurrent rectal carcinoma

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Purpose: Curative treatment for recurrent rectal carcinomas is possible in less then 10%. A multi-modality treatment using IORT was evaluated.

Materials and Methods: A total of 31 patients suffering from a recurrent carcinoma in the pelvis had IORT (minimum follow-up 18 months). Multivisceral or anterior resection (n = 8) yielded a R0-resection in 16 pat. In equally 8 pat. microscopically or macroscopically residual tumor remained. The mean IORT-field size was 7.4 (5–13.2) cm, the mean IORT-dose 13.7 (10–20) Gy. External beam radiotherapy (EBRT) was given with 41.4 Gy (1.8 Gy SD) either preoperatively (n = 21) or postoperatively (n = 10). 22 pat. had simultaneously chemotherapy.

Results: After a median follow-up of 28.2 months 8 pat. died due to progressive disease. 1 pat. died without tumor. 8 pat. suffered from a second local failure, while 3 of these patients developed additionally distant metastases. 7 pat. had distant metastases alone. After non-complete resection the failure rate was significantly higher, due to a higher distant metastases rate (20% vs. 62%). The actuarial 5-year-overall survival was 55% for the entire patient group.

Conclusion: Compared to historical controls local tumor control and overall prognosis was improved. Locally restricted dose application with IORT offers optimum normal tissue sparing to further improve the benefit of multi-modality treatment strategies.

734 POSTER

A seven-years experience with implantable devices for regional hepatic arterial chemotherapy: Usability time, incidence and management of complications

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Background: The successful delivery of chemotherapeutic drugs through an implantable hepatic arterial device depends on the surgeon's understanding of hepatic arterial anatomy, proper cannulation technique and operative as well as postoperative measures to decrease the occurrence of complications. We reviewed the usability of hepatic arterial ports at our department.

Methods: Between March 1st, 1989 and December 31th, 1996 we placed 123 implantable hepatic arterial devices in 95 patients with primary