725 POSTER

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

M. LLeonart, A. Moreno, R. Sánchez, P. Martín, C. Salas, S. Ramón y Cajal. *Department of Pathology, Clínica Puerta de Hierro. 28035 Madrid, Spain*

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

B. Lamezec, C. Alleaume, E. Gamelin, M.J. Goudier, P.E. Cailleux, E. Danquechin-Dorval, M. Sire, M.L. Maillet, M. Maigre, P. Gesta, P. Maillart, F. Larra. *Pays de Loire, Bretagne, Poitou, Centre Paul Papin Angers, France*

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

F. Köckerling, M.A. Reymond, A. Altendorf-Hofmann[1], W Hohenberger. *Department of Surgery; [1] The Tumour Center at the University of Erlangen, Germany*

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.

728 POSTER

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

B. Rau[1], P. Wust[2], M. Hünerbein[1], P. Hohenberger[1], H. Riess[3], P.M. Schlag[1]. *[1] Division of Surgery and Surgical Oncology; [2] Department of Radiation Oncology; [3] Oncology and Haematology, Virchow Klinikum at the Humboldt University of Berlin, Germany*

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

M. Moutinho-Ribeiro[1,3], P. Ribeiro[1], M. Sobrinho-Simões[2,3]. *[1] Dept of Surgery (Cirurgia 4); [2] Department of Pathology, Medical Faculty; [3] Institute of Molecular Pathology (IPATIMUP), Porto, Portugal*

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