Results: With excellent spatial and temporal resolution dynamic T1 mapping revealed distinct Gd-DTPA accumulation level changes within the tumor during radiation. The perfusion index (Pi) of Gd-DTPA versus radiation dose showed a significant increase in the first or second week of treatment, then either returned slowly to the pretreatment level or rose again after an intermediate drop. The average Pi- value at the beginning was 0.16 (±0.054) and at the highest level was 0.23 (±0.06). In all groups the rise from the Pi-maximum was statistically significant, revealing an increase within a range of 8.06% to 82.55%.

Conclusion: The ultrafast T1 mapping MR-technique described here proved to be a practicable tool for monitoring tumor microcirculation during therapy and offers the potential for customized optimization of therapeutical procedures.

204 ORAL

Disseminated tumor cells detected by CK 20 RT-PCR in the blood and the bone marrow of patients with colorectal carcinoma represent an independent prognostic factor

I. Vogel, E. Soeth, C. Röder, B. Kremer, H. Kalthoff, D. Henne-Bruns. *University of Kiel, Dep. of Surgery, Kiel, Germany*

Purpose: The prognostic impact of the detection of disseminated tumor cells by molecular technics in patients with gastrointestinal carcinoma is so far not proven. The aim of our study was to evaluate the prognostic impact of the detection in bone marrow and blood by CK 20 RT-PCR in patients with colorectal carcinoma.

Methods: Bone marrow and venous blood samples of 170 patients with colorectal carcinoma were taken preoperatively. A multivariate analysis to detect independent prognostic factors was performed in 122 patients with curative resection (R0) (Cox regression model).

Results: Univariate analysis revealed the lymph node status ($P = 0.0127$) and the detection of tumor cells in the bone marrow ($P = 0.0081$) and in venous blood ($P = 0.0024$) as prognostic factors. The detection of cells in the bone marrow ($P = 0.0405$) as well in the venous blood ($p = 0.0072$) and the combination of both compartments (venous blood and/or bone marrow ($p = 0.0131$)) showed a significance influence on survival in multivariate analysis.

Conclusion: The detection of disseminated tumor cells by CK 20 RT-PCR in bone marrow and/or venous blood of patients with colorectal carcinoma is an independent prognostic factor and should therefore lead to randomized studies with adjuvant treatment modalities in positively tested patients.

205 ORAL

Phase III trial of 5-fluorouracil (5FU) and leucovorin (LV) with or without trimetrexate (TMTX) as first line treatment in advanced colorectal cancer (ACC)

C.J.A. Punt[1], H.J. Keizer, J. Douma, J. Schüller, T. Skovsgaard, C.H.H. ten Napel, H. Lochs, E.W. Muller, L. Russell[2], D.J.T. Wagener[1]. *Dept. of Medical Oncology, University HospitalNijmegen, Netherlands; [2]USBioscience, United States*

Purpose: In phase II studies TMTX, a non-classical antifolate, plus 5FU/LV has shown promising response rates but a high incidence of severe diarrhea in untreated ACC patients (pts).

Methods: 364 pts were randomized between LV 200 mg/m^2 in 1 h i.v. and 5FU 600 mg/m^2 bolus i.v. (*arm A*) or TMTX 110 mg/m^2 in 1 h i.v. followed after 24 h by LV 200 mg/m^2 in 1 h i.v. and 5FU 500 mg/m^2 bolus i.v. and LV 7 × 15 mg orally q 6 h starting 6 h after 5FU (*arm B*). Treatment was given weekly x6, q8 wks (one cycle) for a maximum of one year. Primary endpoint was progression free survival (PFS), secondary endpoints were overall survival (OS), response rate, toxicity and quality of life. Eligibility criteria included untreated ACC (adj. therapy with ≥1 yr interval allowed), WHO PS ≤ 2, age ≥ 18 yrs.

Results: A planned interim analysis was performed on toxicity and PFS in the first 222 pts entered prior to may '98. Pts characteristics were not significantly (NS) different between arm A (110 pts, 186 cycles) and B (112 pts, 233 cycles). Diarrhea was the major toxicity but occurred less frequently as reported previously due to strict guidelines: grade 3/4 in arm A 25% vs. in arm B 15% (NS). Other grade 3/4 toxicities occurred <10% in both arms. Median PFS was borderline significant (p 0.053) in favor of pts treated with TMTX (3.9 vs.5.3 months).

Conclusion: These promising results will be updated together with an analysis on OS in april '99 when the median follow-up will be 17 months. The results will be presented at the meeting.

206 ORAL

Irinotecan (Iri) in combination with high-dose infusional (HDI) 5FU/FA either weekly or bi-weekly: Evidence of survival advantage and quality of life (QoL) improvement in metastatic colorectal cancer (MCRC)

P. Rougier, D. Cunningham, A.D. Roth, J.R. Germa, R.D. James, P. Karasek, P. Jandik, T. Iveson, J. Carmichael, G. Gruia, M. Alakl, D. Sibaud, J.Y. Douillard. *A. Paré, Boulogne, France; Royal Marsden Hosp. London, United Kingdom; Hosp. Cantonal Geneve, Switzerland; Hosp. Durant y Reynals, Barcelona, Spain; Christie Hosp. Manchester, United Kingdom; Inst. of Oncol. Brno; Univ. Hosp. H. Kralove, Czech Republic; Royal S. Hants Hosp., Southampton; City Hosp., Nottingham, United Kingdom; Rhone Poulenc Rorer, Centre R Gauducheau, St-Herblain, France*

Single agent IRI has been shown to be active in MCRC with significant survival advantage over best supportive care or best 5FU schedule in patients with prior 5FU failure (Lancet, 1998). As of Feb. 1998, 387 pts were randomized to receive (A): combination of IRI at 180 mg/m^2 day (d) 1 and 5FU 400 mg/m^2 as IV bolus followed by 600 mg/m^2/d as a 22 hours (h) continuous infusion (c.i.) + FA on d1–d2 repeated every 2 weeks (wks) or IRI at 80 mg/m^2 and 5FU 2.3 g/m^2 as a 24-h c.i. + FA weekly × 6 every 7 wks, *versus (vs)* (B): the same regimen of 5FU/FA alone. The main pts characteristics are comparable between groups A (199 pts) and B (188 pts): median age 62 *vs* 59, primary colon/rectum 55/45 *vs* 65/35, performance status 0 52% *vs* 51%, prior adjuvant CT, 26% *vs* 24%, number of organs ≥2 38% *vs* 37%, respectively.

Efficacy: group A *vs* B: response rate (RR) 41% *vs* 23% ($p < 0.001$) time to progression (TTP) 6.7 months (m) *vs* 4.4 m ($p < 0.001$) survival 16.8 m *vs* 14.0 m ($p = 0.029$).

Safety: The main NCI grade 3/4 adverse events by pts in group A *vs* B are: neutropenia 42% *vs* 11%, diarrhea 22% *vs* 10%; other toxicities were <5% and comparable in both groups.

QOL: A better QoL in favor of A was maintained during chemotherapy. Iri in combination with HDI 5FU/FA show a significantly better RR, TTP and survival along with at least an equivalent QoL, as compared to HDI FU/FA alone in pts with MCRC.

207 ORAL

Medical resource use in a phase III trial (SO 14796) of XelodaTM (capecitabine) in previously untreated advanced/metastatic colorectal cancer

C. Twelves[1], E. Van Cutsem[2], K. Hieke[3], C. Barker[4], C. Jamieson[4], J. Hornberger[4], L. Garrison[4], B. Osterwalder[3], A. Thibault[5]. *[1]Beatson Cancer Center, Western Infirmary, Glasgow, United Kingdom; [2]University Hospital Gasthuisberg, Gastroenterologie, Leuven, Belgium; [3]F. Hoffmann-La Roche, Basel, Switzerland; [4]F. Hoffmann-La Roche, Palo Alto; [5]F. Hoffmann-La Roche, Nutley, United States*

Introduction: XELODA(TM) (capecitabine) is a novel, orally administered, tumor-activated fluoropyrimidine carbamate. A randomized phase III clinical trial comparing XELODA (TM) (2500 mg/m^2/d × 14 d, q3 weeks, n = 301) vs. Mayo regimen (5-FU 425 mg/m^2; LCV 20 mg/m^2 d1-5, q4 weeks, n = 301) resulted in a higher response rate (26.6% vs. 17.9%, p = 0.013), and similar duration of response (7.3 vs 9.6 months) and progression-free survival (5.3 vs 4.8 months). The most remarkable differences in adverse events (AEs) were lower rates for XELODA (TM) patients requiring treatment for stomatitis, vomiting, and diarrhea and a higher rate of hand-foot syndrome (HFS).

Methods: Patients were recruited from 66 centers in 8 EU-countries, Australia, Russia, Israel and Taiwan. Data on hospital use, IV administration visits, AEs requiring medications or procedures, and all physician encounters were collected alongside the clinical trial for all randomized patients and analyzed.

Results: Administration of the Mayo regimen requires 5 visits per monthly cycle for IV administration of 5-FU and LCV. Data were available on 94% (=6,092) of the IV administration visits on the Mayo regimen. 336 of these administrations lasted >24 hours, implying overnight hospitalization for drug administration. 5,718 visits were <8 hours, and 38 visits lasted 8–23 hours. Patients receiving XELODA (TM) required one outpatient visit at the beginning of each cycle and no further visits for drug administration. Total days in hospital for the following AEs – stomatitis/mucosal inflammation, hand-foot syndrome, neutropenia, pyrexia, infections, diarrhea, nausea, and vomiting – was reduced by 184 hospital days (370 vs. 186, −50%) in the XELODA (TM) arm. For these AEs, the use of cephalosporins, quinolones, fluconazole and 5HT3-antagonists was consistently lower (−16%, −39%,

−93% and −25% respectively) with XELODA (TM). XELODA (TM)-patients received more days of treatment (usually topical preparations) for HFS. Use of colony stimulating factors was infrequent in both arms. Physician consultations and other medical procedures for treatment of these AEs did not involve a significant amount of medical resource use.

Conclusion: Oral administration of XELODA (TM) avoided 336 overnight stays and 5,756 outpatient visits for IV administration of drug. XELODA (TM) treated patients needed 184 fewer hospital days for the treatment of related AEs and less use of high-cost medications for AEs. Despite higher drug acquisition costs for XELODA (TM), overall cost savings are likely if it is used instead of the Mayo regimen.

208 POSTER DISCUSSION

Functional results after total mesorectal excision (TME) in rectal cancer

J.W.A. Oosterhuis[1], C.L.H. van Berlo[1], J.F.M. Reinders[1]. [1]*St Maartensgasthuis, Surgery, Venlo, Netherlands*

Introduction: The primary objective of total mesorectal excision (TME) in the surgical management of rectal cancer is to achieve local tumour control. An important aspect of this technique is preservation of the autonomic nerves and the related sexual and bladder functions, if oncologically feasible. Since a low anastomosis is performed after TME in most patients, preservation of a more or less normal defecation is also important for quality of life.

Methods: A total of 88 patients with rectal cancer were managed by TME and preservation of the autonomic nerves between 1996 and 1999. Functions of defecation, voiding and sexual function were assessed preoperatively and postoperatively during follow-up with a scoring system.

Results: After a mean follow-up period of 13 months erectile or ejaculatory dysfunction in 33% of male patients was observed. Patients who had received preoperative radiotherapy (5 × 5 Gy) had better scores for postoperative sexual function than those who did not receive radiotherapy. Voiding was disturbed in 18% of patients and did not improve significantly with a longer follow-up. In patients with a low anastomosis, 41% experienced a social handicap because of frequency of defecation or soiling.

Conclusion: Quality of life after TME will be determined for a large part by postoperative functional results. In this study a clear relation between the length of follow-up and degree of sexual and bladder dysfunction was not found.

209 POSTER DISCUSSION

Late side effects of combined treatment modalities in rectal cancer

D. Jacob-Heutmann[1], C. Thilmann[1], I.A. Adamietz[2], H.D. Böttcher[1]. [1]*University Hospital of Frankfurt/M., Department of Radiotherapy, Frankfurt am Main;* [2]*Marienhospital Herne, University Bochum, Department of Radiotherapy, Bochum, Germany*

Purpose: Combined treatment modalities are increasingly used for the treatment of rectal cancer. The combination of radio- and chemotherapy is known to increase the severity of acute side effects. The data on the frequency and origin of late sequelae, however, is conflicting. The goal of this analysis was to determine the frequency and extent of late side effects and to define prognostic factors for their occurrence.

Methods: The data of 53 patients with rectal carcinoma (primary tumors n = 33, recurrent tumors n = 20) were evaluated retrospectively with regard to late side effects. The patients received radiotherapy (RT) only (n = 19) or a combined radiochemotherapy with 5-FU (n = 34). 41 patients also underwent surgery prior to irradiation or after it. The follow-up was 580 ± 359 days with a median of 493 days.

Results: Radiation enteropathy was found to be the most frequent late sequela (35/53 cases). It was mild in 23 cases (43.4%, EORTC/RTOG grade 1 and 2), whilst 12 patients (22.6%) suffered from severe enteritis (grade 3, 4 and 5). 8 patients (15.1%) required reoperations for late bowel complications. Median time of complication occurrence was 6.8 months after the initiation of RT. Significant risk factors for late bowel complications turned out to be simultaneous chemotherapy (p = 0.03) and surgical treatment as part of the combined treatment plan (p = 0.03).

Conclusion: Our results indicate that the combination of radio- and chemotherapy in the treatment of rectal cancer increases the frequency of chronic intestinal side effects. These can cause considerable morbidity and reduce the patients' quality of life. Irradiation techniques and supportive care have to be improved to prevent severe late effects.

210 POSTER DISCUSSION

Liver resection after preop. chemotherapy for colorectal metastases: Morbidity and treatment results

P. Hohenberger, B. Kilpert, P.M. Schlag. *Div. of Surgical Oncology, Robert-Rössle Hospital Charité, Humboldt University, 13122 Berlin, Germany*

Problem: In patients with colorectal liver metastases not amenable to surgical resection or presenting with poor risk factors, preoperative treatment may be advisable. We analysed the impact of preop. therapy upon subsequent resection in terms of morbidity, mortality, and survival.

Patients and treatment: From 1993–98, 127 liver resections were performed. Of these, 37 resections (29%) followed systemic or regional chemothp. Median patient age: 61 (35–71 yr). Chemothp: 5-FU/LV (Mayo scheme), HD 5-FU (2.6 g/msq)/LV, or 5-FU/LV/oxaliplatinum. Time interval between start of chemotherapy and liver resection was 12 mos. in median (2–16 mo.)

Results: Resectional procedures: hemihepatectomy (S4/5-8, n = 10), segmental resections (n = 19), plurisegmentectomies (n = 8); mortality: 2.7%. Morbidity: 28 pat. (76%) with uneventful course.; complications: pneumonia (n = 2), bile leakage, (n = 2), bleeding (n = 2), jaundice (n = 2), SIRS/ARDS (n = 1). Radical resection (R0) was possible in 29 patients whil another 8 pat. showed extrahepatic spread at laparotomy. Median survival is 25 mos. (4–38+ mos.)

Conclusion: Resection of residual liver lesions after systemic or regional chemotherapy can be performed with very limited morbidity and mortality This approach may offer cure even for patients not amenable to resection as the treatment of first choice.

211 POSTER DISCUSSION

Artificial neural network prediction of 5-year survival from colon cancer

J.M. Jessop[1], P. Snow[2], J. Brandt[2], C. Bellucco[3], H.R. Menck[4], D.J. Kerr[5]. [1]*University of Pittsburgh Cancer Institute, Pittsburgh;* [2]*Xaim Inc., Colorado Springs, United States;* [3]*University of Padua, School of Medicine, Padua, Italy;* [4]*American College of Surgeons, Chicago, United States;* [5]*University of Birmingham, CRC Institute for Cancer Studies, Birmingham, United Kingdom*

Purpose: To determine the effectiveness of computer-based artificial neural networks (ANNs) in predicting 5-year survival from colon cancer.

Methods: 400,000 cases from the National Cancer Database with 79 variables for each patient were used in the analysis. Advanced computer technology was used to identify the most important variables for predicting 5-years survival. Thirteen variables were identified in this manner and were used as inputs to an advanced artificial neural network. Evaluation of accuracy was based on the ANNs performance on an additional 1000 patients ("validation patients‰) that were not used in the design of the neural network solution.

Results: The area under the Receiver Operator Characteristics (ROC) Curve was 82% for the "validation patients.‰ Choosing a point on the ROC Curve that represented optimized overall accuracy resulted in the following: Sensitivity = 67%, Specificity = 82%, 5-year predictive value = 71%, 5-year death predictive value = 79%, Overall accuracy = 76%.

Conclusion: Artificial neural networks were able to predict with clinically useful accuracy, the 5-year survival of colon cancer patients. In addition, the program generalized very well to patients that were not used in the development of the solution.

212 POSTER DISCUSSION

Postoperative radiation (RT) and concomitant bolus fluorouracil (FU) with or without additional chemotherapy (CT) as adjuvant treatment in patients with high risk rectal cancer. A randomized phase III study conducted by the Hellenic Cooperative Oncology Group

E. Athanassiou[1], U. Dafni[1], A. Liaros[1], E. Briassoulis[1], E. Samantas[1], P. Kosmidis[1], D. Skarlos[1], N. Pavlidis[1], G. Fountzilas[1]. [1]*HeCOG Data Office, Athens, Greece*

Purpose: To compare the impact of postoperative RT with or without additional CT on disease-free survival (DFS) and overall survival (OS) of patients with stage II or III rectal cancer.

Methods: From October 1989 until February 1997, 220 patients were randomized postoperatively to receive either one cycle of CT with FU and leucovorin (LV) followed by pelvic RT with concomitant FU (400 mg/m^2) as