a lower rectum adenocarcinoma. 4 with an anal epidermoid, and 2 with a primitive anorectal melanoma. All patients with an adenocarcinoma had post-operative radiotherapy. Preoperative evaluation, surgical technique, and postoperative care are described.

Results: No deaths occurred in the postoperative period. Nine patients had a perineal separation, one distal colic necrosis and one neorectal perforation by irrigation necessitating an iliac colostomy on days 14 and 21. Two patients had to undergo anal dilatation. Three mucous prolapses and 2 perineal eventrations, all late occurrences, complete the list of complications. Functional results were evaluated with Kirwan's classification: 4 patients had normal continence, 24 gas incontinence, 10 occasional minimal soiling, and 2 cases necessitated a left iliac colostomy.

Conclusion: Peudocontinent perineal colostomy following abdominoperineal resection is a safe reconstruction technique which provides good functional results following strict selection of patients.

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A phase II-study on intense weekly 24-hour intraarterial infusion with 5-fluorouracil (5-FU) and folinic acid (FA) for colorectal liver metastases

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Purpose: The aim of this phase II-study was to demonstrate the toxicity and the improved response rates of weekly 24-h hepatic arterial infusion (HAI) of 5-FU and FA for unresectable liver metastases from colorectal carcinoma.

Methods: In 26 patients (15 male, 11 female), 268 courses of high-dose HAI of 5-FU/FA were administered. The chemotherapy regimen consisted of a weekly HAI of FA 500 mg/sqm over 2 h, immediately followed by HAI of 5-FU over 24 h. 14 patients received a 5-FU starting-dose of 2600 mg/sqm, 4 patients of 2400 mg/sqm and 8 patients of 2200 mg/sqm. One course consisted of 6 weekly applications followed by a two week break.

Results: The applied regimen caused only a low rate of clinical relevant side effects. Diarrhea was most frequently seen with 15 episodes WHO-grade $\geq$3 out of 268 courses. Nausea and vomiting were a minor problem occurring with 3 episodes WHO-grade $\geq$3. There was no evidence of myelosuppression, neurotoxicity and biliary sclerosis. 53 applications (19.7%) were without any side effects. A partial remission was observed in 20 (77%) patients, and a disease stabilization in 4 (15%) patients while the disease progressed in 2 (8%) patients.

Conclusion: The present phase II-study demonstrates that the weekly high-dose HAI of 5-FU/FA was well tolerated despite the dose limiting diarrhea. Because of this extraordinary high response rates without local hepatobiliary toxicity this regimen should be used for further randomized trials comparing intraarterial versus intravenous therapy.

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A phase II trial of trimetrexate (TMTX), 5-fluorouracil (5-FU) and folinic acid (FA) in untreated patients with advanced colorectal carcinoma

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Purpose: TMTX is a non-classical antifolate and has been shown to increase the activity of 5-FU and FA. We evaluated the safety and efficacy of TMTX, 5-FU and FA in patients with metastatic colorectal cancer.

Methods: 34 patients were enrolled into the study. Patients received treatment as follows: TMTX 110 mg/m^2 i.v. infusion over 60 minutes on Day 1; FA 200 mg/m^2 i.v. bolus and 5-FU 500 mg/m^2 i.v. bolus on Day 2; followed by 15 mg of FA po q6 hours $\times$ 7 doses. Treatment was repeated weekly for 6 weeks followed by 2 weeks of rest. Patients were treated until disease progression or the presence of unacceptable toxicity.

Results: No grade 3 or 4 neutropenia was seen. Diarrhoea (grade 3/4 NCI) occurred in 38% of patients and allergic reaction (chills) grade 3/4 in 12% of patients. 32 patients are evaluable for response. 13 patients (38%) achieved a partial response. The median duration of response was 10 weeks.

Conclusion: The combination of TMTX, 5-FU + FA is an effective regimen for the treatment of metastatic colorectal cancer. Further studies comparing this combination with standard treatment are currently underway.

756 POSTER

Phase I/II study of CPT-11 in combination with LV2FU5 (De Gramont-Regimen) every 2 weeks for the treatment of colorectal cancer (CRC) after 5FU failure

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The Topoisomerase I inhibitor CPT-11 has demonstrated outstanding activity in 5-FU resistant CRC. LV5FU2 is considered as reference regimen in 1st line CRC in France. This phase I/II study for determination of the maximal tolerated dose (MTD) of CPT-11 and efficacy assessment combines increasing dosages of CPT-11, given on day 1 before the fixed LV5FU2 regimen (days 1, 2) at full dose repeated every 2 weeks. 30 patients have so far been treated· median age 60 (41–69) years, 23 male, 7 female, 15 colon (C), 9 rectum (R), 6 C + R, nb. of previous 5-FU based lines: 2 (1–6).

CPT-11 dose (mg/m^2)	100	120	150	180	200
No. of patients	6	5	6	6	5
No. of cycles	63	47	29	16	5

No dose limiting toxicity has been observed at 1st cycle of all levels. Out of 160 cycles available for toxicity, 25 were delayed and in 3 cycles dose was reduced. 2 febrile neutropenias were reported: 1 at cycle 5 of 1st dose level (100 mg/m^2), 1 at cycle 2 of 3rd dose level (150 mg/m^2). 2 grade 3 delayed diarrhoeas were observed at cycle 1 of 5th dose level (200 mg/m^2). 20 patients are evaluable for efficacy: 1 CR, 4 PR, 2 MR ($\geq$40%), and 1 patient with significant improvement of respiratory symptoms and X-ray (not measurable since lung involvement >50%).

757 POSTER

Effect of chemotherapy with 5-fluorouracil on intestinal permeability of patients with advanced colon cancer

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Background: A common side effect of treatment with 5-Fluorouracil (5-FU) in association with folinic acid (FA) for advanced colon cancer is diarrhea, which can be fatal and is the major obstacle to using high doses of 5-FU.

Purpose: To evaluate whether therapy with FA and 5-FU induces alterations of intestinal permeability in pts with advanced colon cancer and whether these changes correlate with the gastrointestinal symptoms.

Methods: In 16 pts (7 M, 9 F, mean age 60 $\pm$ 12) with advanced colon cancer, small intestinal permeability was assessed by the cellobiose/mannitol (CE/MA) test before and after a 5-day course of chemotherapy with FA (100 mg/sqm i.v.) and 5-FU (450) mg/sqm i.v.). Gastrointestinal symptoms were recorded by the pts for 1 week before chemotherapy until the second CE/MA test was performed.

Results: (mean $\pm$ SD): After chemotherapy, small intestinal permeability increased from 0.016 $\pm$ 0.011 to 0.029 $\pm$ 0.025 ($p < 0.05$) A correlation between the changes in CE/MA values and the number of days with diarrhea ($p = 0.05$) was observed, while no relationship was found with the number of days with stomatitis.

Conclusions: Diarrhea due to chemotherapy with FA and 5-FU ill pts with advanced colon cancer appears to be related to small intestinal damage, as indicated by the increased permeability.

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CPT11 alternating with 5 fluorouracil (5 FU) folinic acid (FA): A multicentre phase II study in 1st line chemotherapy (CT) of metastatic colorectal cancer (CRC): Preliminary results

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Rationale: CPT11 is a topoisomerase I inhibitor with proven activity as single agent metastatic CRC. 5 FU/FA is the mainstay of chemotherapy in

this disease and the combination with CPT 11 is therefore a priority. Adding these two non-cross-resistant drugs without overlaping toxicities was the rationale of this alternating schedule. **Treatment Schedule:** CPT11· 350 mg/m^2 iv, 90 mn (day 1) and 5 FU. 425 mg/m^2 iv 15 mn, immediately after FA 20 mg/m^2 iv push, daily times 5 (d22 to d26) every 6 weeks.

Population: Pts with metastatic CRC and bidimensionally measurable lesions, no prior CT or only adjuvant regimen ended more than 6 months before study entry. Age. 18–70 years, PS ≤ 2; adequate hematological, renal and hepatic functions Tumor assessment is performed every 2 single cycles.

Results: 33 pts have been treated· 18 men (55%), 15 women (45%), 17 colon (52%), 13 rectum (39%), 3 rectosigmoid (9%), 15 PS = 0 (45%), 18 PS = 1 (55%). Preliminary efficacy results (after at least 2 single cycles completed) reviewed by External Response Review Committee among 29 evaluable patients show: 9 PR, 4 MR, 13 SD and 3 PD. Out of 133 performed single cycles, 22 (16%) have been delayed (14 CPT11 cycles and 8 5 FU cycles) and 11 cycles (8.3%) have been performed with those reduced (8 CPT11 cycles and 3 5 FU cycles). **Toxicity:** (>WHO grade 2): preliminary results on 30 evaluable patients are neutropenia (6 pts – 20%), febrile neutropenia (4 pts – 13%), vomiting (2 pts – 70%), diarrhea (6 pts – 20%), mucositis (3 pts – 10%) and cholinergic syndrome (1 pt – 3.3%).

Conclusion: These preliminary results indicate that an alternating schedule of CPT11 and 5 FU/FA is feasible and that the antitumor activity is promising in metastatic CRC.

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Phase II study of 24 hours-infusion of 5-fluorouracil and high dose folinic acid in patients with progressive or recurrent colorectal cancer (CRC)

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Purpose: To evaluate the therapeutic activity of 24 h continuously infused 5-FU modulated by HD-folinic acid (FA) in pts with metastatic CRC who had recurred or progressed following bolus 5-FU based chemotherapy (CTX).

Patients and Methods: 42 pts, 27 men and 15 women with a median age of 59 years (45–76), were enrolled. Karnofsky status: 90% (80–100); previous CTX regimens. bolus 5-FU/FA acid n = 31 (74%), c.i. 5-FU ± IFN-α2 n = 9 (21%), other n = 2 (4%). Treatment schedule: 500 mg/m^2 FA given as 2-h infusion followed by a 24 h infusion of 2 6 g/m^2 5-FU once weekly × 6 (i.v.).

Results: All pts were assessable for toxicity and for response evaluation having completed at least 1 full course of ctx. No CR but 6 PR were observed [ORR, 14% ($CI_{95\%}$: 3.5–25.1%)]. The median response duration was 7.3 mon (1.4–10.6), median survival 11.6 mon [2–27 ($CI_{95\%}$: 9.4–13.8)] and the 1-year-survival rate 46%. SD/MR were achieved in another 25 pts (61%). Median treatment duration was 19 weeks (range, 6–48). WHO °III/IV diarrhea occurred in 26%, mucositis, nausea/vomiting and hand-foot-syndrome in 5% each of patients. No severe infection/fever or evidence of hematological toxicity was observed, except WHO °III anemia and leukocytopenia (each 5%). Dose reductions in 11 pts and subsequent stop of treatment in 2 pts had to be performed because of unacceptable diarrhea. PD while receiving previous ctx was associated with lower response rate (p = 0.02), shorter PFI (p = 0.02) and survival (p = 0.01) as compared to the subset of pts who achieved temporary SD.

Conclusion: C.i. infusion of 5-FU/FA displays activity in advanced CRC with toxicity being acceptable. Pts who had achieved at least SD during previous bolus 5-FU based CTX appear to benefit from second-line continuously infused 5-FU/FA. Questions remaining to be addressed in order to optimize the approach include (1) the optimal start dose of 5-FU (2) whether FA can be reduced or eliminated to achieve a better toxicity profile and lower costs.

760 POSTER

Quality of life (QL) is a prognostic factor (PF) for survival in patients with advanced colorectal cancer (CRC)

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Recent years have seen a discussion on which group of patients should be offered chemotherapy for advanced CRC regarding the limited efficacy and high costs of treatment and its' possible side effects on patients' QL. In a randomized phase III trial, 142 patients with advanced CRC were treated with 5-fluorouracil and either interferon α-2b or folinic acid. For the QL self-assessment before and during chemotherapy, a major end point of the study, patients used the validated EORTC QLQ-C30 questionnaire, which consists of 5 functional scales (physical state, ability to work, and cognitive, emotional and social state), 9 symptom scales (pain, nausea, vomiting, fatigue, dyspnea, loss of appetite, sleep disturbances, diarrhea, and constipation), and one global QL scale. Next to the above 15 QL scales we tested 20 covariates for their relevance as PF and survival. In univariate analysis, response to therapy, performance status (PS), appetite loss, physical, emotional, and role function as well as AP, SGOT, SGPT, and WBC had a significant impact on survival. However verifying the influence of these variables on survival in a multivariate setting reduced the number of significant prognostic factors to only three: a Karnofsky PS > 70% (p = 0.003), little or no loss of appetite (p = 0.003), and a WBC < 10.000 (p < 0.001). A classification including these three PF was able to distinguish between low-risk patients, who survived a median of 12 months, and high-risk patients, who had a median survival time of only 3 months. Therefore, this prognostic classification can facilitate the decision whether patients with advanced CRC should be considered for systemic chemotherapy

761 POSTER

Orthotopic transplantation of intact human colorectal and pancreatic tumor tissue in nude mice

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Purpose: A relevant model of human gastrointestinal cancer in nude mice will improve our understanding of carcinogenesis and cancer metastasis.

Methods: We have established an orthotopic transplantation model in nude mice with intact tissues of human colorectal and pancreatic cancers. The biological characteristics of the original and the corresponding transplanted tumors were investigated by HE staining, PAS staining and immunostaining.

Results: (1). There were totally 9 of 16 surgical specimens growing in nude mice subcutaneously and/or orthotopically (4/6 colon and 5/10 pancreatic cancer). Freezing of tissue specimens and tumor cell content of the specimens influenced the take rate of transplanted tumor. In the group of fresh tumor tissues with greater than 50% tumor cell content, the take rate was 100% (3/3 pancreatic and 3/3 colon). (2). The transplanted tumor closely resemble the original tumor morphologically and biologically, including TAA expression such as CEA by immunostaining, and CEA level in the serum of mice. (3). The detection of dissemination of cancer cells can be achieved by immunostaining. (4). Antigen expression of Ki-67, K-ras, 17-1A and RA-96 were associated with the potential of tumor growth in nude mice.

Conclusion: An orthotopic transplantation model and a sensitive detection method for human colon and pancreatic cancer in nude mice were established. This study will be helpful for monitoring therapeutic intervention strategies for micrometastatic disease.

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MRI and endoluminal ultrasound result in different staging in 5 out of 17 patients with anal cancer

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Purpose: In cancer of the analcanal endoluminal ultrasound (US) is the staging modality of choice. Treatment of choice is chemoradiotherapy. Accurate staging is extremely important as many clinicians treat patients with T1/2 tumors with a lower dose of RT and CT than in T3/4 tumors. Because there are no data available in the literature we investigated the role of MRI in the staging of analcanal cancer and compared it with endoluminal US.

Methods: 17 patients underwent both, MRI with a body coil and US. Tumor stage by US was the following: uT1 (<2 cm): 3; uT2 (2–5 cm): 9; uT3 (>5 cm): 3 and uT4: 2. Positive lymph nodes were seen in 4 patients.

Results: In 5 out of 17 patients (30%) a higher stage was seen using MRI. In three cases the stage was changed from T1/2 up to T3 and therefore