the limited proteolysis of IGF Binding Protein-3 (IGFBP-3) increases the tissue bioavailability of IGFs, in response to a catabolic stress. The aim of this prospective study (2 years), in 14 colorectal cancer patients was to assess if postoperative induction of IGFBP-3 protease activity may be a prognostic marker of metastatic progression.

Methods: Serum samples were taken before (J0) and after (J6) surgery and analyzed by Western Blot.

Results: Before surgery, we observed a strong increase in IGFBP-2 (+340%) associated to a slight decrease in IGFBP-3 levels whereas IGFBP-3 protease activity was not significantly altered. After surgery, two different profiles were noted: a/ in 7/14 patients, we observed an expected catabolic profile with induction of IGFBP-3 protease activity associated to diminished IGFBP-3 and increased IGFBP-2 concentrations. No metastatic disease was observed in this group. b/ in 7/14 patients, no significant proteolytic mobilization of the IGF system was observed. 4/7 patients had a progression. We hypothesize that such a metabolic anergy could be related to the postoperative persistence of cancer cells that released an IGFBP-3 protease inhibitor. Such an inhibitor was indeed found in conditioned medium from HT29-D4 human colon cancer cells.

Conclusion: Assessment of IGFBP-3 protease activity in postoperative serum might be an useful early prognostic factor of metastatic progression in colorectal cancer patients.

749 POSTER

Diagnostic and prognostic significance of protein patterns in human epithelial cancer

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To improve results of surgical therapy of human epithelial tumors, new diagnostic, prognostic and therapeutic markers are necessary. Available staging systems (e.g. TNM-system) are clinically useful but show severe limitations in defining the prognosis of a particular patient. New approaches, close to the clinical reality, relying on phenotypic patterns are emerging. These markers can be searched by differential display techniques at DNA (PCR), RNA (RAP-PCR) or protein (high-resolution 2-dimensional polyacrylamide electrophoresis) level. The accuracy of such phenotypic comparisons between pathological and normal tissues depends on the purity of the samples.

We have developed techniques of preparation of pure epithelial cell samples from fresh operation specimens without any enzymatic digestion.

Using these techniques, followed by denaturation, gel running, protein microsequencing and immunoblotting, a protein map (master) of the normal colonic mucosa was defined with over 50 reference landmarks and will soon be available on the Internet (http://www.expasy.ch) and can be matched with pathological patterns obtained with these reproducible techniques.

750 POSTER

Safety of adjuvant mAb 17-1A in colorectal cancer (CRC)

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Purpose: Monoclonal antibody (mAb) 17-1A (edrecolomab) has reduced distant metastases and mortality as adjuvant treatment in CRC Stage III (Riethmüller et al , Lancet 343, 1994; Proc. ASCO 15, 1996). After German marketing authorization, a surveillance trial started in 1995 to monitor safety in clinical use.

Methods: 277 patients (52% male, 48% female; age 64 y [35–85]; Stage [I–IV]: 1.5, 19.4, 72.5, 6.6%) were treated with 17-1A.

Results: 142 pts (51.3%) showed no adverse effects. 103 pts (37.3%) developed toxic effects grade 1–2; 21 pts (7.6%) grade 3 and 11 pts (4%) grade 4, requiring discontinuation of 17-1A and symptomatic treatment with full recovery. No lethal toxicity was observed.

WHO-grades (% patients)	0	1	2	3	4
Nausea	79.8	12.3	6 1	1.8	–
Vomiting	92.1	4.7	2.5	0.7	–
Diarrhoea	69.3	13.7	12.3	2.9	1 8
Abdominal pain	81 2	11.9	3.6	2.5	0.7
Flush/Erythema	91.7	4.0	2.5	1.1	0.7
Anaphylactic reaction	97 1	0 7	1.1	0.4	0.7

Conclusion: Adverse effects were predominantly mild to moderate with the exception of a minority of pts (11.6%) developing grade 3–4 gastrointestinal or anaphylactic reactions. Toxicity observed in this large cohort is in accordance with previous reports and underlines the favourable safety profile of 17-1A.

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751 POSTER

Adjuvant chemotherapy of Dukes C colon carcinoma: Comparison of 5-FU + levamisole (LEV) 12 months vs. 5-FU + folinic acid (FA) 12 months VS 5-FU + FA 6 months

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Purpose: Postoperative chemotherapy has been established for stage III (Dukes C) colon cancer. Currently, treatment with 5-FU and LEV for 12 months is still considered standard outside clinical studies. However, optimal duration of therapy and biomodulation of 5-FU with FA might improve adjuvant treatment.

Patients and Method: From 1993 until 1996 116 patients with surgically resected colon cancer (Dukes C) were randomly assigned to A) standard therapy with 5-FU + LEV for 12 months, B) FA 100 mg/m^2 + 5-FU 450 mg/m^2, day 1–5 every 4 weeks for 12 cycles and C) 5-FU + FA 6 cycles respectively.

Results: After a median follow-up of 3.2 years no significant difference concerning disease free survival (p = 0.7) and survival (p = 0.6) was observed. Toxicity among the 3 groups is similar. However, a trend for more pronounced gastrointestinal toxicity under treatment with 5-FU + FA is observed.

Conclusion: In accordance with recently presented results of other studies, the preliminary data of this trial indicate that adjuvant treatment with 5-FU + FA for 6 months may be as effective as treatment with 5-FU + LEV for 12 months.

752 POSTER

Brain metastases from colon- and rectumcarcinoma

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Purpose: We analyzed 20 cases with respect to pattern of spread and prognosis after radiotherapy (RT) or neurosurgery plus radiotherapy.

Methods: 14 patients were treated with RT (30–60 Gy), 6 with neurosurgery plus radiotherapy (OP + RT, 30–40 Gy). All had advanced primary tumors (T3, T4), most of which were poorly differentiated; lymph node metastases were common. In 5 cases the brain was the first site of distant metastases. Ten patients had a solitary brain metastasis.

Results: Results of OP + RT were superior to those of RT, with respect to palliation of symptoms as well as to local tumor remission and survival. Overall median survival was only 51 days (1-year survival rate 6%). In 5 of 14 cases symptomatic improvement was observed after RT. Partial remission of the brain metastases occurred in 3 of 14 cases. The presence of extracerebral metastases was the most important prognostic factor.

Conclusion: Selected patients considered to have a favourable prognosis may profit from combined treatment (OP + RT). Despite the short survival time, stereotactic irradiation should be evaluated as an alternative to conventional RT in the remaining patients because the palliative effect of RT was relatively disappointing.

753 POSTER

Pseudocontinent perineal colostomy following abdominoperineal resection: Technique and findings in 40 patients

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Purpose: This prospective study was designed to evaluate the morbidity and the functional results of pseudocontinent perineal colostomy with free flap of colic muscle following abdominoperineal resection.

Methods: Forty patients (26 men and 14 women) averaging 50 of age were given this type of treatment between February 1989 and February 1997 at the Gustave-Roussy Institute. Thirty-four patients presented with

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.

754 POSTER

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.

755 POSTER

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.

758 POSTER

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