Results: Median followup: 50 months. Overall survival: 71%, 5 years. Actuarial probability of pelvic relapse 10% 5 years. For pT0-1-2 the local control probability is 96% but T4 have a risk of local relapse of 26%. Local relapse at 5 years is 5% in pN0 but 42% for pN1-2. Overall survival at 5 years is strongly correlated with pN: 87%. pNO vs 36% for pN1–2. In 62% of patients a restorative surgery was possible with a 8% risk of fistula. Operative mortality was 2%. There was no grade 3 radiation late toxicity.

Conclusion: Accelerated preoperative RX limited to the posterior pelvis is well tolerated. It appears to decrease local pelvic relapse and may be to increase the chances of sphincter preserving surgery. Its role on survival is still debated.

731 POSTER

RANDOMIZED TRIAL OF IMMUNOMODIFIER THIABENDAZOLE IN COMBINATION WITH MITOXANTRONE. METHOTREXATE AND FLUOROURACIL CHEMOTHERAPY IN THE TREATMENT OF COLORECTAL CANCER

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A double blind randomized clinical study was started in 1987 on patients with advanced colorectal cancer. 49 patients have been treated with MMF chemotherapy consisting of mitoxantrone 6 mg/m^2, methotrexate 150 mg/m^2 followed by fluorouracil 1000 mg after one hour pause and two 400 mg tegafur or carmofur + citrovorum factor on the next day. Chemotherapy was repeated every 2 weeks except mitoxantrone every 4 weeks. Thiabendazole 200 mg or placebo were given twice daily on days 4–10 of chemotherapy. In the thiabendazole arm there are 2 complete responses, 6 partial responses, 13 stable diseases and 3 disease progression, when the corresponding numbers in the placebo arm are 2 CR, 3 PR, 11 St and 9 PD. Median survival in the thiabendazole arm is 11 months (1.5–66+) and in the placebo arm 6 months (1.5–60+). Three patients have survived over 3 years in both treatment arms. Two of the 3 patients in the placebo arm and 1 of the 3 patients in the thiabendazole arm have been treated with successful additional surgery. All these patients in both arms received either as a maintenance chemotherapy or as a second line chemotherapy daily carmofur + leucovorin. The treatment was tolerable. Grade 3–4 toxicity was not encountered. MMF proved to be efficient in colorectal cancer. 27% of patients responded. Thiabendazole proved to be a safe and nontoxic immunopotentiator. More studies are warranted to evaluate its efficacy in the treatment of colorectal cancer.

732 POSTER

MODULATION OF WEEKLY HIGH DOSE INFUSIONAL 5-FLUOROURACIL (FU) BY LEUCOVORIN (LV), α-INTERFERON (IFN) OR LV PLUS IFN IN ADVANCED COLORECTAL CANCER. RESULTS OF A MULTICENTER RANDOMIZED TRIAL OF THE AIO

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Since 7/92 236 patients (pts) have been randomized to receive FU 2.6 g/m^2 i.v. as 24 h infusion combined with LV 500 mg/m^2 as a 2 h infusion (A), or IFN 3 Mio U s.c. 3×/week (B) or LV plus IFN (C), repeated weekly ×6 with 2 weeks rest. A sequential analysis (J. Whitehead, 1993) for objective response was planned with $\alpha = 0.05/3$, $\beta = 0.2$ to detect a difference of $\sigma = 0.25$ or equivalence. After evaluation of the first 93 pts, randomization to arm C was stopped because of statistically equal response rates (RR) to arm A (A 39%, C 38%) but increased toxicity of C (no toxic death in A and B, 10% in C) (Ann Oncol: 4, 1995). Currently 195 consecutive pts are evaluable:

	NPat	Tox. 3/4°	RR	Resp.duration	TTP
FU_{24h}/LV	73	25%	39%	11.6 mo	6.8 mo
FU_{24h}/IFN	75	11%	22%	8.6 mo	3.8 mo
FU_{24h}/LV/IFN	47	23%	27%	9.3 mo	6.3 mo
p-value		n.s.	<.05	n.s.	<.0003

Diarrhea and mucositis were major toxicities (CTC). Median survival for all pts is currently 14.5 mo. *Conclusions:* Infusional FU/LV is superior to FU/IFN. IFN added to FU/LV does not improve the activity of FU/LV.

733 POSTER

RANDOMISED CLINICAL STUDY OF UKRAIN ON COLORECTAL CANCER

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Results from the National Cancer Institute (Bethesda, U.S.A.) showed that Ukrain (NSC 631570) has on human colorectal cell culture lines a more than 100-fold higher cytotoxic activity than broadly used 5-fluorouracil (NSC 19893). In the EORTC study Ukrain was toxic to the colorectal cell lane CXF. That date gave us the basis for the next clinical study. In a randomised study 108 patients with advanced colorectal cancer, average 61.2 years, were included. 54 patients were treated with Ukrain as monotherapy and 54 with 5-fluororacil. The therapy results (clinical, haematological, immunological, biochemical) show that Ukrain has favourable properties in the treatment of colorectal cancer and clearly show advantages in contrary to 5-fluorouracil. Stability of the disease was reached in 88.8% and only 27.7% in the control group. The pretreatment with Ukrain facilitated the operability of the patients. The malignotoxic action of Ukrain in the clinic is confirmed by the results of pathomorphosis that gives more possibilities in operative treatment and increases the survival rate. Ukrain is a new effective drug in the therapy of colorectal cancer.

734 POSTER

TISSUE LEVELS OF 5,10 METHYLENETETRAHYDROFOLATE AND TETRAHYDROFOLATE IN PTS WITH COLORECTAL CARCINOMA WITH OR WITHOUT PRETREATMENT WITH FOLINIC ACID OR 5-METHYLTETRAHYDROFOLATE

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The modulation of 5-fluorouracil (5-FU) with folinic acid (FA) has been established *in vitro* and in various clinical studies for the treatment of colorectal carcinomas. Although pharmacokinetics and metabolism of FA in serum are well established the dose of folinic acid is still debated. As only few data about tissue levels of the modulating metabolite of FA, 5,10-methylentetrahydrofolate (mTHF), in humans are available, we used the "tritium-release-assay", for evaluation of reduced tissue folate pools in mucosa, primary tumor, liver and liver metastases from pts with colon carcinoma with and without pretreatment with various doses of FA or 5-mTHF. Drugs were given i.v. as short term infusion just before surgery. So far, analysis has been completed in 68 pts (23 mucosa, 22 tumor, 11 liver and 12 metastases) without pretreatment as well as 22 pts after pretreatment with 200 mg/m^2 FA and 20 pts with 5-mTHF, respectively. In both treatment groups reduced folate pools in mucosa and primary tumor were expanded, 5-mTHF however was somewhat less effective than FA. Furthermore, mucosa and tumor tissue was obtained after pretreatment with low dose (20 mg/m^2) and high dose (500 mg/m^2) FA from 10 pts. each treatment group. These specimen are currently under investigation regarding combined pools of mTHF and THF, and data will be presented at the meeting. Supported by DFG grant Ku 753-1/2 and MEDAC GmbH.

735 POSTER

L-LEUCOVORIN (LLV) AS A MODULATOR OF 5-DAYS 5-FLUOROURACIL (5FU) IN ADVANCED COLORECTAL CANCER (ACC): HIGH DOSE (HD) VERSUS LOW DOSE (LD)

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LV has a defined activity in the biochemical modulation of 5FU so that in ACC LV + 5FU is superior to 5FU alone in term of objective response