with a two-field technique. The causes of death were cardiovascular in 16 cases, infectious in 24, pulmonary embolism in 5 and miscellaneous in 6 cases. Preoperative cardiovascular morbidity was an independent risk factor for postoperative death in both irradiated and non irradiated patients.

Conclusion: Preoperative radiotherapy in rectal cancer should be given with an optimised regimen, avoiding two-field techniques and extended fields. Patients with clinically significant cardiovascular disease should probably not be recommended this treatment.

699 ORAL

IMPROVED TREATMENT RESULTS IN RECTAL CANCER BY POSTOPERATIVE RADIOTHERAPY AND 5-FLUOROURACIL

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The purpose was to investigate whether a time-scheduled regimen of postoperative radiotherapy and 5-fluorouracil (5-FU) 30 min. before radiation could reduce local recurrence rate and improve survival in rectal cancer Dukes' B and C. 144 patients with rectal cancer Dukes' B and C were randomized to surgery alone or surgery combined with postoperative radiotherapy 46 Gy and bolus 5-FU. 136 patients were eligible. The treatment was well tolerated. After an observation time of 42–93 months, patients within the adjuvant treatment group had a cumulative local recurrence rate of 12%, compared to 30% in the surgery only group ($P = 0.01$). The 5-year recurrence-free as well as overall survival was 64% in the adjuvant group compared to 46% ($P = 0.01$) and 49% ($P = 0.05$), respectively, in the surgery group. *Conclusion:* The one month combination treatment improved treatment results in rectal cancer Dukes B and C, in terms of local and total recurrence rate and survival, without serious side effects. The timing of 5-FU and radiation is probably important.

700 ORAL

PHASE II STUDY WITH TOPOTECAN (T) ADMINISTERED AS A 21-DAYS CONTINUOUS INFUSION TO PATIENTS WITH COLORECTAL CANCER

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T is a watersoluble semisynthetic analog of camptothecin which exerts cytotoxicity during the S-phase of the cell cycle through specific inhibition of topoisomerase I. Preclinical data have indicated that T is more effective with prolonged exposure. The clinical feasibility of this concept was recently reported by Hochster *et al.* (J.C.O. 1009: 12; 553–559) using a 21-days continuous infusion (c.i.). We performed a phase II study with T 0.6 mg/m^2/d as a 21-days c.i. repeated every 28 days, in patients (pts) with metastatic colorectal cancer, not previously treated with chemotherapy. Dose reductions of 0.1 mg/m^2/d were performed if myelosuppression persisted beyond day 28. If no toxicity worse than grade 2 occurred dose increases by 0.1 mg/m^2/d were allowed. The starting dose was reduced to 0.5 mg/m^2/d after in 5/11 pts the second course was delayed. Response was evaluated every 2 courses according to the WHO criteria, toxicity was scored according to the CTC criteria. To date, 41 pts have entered the study. Patient characteristics included: 22 females, 19 males; median age 57 years (range 37–68); median WHO performance score 1 (range 0–2). Two pts were unevaluable; 39 pts assessable for toxicity up to now received a total of 94 courses, median 3 per pt (range 1–9). The main toxicity was myelosuppression, with neutropenia grade 3–4 occurring in 26% of courses, median nadir of ANC occurring on day 25 (range 8–35), and thrombocytopenia being, relatively mild with the nadir also on day 25. Despite this mild myelotoxicity treatment had to be delayed in 24 courses (26%) mainly because of prolonged myelosuppression. As prescribed by protocol treatment delays mandated dose-reduction in the subsequent course. As a result of this median dose intensity (mg/m^2/wk) decreased in the successive courses 1–9 from 2.62–2.62–2.62–2.1–2.1–1.92–2.1 to 2.1. In addition, a marked inhibition of the erythropoiesis was observed. Non-haematological disease effects were mild, nausea grade 1–2 occurred in 25 courses (26%), vomiting in 15 courses (16%), and asthenia and fatigue in 32 courses (34%). Alopecia being grade 2, except in one, was seen in 8 pts (20%). Steady-state (Css) levels of T were determined by HPLC during the first 2 courses and varied widely: 0.65 ± 0.15 ng/ml (range 0.37–0.91, N = 15). No significant correlation was found between Css and absolute dose. In the 30 pts presently evaluable for response 1 CR and 2 PRs were observed. In conclusion, this dosing schedule is relatively well tolerated but has only modest clinical activity in colorectal cancer.

701 ORAL

'TOMUDEX' (ZD1694) HAS A HIGHER RESPONSE RATE, SIGNIFICANTLY LESS LEUCOPENIA AND MUCOSITIS AND A SIMPLER DOSING REGIMEN THAN 5-FLUOROURACIL (5-FU) AND LEUCOVORIN (LV) FOR ADVANCED COLORECTAL CANCER (CRC): FIRST RESULTS OF A PHASE III STUDY

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'Tomudex' (T) (ZD1694) is a direct and specific thymidylate synthase (TS) inhibitor. From November 1993, 439 patients (pts) with previously untreated advanced CRC were randomised in a Phase III trial to either (T) 3 mg/m^2 iv given 3 weekly (n = 222) or to LV 20 mg/m^2 plus 5-FU 425 mg/m^2 given 4–5 weekly (n = 212) on 5 consecutive days. Five pts did not receive protocol therapy. Pts were evaluated weekly for toxicity and 12 weekly for objective response. The median follow-up was 5.3 months. The response rate was higher for pts receiving (T) (20%) than for those receiving 5-FU-LV (13%) ($P = 0.059$, odds ratio 1.7, 95%CI 0.981 to 2.818) indicating that pts receiving (T) were approx 1.7 times more likely to respond. There was no evidence of a statistical difference between (T) and 5-FU-LV for time to progression or survival. (T) was associated with statistically significantly lower incidences of grade 3 and 4 leucopenia and mucositis ($P = <0.001$) and statistically significant higher incidence of increased transaminases, although the latter were generally reversible and self-limiting. Slightly more pts in the (T) group demonstrated an improvement in performance status and weight gain. (T) pts spent less time in hospital for dosing visits and the simpler dosing regimen offers the opportunity for economic benefits of reduced number of outpatient visits, pharmacy time and resource and pt travel costs. (T) therefore appears to be at least as effective as standard therapy for advanced CRC, but has a higher response rate, provides equivalent palliative effects and offers a more convenient administration schedule requiring less time in hospital.

'Tomudex' is a trademark, the property of ZENECA Limited.

702 ORAL

RANDOMIZED PHASE III TRIAL COMPARING 5FU BOLUS AND LOW DOSE LEUCOVORIN VERSUS 5FU BOLUS PLUS CONTINUOUS 5FU INFUSION AND HIGH DOSE LV IN METASTATIC COLORECTAL CANCER

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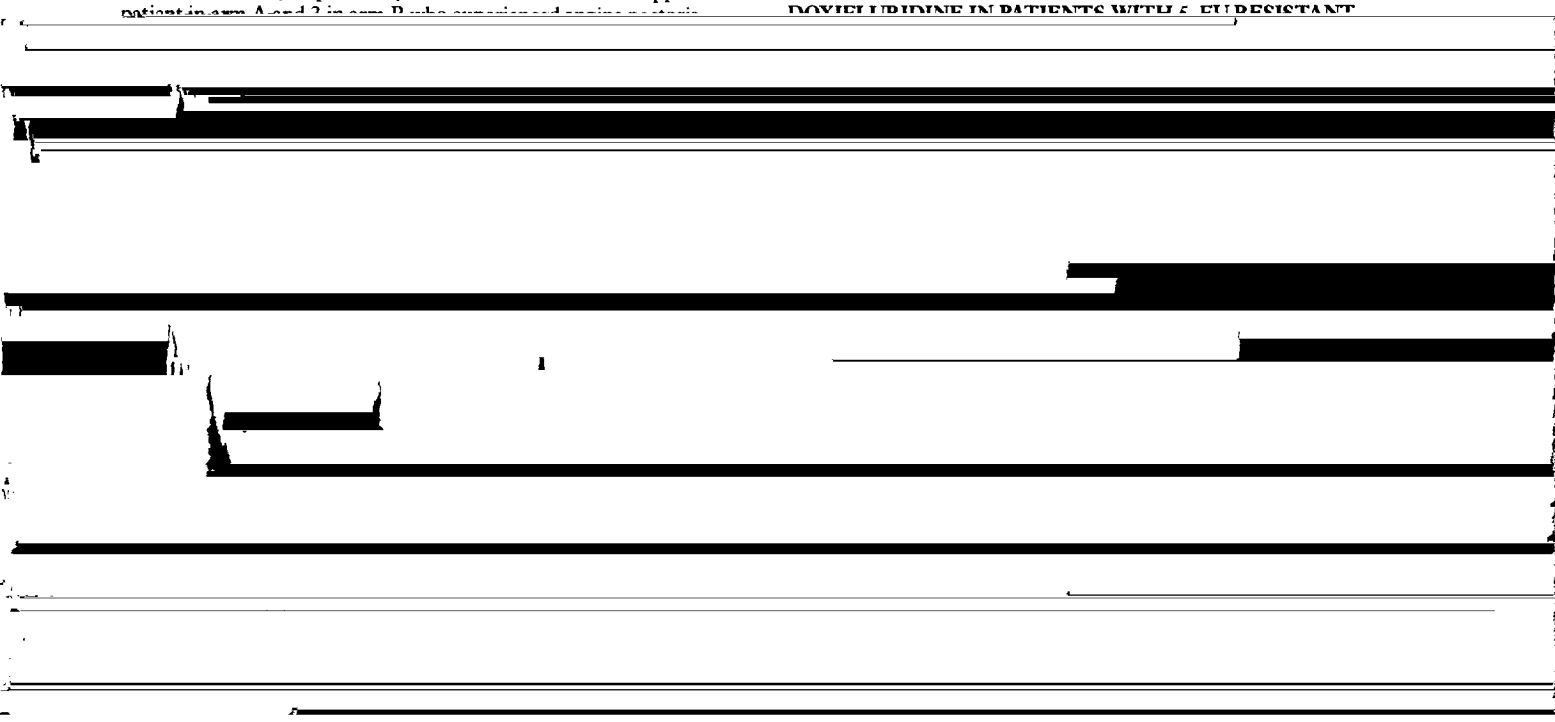
Monthly 5 day course of 5FU bolus infusion with low dose Leucovorin (FUFOL 1d) has the best therapeutic index for 5FU modulation in metastatic colorectal cancer.

Delivering 5FU protracted continuous infusion has also a better index than 5FU bolus. The bi-monthly combination of 5FU bolus followed by 5FU continuous infusion and high dose (LV 5FU2) has show a good efficacy with low toxicity in several phase II studies. The current study compares FUFOL1d and LV 5FU2.

From March 1991 until April 1994, 437 patients (pts), stratified according to performance status, presence of measurable disease, and synchroneous or metachroneous disease, were randomized to (A) FUFOL1d: IV bolus 5FU 425 mg/m^2 d1-5 with folinic acid 20 mg/m^2 IV d1-5 q 4 wk or (B) LV 5FU2: folinic acid 200 mg/m^2 2-hour infusion followed by IV bolus 5FU 400 mg/m^2 and 22-hour infusion FU 600 mg/m^2 d1-2 q 2 wk. Therapy was continued until disease progression and second-line chemotherapy including 5FU continuous infusion was allowed in both arms. Response rate (306 evaluable pts), progression-free survival (PFS) and overall survival (OS) are as follows:

Treatment	Pts	Response	Pts	PFS (wk)	OS (wk)
FUFOL1d	147	17%	218	22.8	57.2
LV5FU2	159	34%	219	29.5	61.4
		P = 0.002		*P = 0.008*	*P = 0.006*

41 pts (21.5%) experienced grade 3–4 toxicities in arm A versus 18 pts (9.2%) in arm B, $P = 0.0004$. grade 3–4 toxicities (%) were in arm A: neutrophils 7.9 platelets 1, nausea 2.6, diarrhea 4.7, mucositis 9.9, alopecia 1, skin 0.5 and in arm B: neutrophils 2, platelets 0.5, nausea 3.1, mucositis 1.5, alopecia 0.5, skin 0.5. Treatment was stopped in one patient in arm A and 2 in arm B who experienced angina pectoris.



We conclude that the bi-monthly combination of 5FU bolus and continuous infusion with high-dose folinic acid is more active and less toxic than monthly 5 day course of bolus 5FU with low dose Leucovorin.

703 POSTER

CRYOSURGERY OF NON RESECTABLE MALIGNANT LIVER TUMOURS

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The aim of this study was to determine the real place of cryotherapy in the therapeutic strategy of liver tumours. From Oct 1993 to July 1994, 41 patients (pts) have been treated by cryotherapy at our institution, either as a single treatment (Group 1–11 pts), as combined with partial resection (Group 2–19 pts) or as complementary to a complete resection with no sufficient margin of normal liver around the tumour (Group 3–11 pts). There were 7 hepatocellular carcinomas all with underlying cirrhosis, 25 metastases of colorectal cancer and 9 metastases of other malignant tumours. We used the LCS 2000 device (Cryogenic Technology) designed specifically for hepatic cryotherapy. There were 2 per-operative complications related to the procedure: 1 rupture of the tumour and 1 perforation of the liver capsule, both easily controlled by suture. Operative mortality within 2 months was 2.4% (1/41), unrelated to cryotherapy (cardiac infarct at day 3). Serum transaminases increased post operatively in relation to the duration of cryotherapy and the number of treated lesions (Mean maximum value AST: 799 IU/L (Range 78–2541), ALT 802 IU/L (Range 106–1902)). They normalized within 5 days. In Group 1 (Cryo alone), a reduction of tumour size was observed in 4 pts (36%), with disappearance of a treated lesion in one case. Tumour markers were decreased in 3/4 pts with preoperative increased levels. In Group 2 (Cryo + Resection), a reduction in cryotreated tumour size was observed in 6 pts (32%). Decreased tumor markers were demonstrated in 4 cases (21%). In Group 3 ("Adjuvant" cryotherapy), no tumor recurred at the site of cryotherapy. When increased, tumor markers decreased in all cases. Overall, the main determinants of recurrence following cryotherapy were maximum tumour size >5 cm and number of lesions >3.

Conclusion: Cryotherapy is a simple and safe procedure. Objective criteria of anti tumoral effects are demonstrated but need confirmation with a longer follow-up. Selection of pts should exclude all those with large multinodular tumours.

704 POSTER

LOCAL EXPRESSION OF CYTOKINES IN HUMAN COLORECTAL CANCER

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5-FU is considered the most active drug in metastatic colorectal cancer, but many pts do not respond to this treatment and some even progress, so the development of a second line therapy is an important aim. We set out to determine the activity of oral and i.v. doxifluridine (5-dFUR), a fluoropyrimidine synthesized by Cook in 1976, in pts with metastatic or advanced measurable colorectal cancer who had previously received a 5-FU based regimen at an adequate total dosage (no less than 3700 mg/m^2). Only 48 of the 118 pts treated with 5-dFUR were considered 5-FU resistant according to our strict criteria of documented tumor progression during 5-FU therapy (adjuvant setting or metastatic line) or within 8 weeks of the last administration. The 48 pts received: either 5-dFUR 3000 mg/m^2 as a one hour i.v. infusion on combined with levo-leucovorin 25 mg/dose i.v. days 1→5 every 3 wks (14 pts) or 5-dFUR 6000 mg/m^2 p.o., for 5 days every 10 days and levo-leucovorin 25 mg/dose 2 hrs before 5-dFUR (34 pts). The characteristics of the pts were: M/F 26/22; median age 56 yrs; PS 0–1/2: 34/14. The WHO response rates were 12% PR (4/34) in the group treated per os, and 29% (4/14) in the group treated i.v. The median duration of response in the p.o. and i.v. group was respectively 6 (range 3–11+) and 5 mos (range 3–5+). Responses were achieved by pts pretreated with a median of 9250 mg/m^2 (range 3700–18650) of 5-FU. No WHO grade IV toxicity was observed, whereas grade III diarrhea in 15% of the orally treated group in 15% and 25% of the i.v. group. The encouraging response rate seems to suggest that 5-dFUR is an effective and well tolerated second line therapy for 5-FU resistant colorectal cancer. The incomplete clinical cross-resistance between 5-FU and 5-dFUR has prompted us to plan a further cross-over study to verify this observation. *Data management by I.T.M.O. (Italian Trials in Medical Oncology) Scientific Service.*

706 POSTER

CLINICAL POLYMORPHISM AND GENETICAL HETEROGENEITY OF COLON CANCER (CC)

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For the past years the role of heredity in predisposition to the CC and its