metastases from colon carcinoma (8 pts) and rectum carcinoma (14 pts) with the combination of continuous infusion of FUDR 0.20 mg/kg/day + LV 7.5 mg/m$^2$/day + 20 mg on days 1–14 and bolus MMC 10 mg/m$^2$ on day 1 via hepatic artery. Cycles were administered every four weeks. Patients characteristics were as follows: (M/F: 17/5), median age 61.5 years (range 43–75), median PS 0. 18 pts were pretreated with systematic chemotherapy including 5-FU + LV. Total number of cycles was 91 with a median of 6 cycles for patients (range 1–10). 16/22 pts are evaluable for response (6 pts are not evaluable: 3 too early and 3 died before the first clinical evaluation); 1 CR (in a pt pretreated with adjuvant chemotherapy), 9 PR (4 in pts pretreated with systemic chemotherapy for metastatic disease, 4 in pts pretreated with adjuvant chemotherapy and 1 in a chemotherapy-naive pt), 2 MR, 2 SD and 1 progression; the overall response rate is 62.50% (C.I. 35.4–84.8). Median time to progression is 6 months (range 2–15+). Overall median survival is 6 months (range 1–19+). 22/22 pts are evaluable for toxicity (WHO) as reported below:

| | grade 1–2 N° (%) | grade 3–4 N° (%) |
|---|---|---|
| nausea/vomiting | 9 (40.9) | 1 (4) |
| diarrhea | 13 (59) | 5 (22.7) |
| bilirubin | 1 (4) | 1 (4) |
| AST-ALT | 12 (54.5) | 0 |
| leukocytopenia | 5 (22.7) | 0 |
| thrombocytopenia | 1 (4) | 3 (13.6) |

The study continues to accrue pts to better define the response rate and the toxicity of this regimen.

712 POSTER

## RESECTION OF NON COLORECTAL HEPATIC METASTASES: LONG TERM RESULTS

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The aim of this multicentric retrospective study was to evaluate survival after resection of non colorectal hepatic metastases (HM).

*Patients and Methods*—Between 1976 and 1990, 91 patients underwent resection of 60 synchronous and 31 metachronous non-colorectal and non-endocrine HM. The most common sites of the primary tumor (PT) were: stomach (n = 16), breast (n = 14), lung (n = 8) and exocrine pancreas (n = 7). The most common histopathologic types were adenocarcinoma (n = 42) and squamous cell carcinoma (n = 15). The surgical procedures were: 20 wedge resections and 71 radical hepatectomies.

*Results*—Resection was curative in 77% of the patients. Operative mortality was 1%. There were seven biliary fistulas and 11 septic complications. Half of the patients underwent adjuvant chemotherapy. Cumulative survival following curative resection was 54% at 1 year, 40% at 2 years, 32% at 3 years and 26% at 5 years. After palliative resection, survival was 33% at 1 year. Survival was not influenced by the time elapsed between resection of the PT and resection of the HM. There was no significant difference in survival between synchromous versus metachronous liver metastases, or according to the site of the PT. Wedge resection was as effective as lobectomy.

*Conclusions.* Surgical resection of HM in patients with PT other than colorectal cancer is advocated: postoperative morbidity and mortality are low; when resection is performed with curative intent, survival is similar to that obtained after resection of colorectal HM.

713 POSTER

## REGIONAL CHEMOTHERAPY IN THE COMBINED TREATMENT OF RECTAL CANCER

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Patients with rectal cancer (RC) were administered preoperative selective intraarterial polychemotherapy (IASP) in the combined treatment for maximum devitalization of tumor tissue and better survival. 135 patients (pt) were stratified into three groups: (1) surgery alone—75 pt, (2) systemic polychemotherapy prior to surgery—eight pt, (3) surgery after IASP—52 pt. Preoperative systemic polychemotherapy did not improve 3-year survival compared to patients treated with surgery alone. Selective IASP respectively with subsequent surgery improved 3-year survival by 13.6% (from 59.4 + 3.8% to 73.0 + 5%, $P$ 0.05). Thus, IASP resulted in a significantly better prognosis for patients with RC compared to surgery alone and in combination with preoperative systemic polychemotherapy.

714 POSTER

## PROTRACTED 5-FLUOROURACIL INFUSION (5FU-PI) WITH WEEKLY LOW DOSES OF FOLINIC ACID (FA) IN METASTATIC COLON CANCER (MCC)

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A high response rate (RR = ±60%) has been reported in MCC with 5FU-PI (200 mg/m$^2$/day) modulated by weekly FA low doses (20 mg/m$^2$) (Leichman *et al.*, ASCO 1990). We used the same drug schedule in 8 consecutive patients with evolutive MCC (M/F 1:1; age: 61 ± 5 y; mainly liver metasases). A subcutaneous port system was implanted and 5FU was delivered with an ambulatory Pharmacia CADD-1 pump. Treatment was administered until progression or grade 3/4 toxicity. After the 1st 4-week cycle, 3 PD and 4SD were documented. 1 patient withdrew for intolerable GI toxicity. A mean of 3.25 courses (<1 to 6) was given. Only one patient had a documented PR after the 3rd cycle but relapsed within 2 months (RR = 12.5%). Survival was 11, 18, 18, 20, 25+, 31, 32, 60 weeks. All deaths were due to MCC. No complication occurred with the infusion system. We observed the following toxicity grades: Hematology gr0:8; Nausea grI:2; Stomatitis grI:1, grII:2; Diarrhea grII:1, grIII:1, grIV:1; Epistaxis grII:1; Hand-foot syndrome grI:1, grIII:1; Myalgia grI:1, grII:1. One patient had 1 episode of angina pectoris during treatment. The high RR as initially reported by Leichman could not be confirmed and this treatment was associated with significant non-hematological toxicities.

715 POSTER

## FLUOROURACIL (5-FU) AND LEVO-FOLINIC ACID (LFA) IN ELDERLY PATIENTS WITH ADVANCED COLORECTAL CANCER: ACTIVE AND SAFE COMBINATION?

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In 36 patients (pts) (22 males, 14 females) older than 65 years (66–81, mean 72.5), P.S. 0–2, suffering from colon cancer with metastasis or inoperable relapses, systemic chemotherapy (CT) according with Machover (1986) scheme was administered. The schedule was: from day 1 to day 5: LFA 100 mg/sqm + 5-FU 370 mg/sqm. in bolus infusion, every 28 days. Metastatic sites were: 11 pts 1 site, 17 pts 2 sites, 8 pts 3 or more sites. The total number of cycles administered was 207 (mean 5.7, median 5).

Therapeutic results and toxicity (WHO, Cancer 1991: 47:207) were: 1 C.R., 5 P.R., 18 N.C., 12 P.D. (P.R. + C.R. = 15%). No life threatening toxicity were recorded: Nausea and vomiting G 3, 11 pts; Diarrhea G 3, 2 pts; G 2, 7 pts; Mucositis G 3, 4 pts; G 2, 3 pts; Leucopenia G 1, 1 pts; Hand foot syndrome, 3 pts.

Overall survival has been 11.6 months (4–23+), with a median of 9 months. The conclusion of this study must be resumed as follows:

(a) The combination of LFA and 5-FU in 5 days schedule is feasible in elderly pts;

(b) Mild toxicity has been recorded, no extreme grade toxicities were seen;

(c) The number of clinical responses seems to be lower than in younger pts (19% in our series);

(d) The real impact of this or different treatment in old patients must be investigated in larger series including different types of CT.

716 POSTER

## OXALIPLATIN WITH HIGH-DOSE FOLINIC ACID AND 5-FLUOROURACIL 48 H INFUSION IN PRETREATED METASTATIC COLORECTAL CANCER (CRC)

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We report a phase II study in pretreated CRC. Regimen (FOLFOX2) was administered every two weeks. It consisted of oxaliplatin 100 mg/m$^2$ iv day 1; FA 500 mg/m$^2$ over 2 h, followed by 5FU 1.5–2 g/m$^2$ 24 h CI days 1&2. Initial 5FU dose was 1.5 g/m$^2$ for two cycles and increased to

2 g/m$^2$ in case of no toxicity > grade 2. 40 pts have been evaluated: 25 M/15 F, mean age 60 yrs, liver metastasis 33 pts, lung 11, peritoneal 4, other 11, multiple 13, performance status (WHO) 0: 20, 1–2: 20. Previous chemotherapy consisted in different optimal FA-5FU modulations ± hydroxyurea. 16 previously received the same high-dose FA and 5FU CI regimen alone or with interferon-α. All pts had disease progression on first-line therapy for metastatic disease or < 6 months after adjuvant therapy. One CR, 18 PR (response rate 49%), 17 stable (44%), and 3 prog. (8%) were observed (1 non-evaluable pt). Nine pts who progressed on the same high-dose FA and 5FU CI regimen responded (56%). From start of FOLFOX, median PFS was 9.6 mths, 12-mth median survival 65%. WHO toxicity ⩾ grade 2 was: acro-syndrome or neuropathy 28% pts (g 3: 8%), nausea 28% (g 3: 3%), diarrhea 36% (g 3: 8%), mucositis 31% (g 3: 11%), neutropenia 42% (g 3–4: 28), thrombopenia 17% (g 3–4: 8%), alopecia 28% (g 3: 8%), allergy 3%. 17 pts (42%) experienced grade 3–4 toxicity. This high-dose intensity schedule achieves a high response rate in pretreated metastatic CRC even in pts who had received the same high-dose FA and 5FU CI regimen. Limiting toxicities are neutropenia and neuropathy.

717 POSTER

## DOES HIGH-DOSE PRE-OPERATIVE RADIOTHERAPY ALTER THE STRENGTH OF COLON ANASTOMOSIS IN RATS?

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The purpose was to study the effect of pre-operative radiotherapy on the strength of colon anastomosis, constructed of one irradiated and non-irradiated segment, as well as the difference between a conventional and a hyperfractionated radiation treatment.

Groups of 15 animals were treated with conventional (2.0 Gy/day to total doses of 40.0, 60.0 or 80.0 Gy) or hyper-fractionated (1.6 Gy, 2×/day to total doses of 41.6, 60.8 or 80.0 Gy) radiotherapy and compared to control and sham treated groups. The strength of the colon anastomosis (constructed the day after ending the radiotherapy) was measured by a bursting experiment. End results were bursting pressure (BP) and bursting wall-tension (BWT).

There was no significant difference in BP or BWT between the irradiated animals and the control groups.

We conclude that high-dose pre-operative radiotherapy to one end of a colon anastomosis does not affect its anastomotic strength.

718 POSTER

## PREOPERATIVE VERSUS POSTOPERATIVE RADIATION THERAPY FOR RESECTABLE RECTAL CANCER

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*Purpose:* To compare the results of preoperative and postoperative radiotherapy in adenocarcinoma of the rectum in terms of survival and control of disease.

*Patients and Methods:* From 1989 to 1993, 52 patients with clinically operable rectal cancer were treated in our department: 25 patients in Group I (pathologic stage B2, B3 or C) received postoperative radiotherapy 50 Gy, and 27 patients in Group II received preoperative radiotherapy 30 Gy. All patients had a Karnofsky index greater than 60% and no evidence of distant metastases.

*Results:* With a median follow-up of 40 months, the overall 5-year actuarial survival was 75% in Group I and 83% in Group II, and the 5-year disease-free survival 52% and 83% respectively ($P = 0.025$). Pathologic complete response was found in one case in Group II, and preservation of the anal sphincter was possible in an increased number of cases (16 patients) in this group.

*Conclusions:* We observed better results with preoperative radiation therapy and would recommend this treatment for rectal carcinoma.

719 POSTER

## DOXIFLURIDINE IN ADVANCED COLORECTAL CARCINOMA. PARALLEL MULTICENTRE RANDOMIZED PHASE II TRIAL

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Doxifluridine (5-dFUR) is a fluoropyrimidine derivative with a better therapeutic index than FU (Bajetta, *Eur J Cancer*, 1993). This study independently evaluated the activity of two different schedules of oral or i.v. 5-dFUR plus levo-leucovorin. Between April 1993 and September 1994, a total of 130 untreated (in an adjuvant and metastatic setting) pts with measurable colorectal cancer were randomized to 5-dFUR 750 mg/m$^2$ p.o. on days 1→4 and levo-leucovorin 25 mg/dose p.o. two hours before 5-dFUR, repeated every 12 days (Arm A); or 5-dFUR 3000 mg/m$^2$ as a one hour i.v. infusion for 5 consecutive days combined with levo-leucovorin 25 mg/dose i.v. immediately before 5-dFUR every 21 days (Arm B). The first response evaluation was made after 2 mos of treatment. The two arms were well balanced in terms of age (median 61 yrs, range 31–80), sex (M/F: 69/61) and disease extension. A preliminary intent-to-treat analysis was made of 126 adequately treated pts (4 too early to evaluate), of whom 67 were in Arm A and 59 in Arm B. The response rates were 15% in Arm A (2 CR, 8 PR, 29 SD, 28 PD) and 39% in Arm B (5 CR, 15 PR, 15 SD, 21 PD). Toxicity included WHO grade 3 and 4 diarrhea in respectively 16% and 7% of Arm A and 16% and 15% of Arm B respectively. Mucositis was mainly observed in Arm B (grade 3 in 13% and grade 4 in 1%). The preliminary data confirm the good tolerability profile of both the oral and the i.v. schedule. The oral route seems to be promising and is interesting, because it could be benefit for pts suitable for home treatment. Moreover, this study confirms the efficacy of i.v. doxifluridine as a fast line therapy in advanced colorectal cancer. *Data management by I.T.M.O. (Italian Trials in Medical Oncology) Scientific Service.*

720 POSTER

## 5-FLUOROURACIL (FU) AND LEVAMISOLE (LEVA) VERSUS FU, LEVA AND 6-S-LEUCOVORIN (6-S-LV): AN ITALIAN INTERGROUP STUDY OF ADJUVANT THERAPY FOR RESECTED COLON CANCER (B2-C)

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In order to determine whether the addition of 6-S-LV to the combination FU + LEVA reduces the rate of recurrence and prolongs DFS and OS in patients with radically resected colon cancer, Dukes' stage B2–3, and C we conducted a large scale randomized clinical trial accruing patients from five Italian cooperative groups. After stratification for center, treatments were as follows: ***arm A, 5FU 450 mg/sqm iv d 1–5 + LEVA 150 mg po d 1–3; arm B, 6-S-LV 100 mg/sqm iv d 1–5, FU 370 mg/sqm iv d 1–5 + LEVA*** *given as arm A.* In both arms courses were repeated every 28 days × 6 cycles. A minimum sample size of 725 pts. per arm was set to ensure an 80% probability ($\alpha$ *error* .05) of detecting a 20% reduction in overall mortality at 5 yrs, calculated on the basis of the experimental group. The study was activated in March 1992 and was closed in February 1995, 1827 pts. were accrued with a monthly accrual of 51 pts. At December 1994, 54% of these pts were men and 46% women with median age 63 yrs (range 26–84) and median PS 0 (0–1). Forty-seven percent had B2–3 Dukes while 53% C. The sites of the resected tumors were: ascending colon (29%), transverse (16%) and descending (55%). There were 4 toxic deaths: 1 in the arm with LV (diarrhea with dehydration) and 3 in the control arm (neutropenia-related septic shock diarrhea with dehydration). Severe toxicity (gr 3–4 WHO) was observed in 18% of pts. in arm A and 31% in arm B.

(Supported by CNR grant ACRO 93.02333.PF 39).