weeks). Seventy-nine pts were treated with a 2-field technique, 66 pts with a 4-field technique and 2 pts with a direct perineal field. Median treated volume was 4.4 liters (1.2–9.4). One hundred and twenty pts were treated with X25 MV, the other 27 pts with 1.25 Mev ^{60}Co. All irradiated rectal tumors have been reanalyzed by the same pathologist in order to quantify tumor sterilization. Three groups were individualized according to the residual tumor cell density (RTCD): absence or low, intermediate and high.

All pts underwent surgery in a median delay of 4 weeks. Fifty-five tumors (37%) showed no (9/147) or low (46/147) RTCD; 51 (35%) showed an intermediate RTCD and 39 (27%) a high RTCD. The distribution of the pts according to age, tumor stage, tumor location, delay before surgery and RT parameters (total dose, fractionation, duration of treatment, 2 or 4-field technique, treated volume, X25 MV or 1.25 Mev ^{60}Co photons) was not statistically different in the 3 groups. Five-year actuarial survival rates were 100% in the group of pts with no RTCD, 54% in the group with low RTCD, 44% in the group with intermediate RTCD and 53% in the group with high RTCD. The difference did not reach significance, probably because of the small number of sterilized tumors. These results suggest however that tumor sterilization is a favorable prognostic factor after preoperative RT in rectal cancer.

708 POSTER

IL-8 INVOLVEMENT IN IMMUNE DISREGULATION OF CANCER PATIENTS

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The mechanisms for the recruitment of immune cells to sites of inflammation have not been fully elucidated. In order to understand the mechanisms of IL-8 a potent chemotactic and activating chemokine, during immune response, we examined in colon cancer patients and controls, serum levels of IL-8, IL7, IL-6, IL-4, TNF-α, IFN-γ IL-2, sIL-2R: IL-8 production in supernatants of PBMC with and without activation agents: PBMC phenotype (CD3, CD4, CD8, CD16, CD56, CD57, CD25): PBMC proliferative responses to IL-2, IL-4, anti-CD3. Our results show that IL-8 serum levels in patients (p) were higher than in controls (c) (n.p = 65, n.c = 51 $P = 0.007$) and this was significant only at stage II (n.p = 25 n.c = 51 $P = 0.01$) and III (n.p = 8 n.c = 51 $P = 0.03$). It is of great interest to note that our preliminary data of IL-8 production from: PBMC (n.p = 14 n.c = 4 $P = 0.0002$), plus PHA (n.p = 15 n.c. = 3 $P = 0.008$), plus anti-CD3 (n.p = 3 n.c = 3 $P = 0.03$) show that levels in patients are significantly lower than in controls. Correlation between IL-8 serum levels and other serum cyokines evidenced no significant values, but at stage I (n.p = 9 $P < 0.00001$), II (n.p = 23 $P < 0.00001$) and IV (n.p = 5 $P < 0.00001$) correlations with TNF-α levels were found. The phenotypic analysis showed only a positive correlation between IL-8 serum levels and CD8 expression (n.p = 34 $P = 0.01$). PBMC proliferative responses of patients showed no significant correlations with all examined agents. Analysing our data, it seems that in cancer patients there is a disregulation in IL-8 production. It is to note that in the serum, in this situation are involved the stage II and III, where principally are regulated the mechanisms for lymphonodal infiltration and host invasion. In this contest, the positive correlation between IL-8 and CD8 expression can be interesting information. So, our results support the hypothesis that IL-8 can be an active participant in the disregulation of immune response which allows the tumor to locate and progress in the host.

709 POSTER

COLON CANCER: SIL-2R AND CORRELATED MECHANISMS

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The current research has still not clarified why serum levels of sIL-2R increase in cancer patients. In order to establish whether this could be an independent event or there are correlated mechanisms, in colon cancer patients and controls we examined the level of this soluble receptor in correlation with phenotype of PBMC; serum levels of IL-6, TNF-α, IL-4, IFN-γ, IL-2; changes of HLA-I and HLAII antigen expression on tumor tissue respect to normal mucosa; PBMC proliferative response to IL-2, IL-4, anti-CD3. Correlations with the disease progression were evaluated. Our results show that sIL-2R level of patients (p) was higher than in controls (c) (n.p = 72, n.c = 79 $P < 0.0001$). There were no significant correlations between sIL-2R and the expression of CD3, CD4, CD8, CD16, CD56, CD57, CD25 antigens on PBMC of both patients and controls. In patients compared to controls, even if the serum levels showed an increase of IL-6 (n.p = 56, n.c = 49 $P = 0.0001$), IFN-γ (n.p = 73, n.c = 43 $P = 0.003$), IL-4 (n.p = 24, n.c = 33 $P < 0.0001$) and a decrease of IL-2 (n.p = 42, n.c = 27 $P < 0.0001$), sIL-2R level showed only a positive correlation with IL-4 (n.p = 19 $P = 0.033$). Moreover, from the evaluation of HLA antigens it is possible to note that when the expression of HLAI is the same in tumor tissue and normal mucosa (situation more often present at stage I: 66.7%), sIL-2R of patients was higher than controls ($P = 0.018$). With regard to the correlations with the proliferative response, merely a positive association with IL-2 plus anti-CD3 was determined (n.p = 29 $P = 0.013$). So, from our overall results, as IL-4 is produced by CD4$^+$TH2 cells and the anti-CD3 addition to IL-2 is well-known to be discriminant for the activation of these cells, it seems that the increase of sIL-2R in serum of cancer patients is an event dependent on CD4$^+$TH2 cells. This hypothesis is confirmed by the fact that when HLAI antigen expression was lower than normal, the HLAII antigens was higher, supporting an inflammatory situation.

710 POSTER

CANCER ESTABLISHMENT AND PROGRESSION

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Immunological evaluations on cancer patients provide informations to understand the disregulations which allow the tumor to locate and progress in the host. In colon cancer patients and controls we examined the serum levels of various cytokines and the proliferative response of PBMC to IL-2, IL-4, anti-CD3mAb. Our results show that in patients there was a significant serum increase of IFNγ, IL-4, IL-6, whereas IL-2 significantly decreases. This situation is indicative for the functional presence of inflammatory CD4$^+$TH2 cells. In patients it is possible to note a negative correlation between the proliferative response to IL-2 and stage of the disease ($^*P = 0.0024$), which changes into positive when anti-CD3 is added ($^*P = 0.007$) (indicative for a functional increase of CD4$^+$TH2 cells with the disease progression). Moreover in patients the proliferative response to IL-2 + anti-CD3 was comparable to controls ($\S P = 0.42$), whereas in the former there was a significant reduction after IL-4 addition ($\S P = 0.005$). This effect of IL-4 on IL-2 + anti-CD3 starts at stage II, whereas at stage I the response is still comparable to controls and there is a greater response to IL-2 alone ($\S P = 0.0035$). Analysing our data, it seems that the start of the immunological response in patients is of inflammatory type and it degenerates because IL-4, which raises with the disease progression, interferes with IL-2 mechanisms.

Serum levels	patients compared to controls				*stage correlations	
§ IFN-γ	n = 73	P = 0.003	n = 43	n = 63	r = 0.19	P = 0.14
§ IL-4	n = 24	P < 0.0001	n = 33	n = 24	r = 0.89	P < 0.0001
° IL-6	n = 56	P = 0.0001	n = 33	n = 55	r = 0.21	P = 0.12
° TNFα	n = 56	P = 0.1	n = 33	n = 51	r = 0.35	P = 0.014
§ IL-2	n = 42	P < 0.0001	n = 27	n = 41	r = −0.56	P = 0.0004

*Spearman rank correlations; §Student's t-test; °Mann-Whitney test

711 POSTER

INTRAHEPATIC CHEMOTHERAPY WITH FLOXURIDINE (FUDR) L-LEUCOVORIN (LV), DESAMETAZONE (D) IN CONTINUOUS INFUSION AND BOLUS MYTOMICIN C (MMC) IN HEPATIC METASTASES FROM COLORECTAL CANCER: A PHASE II STUDY

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Intrahepatic continuous infusion FUDR induces 50% response rate (RR) in patients (pts) with hepatic metastases from colorectal cancer (CRC). Lower RR are observed in pretreated pts. The combination of FUDR + LV has given over 70% RR with high hepatic toxicity. The use of D can decrease the hepatic toxicity. In a randomized study Kemeny *et al.* have observed an increase in RR and a decrease in hepatic toxicity in the group of pts treated with FUDR + D compared to the group receiving FUDR only. Moreover the combination of MMC, Carmustine and FUDR is effective also in pretreated pts. On these premises since July 1993 we have treated 22 pts affected by unresectable hepatic

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