(colon/rectum): A:43/36, B:51/26; metastatic sites (A/B): liver 61/62, lung 13/16, lymph node 15/14, multiple sites 39/35. Tumor response rates (CR + PR) were 23% in the FA-FU group (1 CR, 17 PR; 95% CI: 17%–32%), and 30% in the FA-FU + IFN group (5 CR, 18 PR; 95% CI: 20%–40%). No significant difference was found in overall response rate between the two arms. A total of 180 pts (A:88; B:92) are evaluable for toxicity; grade 3–4 toxicity (WHO criteria) were (A/B): leukopenia 2%/1%, diarrhea 8%/22%, mucositis 5%/12%, nausea and vomiting 2%/7%. Our preliminary results shown better response rate in FA-FU + IFN arm, but a more severe (grade 3–4) gastrointestinal toxicity.

740 POSTER

CYTOGENETIC ANALYSIS IN ADVANCED COLORECTAL CANCER

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We analyzed short term cultures from tumor material of 26 patients with advanced colorectal carcinomas. Clonal anomalies were found in 20 patients. Five tumors showed only slight numerical changes (+7, −Y in 2/5 pt). The remaining 15 tumors had highly complex karyotypes. Structural aberrations affected all chromosomes, except Y. The most frequently rearranged bands were 5q21, 7p15, 9p21, 13q11, 16p12, 17p13, 18q21, 21q11. Anomalies of chromosomes 5, 17 and 18 occurred concomitantly in 9/20 patients. Tumors of the proximal colon (n = 6) were with one exception diploid or near diploid and showed no particular pattern of aberrations. All patients with deletions of 17p (n = 6) had near tetraploid karyotypes with high cell to cell variability and a median of 9 structural aberrations ($P < 0.05$); 4 of them presented with parenchymal metastases. The tumor karyotypes of patients with hepatic metastases at the time of surgery (n = 6) revealed a trend to more numerical and structural aberrations (8 structural aberrations in median, versus 3). Changes involving 8p22 or loss of 8 were found in tumors of all parts of the colon and potentially associated with an unfavorable prognosis (4/6 deceased patients). A deletion in 16p12 was found in 4 patients with advanced tumors, three of them in patients with tumors of the proximal colon.

741 POSTER

BRAIN METASTASES IN COLORECTAL CANCER: AN UNUSUAL METASTATIC SITE. REPORT OF 15 CASES TREATED WITH RADIOTHERAPY

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From August 1991 to November 1994, we observed brain metastasis in 15 pts with colorectal cancer (CRC):4 Males/11Females, median age 59 y (43–69), CRC staging 7B, 4C, 4D. Treatment of the primitive tremor consisted with surgery (8 pts) plus chemotherapy (CT) (4 pts) or radiation therapy (RT) (3 pts). 12 pts developed non CNS metastases mostly, hepatic and/or pulmonary (9 pts). 3 pts had isolated CNS metastases. Median time to first metastasis was 18 months (0–66) and median time to CNS metastases was 27 months (1–129). CNS treatment was RT (36 Gy) in all pts, 2 had a previous surgical excision. 10 pts died of CNS metastases, 3 pts of other metastases ± local recurrence. Median survival time was 3 months (0–17). 2 pts are alive with disease at 2 and 17 months. Brain metastases, classically unusual In CRC become more frequent, potentially because of the wider use of systematic CT. Despite RT, their prognosis remains very poor.

742 POSTER

PATHOPHYSIOLOGY AND THERAPY OF IRINOTECAN (CPT-11) INDUCED DELAYED ONSET DIARRHEA (DD): A PROSPECTIVE ASSESSMENT

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DD is the main toxicity of CPT-11 at the currently recommended dose (RD) of 350 mg/sqm IV (30′) q 3 weeks. In previously treated colorectal cancer patients (pts), we tried to determine the mechanism of DD and assess the efficacy of combined antidiarrheal medication. From Dec 93 until March 95, 24 pts having failed $\geq 1 \leq 3$ lines of 5-FU based treatment, entered a CPT-11 Phase II trial at the above RD. In the first cohort (14 pts), Acetorphan (Acet), a specific enkephalinase inhibitor, was given as 100 mg tid PO after the second loose stool, and supplemented, if DD > 48 hrs, with Loperamide (Lop) 2 mg q 2 hrs PO till 12 hrs after last loose stool. Pts had at baseline and if DD occurred endoscopy, with biopsies for Topo I and CPT-11 assays as well as transit time, stool frequency, weight, culture, electrolytes, osmotic gap, pH, fat and protein excretion, α1 antitrypsin (α AT) clearance, D-xylose test; blood tests for VIP, glucagon, somatostatin, gastrin. Twelve/14 pts (first cohort) had CFT-11 DD: 5 responded to Acet alone, and the other 7 responded within 24 hrs to addition of Lop. Transit time normal in 5/7 pts, α AT increased in 4/4 pts. Stools weight >800 gr/day and fecal Na/K increased in 6/6 pts. Osmotic gap small in 3/6 pts. The second cohort (pts 15–25) received simultaneous Acet/Lop after first DD loose stool. Eight/11 pts had DD, and 7/8 had resolution of diarrhea within 12 hrs of treatment start. Available PK's of CPT-11 and SN-38 (active metabolite) show no pharmacodynamic relationship. Results suggest that CPT-11 DD is due to a secretory exudative mechanism, as attested by its response to early simultaneous antisecretory medications.

743 POSTER

PREOPERATIVE RADIATION DOSE ESCALATION ± CHEMOTHERAPY FOR ADVANCED RECTAL CANCER

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Purpose: To assess the influence of preoperative radiation does escalation ± concurrent chemotherapy in patients with advanced rectal cancer. *Methods:* Patients with clinical T3/T4 rectal cancer received preoperative XRT ± chemotherapy, followed by surgery. 74 patients received 45 Gy XRT (low-dose group). 82 patients received 55.8 Gy XRT (high-dose group). 33 patients received 55.8 Gy XRT with concurrent 5-FU chemotherapy (CRT group). The 3 groups were compared with respect to post-radiation pathologic stage, local tumor control (LC), disease-specific survival (DSS), freedom from distant metastasis (FDM), and acute toxicity. *Results:* The high-dose XRT and CRT groups had significantly fewer pT3/4 tumors relative to the low-dose XRT group (53% and 51% vs. 70%, respectively, $P < 0.03, \chi^2$). The proportion of pT3/4 tumors in the high-dose XRT and CRT groups was the same, despite the fact that there was a larger proportion of clinically fixed (unresectable) tumors in the CRT group (43% vs. 76%, respectively, $P < 0.005, \chi^2$). The proportion of pN+ patients and the 5-year actuarial LC, DSS, and FDM rates were not significantly different between the groups. There was a significant increase in Grade 3 GI toxicity in the CRT group (24%) vs. the low-dose and high-dose XRT groups (5% and 6%, respectively, $P > 0.005, \chi^2$.) *Conclusions:* The addition of 5-FU chemotherapy to preoperative XRT results in greater downstaging of clinically fixed tumors than XRT alone. The acute toxicity of CRT is greater than that of XRT alone. Patients with clinically fixed rectal cancer benefit most from preoperative CRT.