1-2 in 44, gr. 3 in 6 and gr. 4 in 4) and 34 pts (29.8%) cutaneous toxicity (gr. 1-2 in 29 and gr. 3 in 5). All patients underwent surgery after a median interval of 43 days from completion of adjuvant therapy. Surgical procedures were: low anterior resection in 92 (80.7%) and abdominoperineal resection in 22 (19.3%). Downstaging was obtained in 76 pts (66.6%) while complete pathological response was found in 18 (15.7%). No early mortality due to adjuvant or surgical treatment was found. Major postoperative complications occurred in 22 pts (19.3%): 7 clinical anastomotic leaks, 3 pelvic abscesses, 5 delayed perineal wound healing, 2 rectovaginal fistulas, 1 stoma ischemia and 4 postoperative ileus. After a median follow-up of 24 months (range 5-86), 4 (3.5%) local recurrences and 24 (21%) distance metastasis were observed. Eighty-eight pts were alive and disease free and 12 were alive with distance metastasis. Fourteen had died (12 of cancer related causes and 2 of other causes).

Conclusions: Local control compared favourably with recently published data. A high rate of downstaging and sphincter saving were obtained with acceptable toxicity, however a longer follow up is necessary to verify the impact on survival.

1096 POSTER

Relationship between high dose irinotecan (260mg/m2) and response rate, without increased toxicities in metastatic colorectal cancer (MCRC) combination with bi-weekly 5FU/FA in a phase II study

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The recommended dose of irinotecan with LV5FU2 is 180 mg/m2. In this phase I study the MTD was 300 mg/m2. In monotherapy, level 500 mg/m2 was safe in 2/3 patients(pts) with good response rate. The rationale of this study is to confirm safety and efficacy irinotecan 260 mg/m2 combined with LV5FU2 (group 1) then with LV5FU simplified regimen (group 2) after better safety published results of this schedule. The primary endpoint is the ORR.

Results: 34 pts with MCRC (10 had received adjuvant chemotherapy) were included for 1rst line, prophylactic G-CSF after hematological toxicity to maintain dose intensity; sex ratio (H/F)=20/14; median age 55y[41-73]; PS 0/1=16/18; number of sites involved 2[1-4].

	Group 1 (%cy/%pts)	Group 2 (%cy/%pts)
N cycles/N patients	209/20	46/14
Median cy/patients	8.0 [1-16]	5.0 [1-8]
Diarrhea G3/G4	(1.0/4.2)/(0/0)	0/0
Asthenia G3	1.5/13	4/10
Vomiting/Nausea G2	(2.5/17)/(5/21)	(6/20)/(10/30)
Neutropenia G3/G4	(15/58)/(2/21)	(17/60)/(0/0)
Febrile neutropenia	0.5/5	0/0
ORR (%RP-SD-PD)	(20 pts) 55*-35-10	Too early**

*3 pts with surgical resection of liver metastases. **Only one evaluation per patient.

Conclusion: Preliminary results, CPT-11 260mg/m2 demonstrates a good safety profile, more especially when combined with simplified LV5FU than LV5FU2, with an overall better efficacy when compared to 180 mg/m2.

1097 POSTER

Significance of different classes of p53 gene mutation in patients with colorectal cancer

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Purpose: The p53 tumor suppressor gene controls many critical processes related to tumor development and progression. Specific p53 mutations have been found to be associated with various clinical phenotypes. The clinical and pathological significance of p53 mutations in defined structural and functional domains were prospectively investigated in a large series of colorectal cancer patients.

Methods: Surgical specimens from 335 consecutive patients with stage I-IV colorectal adenocarcinoma were collected between 1991 and 1998. p53 gene mutations in exons 4 to 8 were searched for by PCR-SSCP analysis, followed by direct DNA sequencing. Comparison between groups was made using the Chi-square test. Survival analyses were carried out by the log-rank test and the Cox's proportional hazards model.

Results: p53 gene mutations were detected in 141/335 (42.1%) cases. The higher mutational frequencies were found in exons 5, 7 and 8 (37.6%, 24.8% and 29.1% respectively). p53 gene mutations were associated with left-sided tumors ($p<0.001$) and more advanced lesions (stage III and IV) ($p<0.01$). In particular, mutations located on exon 5 and in the L2 loop region were significantly associated with tumors in stage III and IV. At univariate analysis of survival, no significant differences were found in relation to p53 gene status. However, among cases with p53 gene mutations, those with alterations in exons 4 to 6 had a worse outcome than those with alterations in exons 7 and 8 ($p<0.02$). On the other hand, cases with L3 loop region mutations had a better outcome than cases with mutations in other sites of the gene ($p<0.05$). At multivariate analysis, the only factors which independently predicted survival were tumor site and stage.

Conclusion: Our results indicate that p53 gene mutation is not a prognostic marker in patients with colorectal cancer. Specific p53 gene mutations in defined structural and functional domains are associated with different clinical and pathological findings.

1098 POSTER

Colorectal cancer (CRC) patients surveillance with virtual computed tomography colonography(CTC): preliminary results

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Purpose: Which is the best follow-up schedule in colorectal cancer (CRC) patient is still controversial. The aim of our analysis was to asses the role of virtual computed tomography colonography (CTC) in the follow-up of patients who underwent surgery for colorectal cancer (CRC).

Methods: From January 1998 through March 2001, 35 CRC surgical treated patients (all adenocarcinoma, 18 female, 17 male, 14 rectum, 20 colon, 1 r-s junction, grading 2 G1, 23 G2, 3 G3, 7 GX, 8 Dukes A, 14 Dukes B, 13 Dukes C, mean age 63 years, age range 43-78), entered our surveillance program with CTC. Patients were following a schedule which consist in annual conventional colonoscopy, liver US and chest X-ray, physical examination and serum CEA every 3 months for the first 3 years from diagnosis, every 6 since 5th year. Bowel was regularly prepared with standard setting for traditional colonic exam and after air insufflate; multislice spiral CT (Somaton Plus 4 Volume Zoom, Siemens) examination of the abdomen and pelvis was performed. Patients were scanned in supine and prone position using the following parameters: 1 mm collimation, 1 mm reconstruction index, 8 mm/sec table speed, and mAs 80 with the patient in the prone position, and then after the injection of intravenous contrast medium (60 sec delay), with the patient in the supine position, using 120 mAs. Images were evaluated on a dedicated workstation.

Results: We consider as gold standard for virtual exam the conventional colonoscopy and related pathologic exam. Thirty patients were negative for any pathologic aspect. We checked only one false positive. We found: 3 patients with liver metastases confirmed by RMN, 1 patient with 2 basal pulmonary nodules, 5 patients with 6 polyps and 1 local anastomotic relapse.

Conclusions: We think that CTC is feasible and can offer, unlike conventional, the opportunity to have a complete TNM owing to liver scan with I.V. contrast, with low patient discomfort; it can also check extra-colonic findings. Our study is still ongoing to subsequently assess if CTC can be considered as first choice exam in the follow-up of patients surgically treated for CRC.

1099 POSTER

Tomudex + folinic acid + 5-fluorouracil (5FU) and preoperative concomitant radiotherapy for locally advanced rectal cancer(LARC): a phase I study

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Background and Purpose: Preoperative chemoradiation in rectal cancer (RC) is still investigational: improved resectability rates and sphincter preservation with low toxicity are reported. Prolonged venous infusion (PVI) of 5-FU concomitant with postoperative radiotherapy has shown good results in both local tumor control and survival. Nevertheless PVI 5-FU is cumbersone and expensive. Accurate preoperative evaluation by endoscopic ultrasound (EU) is mandatory for a careful selection of patients.

Tomudex (TOM) is a direct and specific thymidilate synthase inhibitor with radiosensitising properties and activity in advanced colorectal cancer. Pharmacokineticand in vitro data have shown a synergy when Tomudex is followed 24 h later by bolus 5-FU. Furthermore, preclinical data reveal that the growth inhibition induced by Tomudex is not reduced when LFA is added 24 h later, but a greater synergism is noted when LFA is added to 5-FU.Based on the above observations, we started a phase I study with TOM+LFA+5-FU and preoperative concomitant radiotherapy in LARC.

Patients and methods: Patients with LARC underwent pre-treatment assessment by EU and CT scan. Those eligible for the study underwent radiotherapy to a total dose of 45 Gy and a combination of TOM on day 1, and LFA + bolus 5-FU on day 2. Chemotherapy was administered 1 hour prior to radiotherapy every 2 weeks, and given up to three courses. Doses of TOM and 5-FU were alternately escalated up to maximum tolerated dose (MTD), which was defined as the dose level at which more than a third of patients had dose limiting toxicity. Nine patients have been enrolled up to date.

Results: The table shows the preliminary data on DLT and response.

Step	TOM	LFA	5-FU	PTS	DLT	Response
1	2.5	250	600	3	0/3	3 PR
2	2.5	250	750	3	0/3	Not evaluated
3	2.5	250	900	3	0/2	Not evaluated
4	3.0	250	900	0	0	

Grade 1 toxicity was observed in all but one patient at third dose level, who had a grade 3 neutropenia. All patients completed the chemoradiation treatment without any complication. Three patients were restaged six weeks after chemoradiation and then underwent surgery. All had a down-size tumor and were able to receive sphincter saving procedures without major complications.

Conclusions: Tomudex +5FU+ LFA given concomitantly to radiotherapy is a feasible approach to rectal cancer in the preoperative setting. Accrual is continuing and updated results will be presented.

1100 POSTER

Thymidylate synthase expression and ts gene polymorphism in colorectal cancer: implications on therapeutic response to 5-FU

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Purpose: Thymidylate Synthase (TS) is a target enzyme of 5-fluorouracil (5-FU). TS gene has a unique tandemly repeated sequence in the 5f-untranslated region that was recently described to be polymorphic, containing two or three 28-bp tandem repeats, which may be involved in increased gene expression. It has been reported that high intrinsic tumour TS levels may be related to 5-FU resistance. It was our aim to evaluate the impact of TS polymorphism and TS expression on therapeutic response to 5-fluorouracil (5-FU) treatment in human colorectal tumours.

Methods: Formalin-fixed, paraffin-embedded sections of colorectal tumour tissues, of 37 patients treated postoperatively, were analysed for TS genotyping and for immunohistochemical TS protein expression. Overall survival and disease free survival were calculated by Kaplan-Meier method and curves were compared by log-rank test.

Results: In this study we found that TS polymorphism was not associated with protein expression (p=0.936). We also observed that overall survival rate seem to be shorter in patients carrying a 3 repeat genotype (p=0.1787), and in patients whose tumours had negative TS expression (p=0.0480). Although no differences were observed concerning recurrence vs. TS polymorphism (p=0.2102) we verified that 6 out of 8 individuals with recurrent tumour were 3R genotype carriers.

Conclusions: This preliminary study suggests that TS repetitive-sequence polymorphism may be useful as a novel mechanism for predicting response to 5-FU- based chemotherapy. TS expression should be further investigated in a larger study, to verify its association with prognostic and TS gene polymorphism.

1101 POSTER

A nude mouse model for studying radiofrequency ablation

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Introduction: Radiofrequency ablation is an emerging treatment for colorectal liver metastasis. We wanted to assess the precision and accuracy of radiofrequency ablation. If, in fact, significant non-uniform heating occurred at the cellular level, it would be manifested by stress protein induction. It has been reported that thermal energy induces heat shock protein (hsp) expression. This suggests that hsp induction may be a characteristic cellular level response to radiofrequency. An animal model to study this phenomenon was established using nude mice and human colon carcinoma cell lines. Methods: The human colon adenocarcinoma cell line HT29 was implanted into athymic mice by bilateral dorsal subcutaneous inoculation. After tumors grew to 1-2 cm2, one tumor was exposed and ablated with a RITA Starburst probe until a peripherally placed thermister registered 50 degrees C, while the other served as a sham control. Radiofrequency was supplied via a RITA Model 1500 RF generator. Settings were standardized to 50 watts and impedence between 0-400 ohms. Paired tumors were harvested at different time points: 4 hours (n=2) and 10 hours (n=2). RNA were collected and subjected to RT-PCR analysis with primers for hsp's 90 beta, 70, 27, and beta-actin as an internal control. Densitometry was used for quantitative analysis. Recurrence of tumor (n=4) after radiofrequency was assessed after 2 months in comparison to sham control (n=2). Results: Hsp 70 was increased 4 (35%) and 10 hours (85%) after radiofrequency, relative to the sham control group. No recurrence of tumor was noted after 2 months. Conclusion: Cellular level responses to radiofrequency ablation can be adequately studied in vivo via a nude mouse model. Hsp 70 was increased after radiofrequency ablation.

1102 POSTER

Treatment of peritoneal carcinomatosis by complete cytoreductive surgery followed immediately by intra-peritoneal chemotherapy use in normothermia in human

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Aim: To evaluate the feasibility and the results of the Sugarbaker's procedure in the treatment of peritoneal carcinomatosis. Material and method: From our prospective data bank, we have analysed 31 consecutives patients treated by the Sugarbaker's procedure or its variants in our institution between september 1997 and december 2000. Primary tumor was colorectal adenocarcinoma in 22 patients, pseudomyxoma peritonei (appendix) in 7 patients, mesothelioma in 1 patient and sarcomatosis in 1 patient. No evidence of extra-peritoneal tumor, except in one patient, was mandatory to be eligible. Treatment consisted in a complete cytoreductive surgery followed immediately by intraperitoneal mitomycin-C administered in the recovery room and intraperitoneal fluorouracil every day for 4 day starting the day after surgery. Results: Six patients had a non-resectable disease discovered at laparotomy and were included in a phase I study. Twenty-five patients had the Sugarbaker's procedure and full dose of chemotherapy was administred to 22 patients (88%). Mean hospital stay was 20,5 days and 44 complications were reported, the most frequent being wound infection. None died within the postoperative period. One patient with mesothelioma and one patient with sarcomatosis are alive and disease free (DF) at 90 days. Five patients with pseudomyxoma are alive after a mean followup of 578 days: 4 are DF and 1 had a reccurence. Of the 18 adenocarcinoma patients: 7 died after a mean survival of 577 days (after a mean DF of 320 days) and 11 are alive and DF after a mean survival of 444 days. Conclusion: Sugarbaker's procedure in normothermia is a feasible and safe treatment. It can be offer with curative intent to patients with "localized" PC from colorectal origin and a good performance status. Although it should never be offer as a palliative treatment, survival benefit is better in the non-cured patient group than any other form of treatment of PC reported in litterature.