(16%) and 49 partial response (54%), including 21 (43%) with microscopical residual disease. In 24 patients (27%), stable disease was achieved. No pts progressed locally. There was 1 postoperative death (1.1%). The overall survival in 12 months is 93.5%. With a median follow up of 15 months, 72 patients with radical surgery still alive and disease-free (84.7%), 8 are alive with disease (9.4%) and 5 have died (5.8%): 1 from PD, 2 from treatment complications (1 surgery, 1 postoperative ChT) and 2 from other causes. 9 recurrences were detected: 8 systemic and 1 local plus systemic.

Conclusions: Preoperative treatment with CI of 5-FU and RDT in locally advanced RC was well tolerated, with a remarkable response rate and anal sphincter sparing. Our pathological complete responses are lower than other authors. This may be due to more stage III pts, or the performance of an exhaustive pathological finding of residual microscopic disease after surgery. Results are too preliminary to ascertain if this approach will impact on survival.

1081 POSTER

Multicenter phase II study of irinotecan as second line chemotherapy in metastatic colorectal cancer after prior exposure to infusional 5-FU based chemotherapy

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Purpose: The present study investigated Irinotecan as second line chemotherapy in patients (pts) with prior exposure to a weekly schedule of folinic acid 500 mg/m^2 i.v. followed by 5-FU 2.6 g/m^2 given i.v. over 24 hours for metastatic disease. Patients with histologically confirmed adenocarcinoma of the colon or rectum, measurable metastatic progressive disease and adequate bone marrow, liver and renal function were entered into the study after informed consent. Previous 5-FU based adjuvant CT and/or radiotherapy were allowed.

Methods: Irinotecan was given at a dose of 350 mg/m^2 (300 mg/m^2 for pts with WHO performance status of 2 and/or age > 70 years) i.v. over 30 min. every 3 weeks until progression of disease or occurrence of unacceptable toxicity.

Results: 111 pts. entered the study. 67 male, 44 female, median age 58 (33–84) years, median performance status 0 (0–2). After exclusion of 1 pt who never received treatment 110 pts were assessable for safety and 102 pts for tumor response. 110 pts received a total of 529 cycles of Irinotecan with a median no of 4 cycles per patient. The response rate was 11% [95% CI 5–17] and the NC rate was 65% [95% CI 54–79%]. The median time to progression and median survival were 4 and 9 months. 9% responses, and 65% NC were obtained in 96 pts with resistant disease. 2 PR and 4 NC were achieved in 6 pts with progressive disease between 4 to 12 months after end of first line CT. NCIC-CTC grade 3/4 toxicities included neutropenia 39% of pts., thrombopenia 2%, delayed diarrhea 20%, infection 7%, fatigue 7% and elevation of bilirubin 10%.

Conclusion: In case of failure of infusional modulated 5-FU, Irinotecan had considerable efficacy and an acceptable safety profile. The efficacy of Irinotecan in the present study is comparable with that obtained in other phase II studies using various 5-FU based regimen as first line CT. These results indicate that the efficacy of Irinotecan in second line treatment is widely independent of the previously used 5-FU based regimen.

1082 POSTER

Activity and safety of capecitabine and irinotecan (CPT-11) in association as first line chemotherapy in advanced colorectal cancer (ACRC)

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Purpose: The primary endpoint of this multiinstitutional phase II study is to evaluate activity and tolerability of the combination of CPT11 + Capecitabine. Both drugs are active against ACRC with synergist cytotoxicity in preclinical studies.

Methods: Between July 1999 and March 2001, 102 pts with ACRC were enrolled and randomized to receive: arm A: CPT11 300 mg/m2 on day 1 every 3 weeks; arm B: CPT11 150 mg/m2 day 1 and 8 every 3 weeks; Capecitabine was administered in both arms at the dose of 1250 mg/m2 twice daily from day 2, for 14 days. Preliminary results are available about the first 47 consecutive pts enrolled in the trial. The main characteristics are: arm A 24 pts; Arm B 23 pts; M/F 23/24; median age 59 years (38-76); primary tumor: colon 30, rectal 17.

Results: 34 pts are valuable for response: 6 CR (A:2 B:4) and 15 PR (A: 11; B: 4) were achieved with an overall response rate of 61.7% (21/34). Fortyfour pts are valuable for toxicity. Grade 3-4 treatment-related toxicity observed per pts was: Arm A hand-foot syndrome (4), diarrhea (5), anemia (2) and neutropenia (1); Arm B nausea (3), diarrhea (4) and neutropenia (2). One drug-related death occurred for gastrointestinal toxicity in arm B. Thus, the dose of both drugs have been reduced as follows: CPT11, A: 240 mg/m2 day 1 q21, B: 120 mg/m2 days 1 and 8 q21; capecitabine twice daily 1000 mg/m2 from day 2 for 14 days q21.

Conclusions: The preliminary results suggest that the combination of capecitabine and CPT11 is clinically active. In order to improve the safety of the combination the schedule has been modified, with a better toxicity profile.

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1083 POSTER

Acute morbidity following short course preoperative radiotherapy in operable rectal cancer: identification of associated factors

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Introduction: Short course preoperative radiotherapy (SCPRT) (25Gy in 5 fractions over 1 week) has been shown to reduce locoregional recurrence and improve overall survival in operable rectal cancer. However, there are concerns regarding the toxicity of SCPRT. The aim of this study was to document the early complications (within 3 months) in patients receiving SCPRT and to identify the factors associated with acute morbidity.

Methods: All patients receiving SCPRT between 1 Jan 1998 and 31 Dec 1999 were included. Information on each patient including age, sex, radiotherapy (RT) technique (field dimensions, beam arrangement and energy), surgical details (time from starting RT to date of surgery, type of operation, in-patient stay and morbidity/mortality within 3 months), histology (Dukes stage and circumferential margin) were obtained. Univariate and multivariate analysis were performed on the above co-variates.

Results: One hundred and seventy seven patients referred from 8 centres were identified. Mortality at 30 days and 3 months was 6% and 8% respectively. Complications occurred in 38% of patients (wound 13%, pelvic sepsis 7%, anastamosis 6%, thromboembolic 4%, haemorrhage 3%, other 11%). Age (p=0.030), RT field length (p=0.027) and time to surgery (p=0.017) were significantly associated with an increased risk of complications on multivariate analysis.

Conclusions: Based on our results we would advocate surgery within ten days of commencing SCPRT. This recommendation is consistent with the protocols of the Swedish Rectal Cancer Trial and the ongoing MRC CR07 trial.

1084 POSTER

The addition of continuous infusion 5-FU to preoperative radiotherapy increases sphincter preservation in locally advanced low rectal cancer

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Purpose: To compare the results of preoperative chemoradiotherapy (CXRT) to radiotherapy alone in two large, single institutional experiences.

Patient and Methods: Between 1978 and 2000, 455 localized, non-metastatic clinically staged T3 rectal cancer patients from two institutions were treated with preoperative radiotherapy. Patients at institution 1 (INT1, n=245) were treated with pelvic CXRT exclusively. They were compared to patients at institution 2 who were treated with pelvic radiotherapy alone (INT2a, n=144) initially, and CXRT (INT2b, n=66) more recently following a policy change. Both institutions used 45 Gy/25fx, while INT2 used 20 Gy/5fx in selected cases (n=20). Concurrent chemotherapy consisted of concurrent continuous infusion 5-FU 1500 mg/(m2-week) in both institutions. The endpoints were sphincter preservation (SP), relapse-free survival (RFS), and local control (LC).

Results: Median follow up was 56 months for all living patients in INT1 and INT2a. In the subset of patients receiving 45 Gy with rectal tumors 6cm from the anal verge (INT1: n=143; INT2a: n=52;INT2b: n=29), there was a significant improvement in SP with the use of concurrent chemotherapy (41% at INT1 compared to 13% at INT2, $p < 0.0001$). This finding was supported by a 38% SP rate in the INT2b group. A logistic regression analysis evaluating clinical prognostic factors (gender, year of treatment, diagnostic grade, tumor downstaging, circumferentiality, and length) confirmed that concurrent chemotherapy was the only independently significant factor influencing SP ($p < 0.032$). RFS and LC were not significantly different between INT1 and INT2a. Follow-up for INT2b is insufficient to analyze these endpoints.

Conclusions: The use of concurrent 5FU with preoperative radiotherapy for T3 rectal cancer independently increases SP in low rectal cancer. RFS and LC appear to be unaffected.

1085 POSTER

Distinct pronostic value of p53 overexpression and gene alterations in colorectal cancer

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Introduction: Pronostic value of p53 mutations in colorectal cancer (CRC) is still controversial.

Objective: To assess the short-term prognostic value of p53 protein overexpression and gene mutation in CRC.

Patients and methods: Between 1/96 and 12/98, 512 patients (pts) were diagnosed with CRC. Among them, 419 had tumor tissue samples available for genetic tests. The present study is restricted to 126 pts. Mean age 67 years, 59% were male. Tumors were located in colon 68% and rectum 32%. Stage was I:11%, II:40%, III:36%, IV:13%. Pts with initial stage IV were excluded. Median of follow up was 25,5 months. Mutations in p53 at exons 5-9 were detected by PCR/SSCP and sequencing. p53 protein overexpression was analysed by IHC using antibodies DO-7. Also mutations in the K-ras oncogene were available. Cox proportional hazards models were used to assess association with disease-free survival and to estimate hazards ratio and 95% confidence intervals.

Results: Overexpression (O+) in p53 protein was evident in 75% of the tumours. Mutation (M+) in p53 gene were founded in 55% of the tumours. Agreement between results was: 52% both positive (O+M+) and 14% both negative (O-M-). Major disagreement was overexpression without mutation:27% (O+M-). Only 6% were mutated and did not overexpressed protein (O-M+). Overall, p53 mutations did not associate with worse prognosis (HR=0.9/0.5-1.5/). However, a trend was observed towards shorter survival in tumours overexpressing p53 protein (HR=1.6/0.9-3.0/). Discordant cases (O+M-) showed poorer prognosis than negative concordant (O-M-) HR= 2.1 (0.7-5.8). K-ras mutations were detected in 38% of the cases. Mutations in K-ras were independent of p53 alterations and also showed a trend towards poorer prognosis, HR=1.3 (0.9-1.9).

Conclusions: This preliminary analysis has shown that prognostic value of p53 protein overexpression is higher than that of p53 gene mutations. In the absence of detected gene alterations p53 protein overexpression depicts a group of CRC tumours with poorer outcome.

1086 POSTER

Any usefulness of oncofoetal markers (CEA and CA19-9) in the management of chemotherapy (CTH) of patients (PTS) with metastatic colo-rectal carcinomas (MCRC)?

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Purpose: CT scan is accepted as gold standard for evaluation of response to CTH in MCRC. The potential helpfulness of less aggressive and expensive procedures, i..e., CEA and CA19-9 dosages, was prospectively investigated.

Methods: From 03/97 to 01/99, radiological tumor response was assessed using spiral CT scan of the thorax abdomen and pelvis every 2 or 3 CTH courses (8 weeks) until disease progression and for a maximum of 5 consecutive visits in 91 consecutive pts receiving 1st (82.4%) or 2nd line CTH for MCRC. At each visit, CEA and CA 19-9 dosages were performed.

Results: CEA and CA19-9 values are available at baseline in 91 and 89 patients and upper the normal value in 78 (85.7%)and 62 (69.7%) respectively. According to the RECIST response criteria (J Natl cancer Inst 2000; 92:205-16), the response rates are: CR=3, PR=22, NC=25, PD=41. In the majority of patients, the response status was determined during the first evaluation (visit #2). The percentage of relative variation of the CEA and CA19-9 values between visits #1 and 2 poorly correlates to tumor response. In fact, a decrease is even observed in 55% of NC and 44% of PD pts with CEA (60% and 45% with CA 19-9). However, all 12 pts experiencing a more than 3 fold increased CEA and/or CA 19-9, regardless the baseline value, are classified as PD.

Conclusion: The use of tumor markers cannot be recommended for tumor response evaluation. Only 13% pts who present a 3 fold increase of CEA and/or CA 19-9 can be considered as PD without the need of a radiological confirmation. Taking into account the hospital costs, the cost benefit ratio of the use of tumor markers in addition to CT scan versus CT scan alone is minus 30400 FF (4635 euros).

1087 POSTER

Anemia in colorectal cancer patients: a prognostic parameter

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Anemia is a common finding in cancer patients. In a variety of human malignancies the prognostic value has been demonstrated already. In colorectal cancer, however, these studies have not yet been performed. Therefore, the aim of the present study was to compare preoperatively obtained hemoglobin blood levels with various clinico-pathological findings in a series of 485 consecutive colorectal cancer patients treated at the Department of Surgery, University Hospital Innsbruck, between 1992 and 1999.

Blood hemoglobin concentrations ranged from 5.7 g/dl to 18.1 g/dl. 132 out of 485 (28%) patients were anemic (hemoglobin levels $\leq$ 11 g/dl) prior to operation. Hemoglobin values were statistically significantly related to gender ($P < 0.0001$), tumour site ($P = 0.0001$), pT stage ($P < 0.01$) and tumour stage according to UICC ($P < 0.001$). Anemia was more frequently diagnosed in female (33%) than in male (22%) patients. 58 out of 140 (41%) patients with tumours of the right hemicolon were anemic, whereas the remaining patients showed anemia in only 21% (74 out of 345). The proportion of anemic patients increased with pT stage. 10% of pT1, 21% of pT2, 29% of pT3, and 38% of pT4 tumours showed anemia. 30% of patients were found anemic in tumour stages II, III, and IV according to UICC. In contrary, only 14% were anemic in tumour stage I. Furthermore, anemia was associated with shorter survival times in colorectal cancer patients ($P < 0.001$) and Hazard rate rations showed that anemia increased mortality by 53% (95% CI 15% - 103%).

The results of the present study strongly support the prognostic value of anemia in human malignancies. Further studies are required to evaluate the impact of anemia treatment on survival.

1088 POSTER

A phase I and pharmacokinetic study of irinotecan given as a 7 days continuous infusion in metastatic colorectal cancer patients pretreated with 5-FU or raltitrexed

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Rationale: Irinotecan (CPT-11) is a cell cycle specific drug which, binding to topoisomerase I-DNA complex, causes single strand-breaks. However this is a reversible process and it is necessary that the topoisomerase I-DNA-SN-38 cleavable complex remains stable until the DNA replication fork reaches it to result in an irreversible double-strand break. This process may require several hours or days and therefore, although CPT-11 and SN-38 have terminal half-lives of approximately 12 and 24 hours respectively, a more prolonged exposure might enhance the formation of lethal double-strand breaks and cytotoxicity. Experimental studies also support this hypothesis.

Purpose: We have initiated this phase I study to determine the plasma pharmacokinetic and the maximum tolerable dose (MTD) of CPT-11 administered as a 7 days continuous infusion every 21 days in metastatic colorectal cancer patients pretreated with 5-FU or raltitrexed.

Results: Thirteen patients (pts) have entered the study. Three have received CPT-11 at 20 mg/sqm/day, 4 at 22.5 mg/sqm/day and 6 at 25 mg/sqm/day. Dose-limiting toxicity was WHO grade III-IV diarrhea which