

rest. Patients are treated until unacceptable toxicity or disease progression. Statistical tests to assess survival include Wilcoxon supported by Log Rank and a nonparametric analysis of covariance (Tangen and Koch, 1999 and 2000).

Results: Patient accrual of the integrated cohort was completed in March 1999. Median follow-up time is 36 months by February 2001. Analysis of the data will occur following the unblinding of TMTX-0034.

Conclusion: TMTX-0034 and TMTX-509 are two definitive Phase III trials in first-line ACC. Final results will be available at the time of the presentation.

1077

POSTER

Comparison of 5 classifications of colorectal carcinoma

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Purpose: The New Classification has been shown to be superior to Dukes, Astler-Coller and TNM as a predictor of individual prognosis in Israeli and American CRC pts after surgery with curative intent (Cancer 86: 782-792, 1999). This study compares five classifications of CRC in a cohort of Japanese pts, after surgery with curative intent.

Methods: Retrospective study of 504 Japanese CRC pts. Minimal follow-up: 5 years after surgery with curative intent. Sources of data: Japanese cancer registry forms, inpatient and outpatient files, and departmental follow-up registers. Tumors were staged according to Dukes, TNM, Astler-Coller, Japanese Society of Colorectal Cancer (JSCCR), and the New Classification. Kaplan-Meier survival curves (disease-free, observed, and adjusted for CRC deaths only) were calculated for each classification. Statistical significance of differences among the various survival curves was assessed by Log Rank. The 5 classifications were compared by multivariate regression analysis (Cox).

Results: All 5 classifications yielded disease-free, observed, and CRC-related survival curves that were highly significant ($p < 0.0001$). JSCCR stages 3a, 3b (in which JSCCR differs from TNM) did not differ significantly in any survival parameter ($p = 0.0756$, $p = 0.1644$, $p = 0.1791$ respectively). Multivariate regression analysis identified the New Classification as the most predictive of recurrence and survival ($p < 0.0001$).

Conclusions: 1. The New Classification is a superior predictor of individual prognosis following curative resection of CRC in Japanese pts as well. 2. The JSCCR classification of stage III CRC is not superior to TNM.

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1078

POSTER

Venous Invasion (V.I.) as a prognostic indicator in TNM-II colorectal carcinoma (CRC)

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Purpose: In Israeli CRC pts after surgery with curative intent, V.I. +/- has been shown to define two subsets in each Dukes and Astler-Coller stage, that differ significantly in recurrence and survival (Europ J Cancer, vol 29A, Suppl 6, p S99, 1993). This study assesses if V.I. defines two prognostically distinct subsets among Japanese TNM-II CRC pts as well.

Methods: Retrospective study of 504 Japanese CRC pts. Minimal follow-up: 5 years after surgery with curative intent. Sources of data: Japanese cancer registry forms, inpatient and outpatient files, and departmental follow-up registers. 151 pts (30%) had TNM-II tumors; V.I. was identified in 56 (37.1%) of them. Disease-free, observed, and CRC-related survival curves (Kaplan-Meier) were calculated for TNM-II V.I.(+) and for TNM-II V.I.(-) pts, and compared for statistical significance (Breslow).

Results: V.I.(+) was associated with an increase in local/regional as well as in distant recurrence in TNM-II CRC following surgery with curative intent. Disease-free, observed, and CRC-related survival of TNM-II V.I.(+) pts were significantly worse than those of TNM-II V.I.(-) pts ($p = 0.0129$, $p = 0.0077$, $p = 0.0141$ respectively). DFS at 5 years was 93% for TNM-II V.I.(+), and 78% for TNM-II V.I.(+).

Conclusions: 1. As in Israeli pts, substaging Japanese TNM-II CRC pts by V.I. defines two patient subsets that differ significantly in recurrence and survival. 2. Consequently, it is suggested that selection of TNM-II CRC pts for adjuvant treatment could be based on the presence of V.I. 3. This

method requires no sophisticated or expensive equipment or tests, and it is immediately applicable in any health-care system worldwide.

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1079

POSTER

Comparison of five methods for substaging node-positive colorectal carcinoma

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Purpose: Future developments in adjuvant modalities may require substaging of node-positive CRC that is accurately indicative of individual prognosis, and upon which choice of agents, dosage and intensity of adjuvant treatment may be based. Venous invasion (V.I.) has been shown to be a superior definer of subsets of Israeli and American node-positive CRC pts, that differ significantly in recurrence and survival (Ann Surg Oncol 6: 161-165, 1999). This study compares 5 methods for substaging node-positive CRC in a cohort of Japanese pts following surgery with curative intent.

Methods: Retrospective study of 504 Japanese CRC pts. Minimal follow-up: 5 years after surgery with curative intent. Sources of data: Japanese cancer registry forms, inpatient and outpatient files, and departmental follow-up registers. 148 pts (29.4%) had node-positive disease [epicolic/paracolic LNs (N1 by the Japanese (JSCCR) classification) in 103 pts; intermediate LNs (N2) in 41 pts; main LNs (N3) in 4 pts]. These 148 pts were substaged according to 5 methods: 1-3 versus 4 or more (TNM N1/N2); 1-4 versus 5 or more (GITSG C1/C2); Astler-Coller C1/C2; JSCCR N1/N2+3; and by V.I. +/- . Disease-free, observed, and CRC-related survival curves (Kaplan-Meier) were calculated for each method, and compared for statistical significance (Breslow).

Results: Substaging by TNM N1/N2, GITSG C1/C2, and V.I. +/- defined subsets that differed significantly in disease-free, observed, and CRC-related survival. Substaging by Astler-Coller C1/C2, and JSCCR N1/N2+3 was not statistically significant ($p = 0.6079$, $p = 0.1171$, $p = 0.0996$; and $p = 0.0845$, $p = 0.2000$, $p = 0.2513$ respectively).

Conclusions: 1. Substaging node-positive CRC by V.I. was the only method that defined subsets that differed significantly in disease-free, observed, and CRC-related survival in Israeli, American and Japanese CRC pts alike. 2. This method has obvious biologic and oncologic significance, for it separates pts that have only lymphatic spread from pts that display microscopic hematogenous spread as well. 3. Consequently, we believe that V.I. is the method of choice for substaging node-positive CRC.

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1080

POSTER

Preoperative chemoradiotherapy (ChT-RDT) in locally advanced rectal cancer (RC). Preliminary results

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Objective: To assess the efficacy and toxicity of neoadjuvant ChT-RDT with 5-fluorouracil(5-FU) continuous infusion (CI) in locally advanced RC.

Materials and methods: From 4/96 to 3/2000, 90 patients (pts) with locally advanced RC (stage II y III) have been treated in a single centre with 5 days CI of 5-FU 300 mg/m²/day every week (w) concurrently with external beam RDT 45 Gy (1.8 Gy/session/5 session/w). Between the sixth and the eighth w after preoperative treatment, radical surgery was planned followed by postoperative ChT with 5-FU-Folinic Acid bolus, if there wasn't any evidence of progression disease (PD).

Results: 90 pts, 62 men and 28 women, with a median age of 62 years (20-76) were included. There were 78 resectable and 12 unresectable tumors. Stages: III, 72 pts (80%); II, 14 (15.6%); T3-T4 Nx 4 (4.4%). One evaluable patient didn't finish ChT because of an anginous pain. Grade III-IV gastrointestinal toxicity was observed in 1 pt. In 3 pts (3.3%), systemic PD was detected at the end of preoperative ChT-RDT. Surgery was performed in 89 pts: radical in 85 (96%) and palliative in 4 (4%). Surgical procedures included: anterior resection in 51 (57.3%), abdominoperineal resection in 36 (40.4%) and other procedures in 2. In 25 pts (41%) anal sphincter was spared. Pathological response rate was 70%: 14 complete response

(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/m² i.v. followed by 5-FU 2.6 g/m² 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/m² (300 mg/m² 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 evaluable 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 evaluable 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-variables.

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%, anastomosis 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).