cancer. Secondary objective was to establish treatment related variables which correlate with oncological prognosis.
Methods: From 1994 until 2004, 203 patients with locally advanced and 117 patients with locally recurrent rectal cancer underwent multimodality treatment. All patients have been staged by MRI for the rectal cancer and by CT of the thorax and abdomen in order to rule out metastatic disease. In all primary cases the circumferential margin was involved or less than 2 mm free according to MRI. All pelvic locally recurrent cases were eligible. Multimodality treatment consisted of neoadjuvant radio-(chemo) therapy, resection, extended if necessary and Intraoperative Electron Radiotherapy (IOERT) at the area of risk. Concomitant chemotherapy was added to the radiotherapy since 1999.
Patients were referred from over forty different hospitals in the Netherlands. However, surgery and IOERT were performed in one institution.
Results: Five-year survival rate and local recurrence rate were 55% and 17% for locally advanced rectal cancer and 32% and 39% for locally recurrent rectal cancer respectively. After radical resection (R0) with negative circumferential margins, 5 year survival and local recurrence rate were 60% and 10% for locally advanced (n = 168) and 48% and 24% in locally recurrent cases (n = 68). Response to neoadjuvant treatment, and type of neoadjuvant treatment were statistically significant variables for obtaining radical resections. In primary advanced cases 30% showed poor response to neoadjuvant treatment, but were responsible for 86% of all irradical resections (30/35) In primary advanced rectal cancer cases R0 resection rate was 72% after neoajuvant radiotherapy only, and 89% after combined radiochemotherapy. In locally recurrent cases these figures were 56% and 68% respectively.
Conclusion: Combined multimodality treatment is effective in the treatment of locally advanced primary rectal cancer and can be used as salvage strategy for patients with locally recurrent rectal cancer. Treatment related factors: response to neoadjuvant treatment and the ability to perform a radical R0 resection strongly correspond with oncological outcome.

634 POSTER

Post-study treatment does not influence outcome in the X-ACT phase III trial of capecitabine (X) vs. bolus 5-FU/LV as adjuvant therapy for patients (pts) with Dukes' C colon cancer

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Background: The X-ACT trial evaluated adjuvant X vs. 5-FU/LV in pts with resected Dukes' C colon cancer. Between Nov 1998 and Nov 2001, 1987 pts were randomised to receive either oral X (1250 mg/m^2 bid d1–14, q3w) or i.v. bolus 5-FU/LV (Mayo Clinic regimen: LV 20 mg/m^2 + 5-FU 425 mg/m^2 d1–5, q4w) for 24 weeks. X was at least equivalent to 5-FU/LV in terms of disease-free survival (DFS; HR 0.87, 95% CI 0.75–1.00, $p < 0.0001$), with a strong trend towards superior DFS ($p = 0.053$). X significantly improved relapse-free survival (HR 0.86, 95% CI 0.74–0.99, $p = 0.041$), with a trend towards improved overall survival (HR 0.84, 95% CI 0.69–1.01, $p = 0.071$). The primary safety endpoint was met with fewer key grade 3/4 adverse events and later onset with X vs. 5-FU/LV ($p < 0.001$).
Materials and methods: In a separate analysis, we looked at post-study treatment in both arms of the X-ACT trial to determine whether there were any differences that could influence survival outcome.
Results: At the time of this analysis, 632 pts in the X and 579 in the 5-FU/LV arms are alive and disease-free, with 131 and 142 pts alive with relapse/new recurrence in the X and 5-FU/LV arms, respectively. Of the pts receiving post-study chemotherapy, 25 in the X and 10 in the 5-FU/LV arm received other adjuvant chemotherapy following randomisation into X-ACT either because they never received study treatment or at the investigator's discretion (after early termination of study treatment for any reason). In addition, 13 pts in the X and 16 pts in the 5-FU/LV arm received post-study chemotherapy for new occurrences of cancer other than colon cancer (breast, prostate, lung) prior to relapse. Pts meeting the entry criteria (free of disease at study entry and receiving $\geqslant$1 doses of study treatment) who were treated according to the protocol and experienced relapse formed the largest group receiving post-study chemotherapy. There were no major imbalances in post-study chemotherapy for metastatic disease (see table) or radiotherapy (6% in both arms).
Conclusions: These data suggest that there are no differences in post-study chemotherapy that could influence survival outcome in pts who received either X or 5-FU/LV as adjuvant therapy in the X-ACT trial. Efficacy, safety and pharmacoeconomic findings indicate that X should replace 5-FU/LV as adjuvant treatment for colon cancer.

% of pts receiving post-study chemotherapy for metastatic disease

	X (n = 372)	5-FU/LV (n = 404)
Irinotecan-based	39	35
5-FU-based	17	16
Oxaliplatin-based	32	29
X single agent	4	10
Other chemotherapy	9	6

635 POSTER

Arterial thromboembolic events in a pooled analysis of 5 randomized, controlled trials of bevacizumab with chemotherapy

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Background: Bevacizumab (Avastin^{TM}) is a monoclonal antibody to VEGF with demonstrated survival benefit when combined with chemotherapy in metastatic colorectal cancer (mCRC). Individual safety data from several randomized controlled trials suggested that adding bevacizumab to chemotherapy may increase the risk of arterial thromboembolic events. We conducted a pooled analysis to evaluate this potential safety signal.
Methods: Data from 1745 pts with metastatic carcinomas (breast, colorectal, and non-small-cell lung) pooled from 5 randomized controlled trials of bevacizumab with chemotherapy were analyzed to assess arterial thromboembolic event risk and identify predisposing factors in the context of overall clinical effect. Clinical parameters, including age, gender, development of proteinuria on study, and history of hypertension, diabetes, atherosclerosis, arterial thromboembolic events, venous thromboembolic events, and use of aspirin or a statin, were assessed for relationship to arterial thromboembolic event occurrence by univariate analysis and a Cox proportional hazards regression model.
Results: Within this pooled population, the addition of bevacizumab to chemotherapy increased the risk of arterial thromboembolic events compared to chemotherapy alone (3.8% vs 1.7%, $p < 0.01$ by Chi-square test). In addition to bevacizumab treatment, history of arterial thromboembolic events and age $\geqslant$65 years were identified as independent risk factors by multivariate analysis (hazard ratios of 1.9, 2.9, and 2.2 respectively).
Conclusion: The addition of bevacizumab to chemotherapy is associated with an increased risk of arterial thromboembolic events in patients with metastatic carcinoma, especially those $\geqslant$65 years old with a prior history of arterial thromboembolic events. The risk/benefit of bevacizumab in mCRC by arterial thromboembolic event-risk group will be presented.

636 POSTER

Initial safety findings from a phase III study of capecitabine (X) plus oxaliplatin (XELOX) vs. infusional 5-FU/LV plus oxaliplatin (FOLFOX-6) in first-line treatment of patients (pts) with metastatic colorectal cancer (MCRC)

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Background: The oral fluoropyrimidine X is replacing 5-FU/LV as the backbone of colorectal cancer therapy, in both the metastatic and adjuvant settings. The combination of X and 3-weekly oxaliplatin (XELOX) has demonstrated good efficacy and safety in phase II clinical trials in MCRC. We initiated a phase III trial to compare XELOX with FOLFOX-6 as first-line therapy in pts with MCRC. This abstract provides the initial safety findings from a planned interim analysis.

Methods: From 16 May 2003 to 31 August 2004, 177/304 pts have been randomized to receive either XELOX (91 pts: X 1000 mg/m^2 bid d1–14, oxaliplatin 130 mg/m^2 d1, q3w, maximum 8 cycles) or FOLFOX-6 (86 pts: 5-FU 400 mg/m^2 i.v. bolus then 2400–3000 mg/m^2 46-hour infusion, LV 400 mg/m^2 2-hour infusion, oxaliplatin 100 mg/m^2 d1, q2w, maximum 12 cycles).
Results: Baseline pt demographics were comparable in the XELOX vs. FOLFOX-6 arms: M/F (60%/40% vs. 62%/38%); median age: 65 (range32–83) vs. 63 (45–84). 91% of pts in the XELOX and 93% in the FOLFOX-6 arms had ECOG PS 0–1. Other baseline characteristics were well balanced. To date a median of 6 XELOX cycles (range 1–8) and 11 FOLFOX-6 cycles (range 1–12) have been administered. It is important to note that 1 cycle of XELOX = 3 weeks and 1 cycle of FOLFOX-6 = 2 weeks. Clinical adverse events were acceptable and generally similar in the XELOX and FOLFOX-6 arms (see table). There was a similar rate of diarrhea, nausea, vomiting and fever in both groups. XELOX led to more hand–foot syndrome, but less neuropathy, asthenia, alopecia and stomatitis. There was a similar rate of grade 3/4 diarrhea, nausea, vomiting, fever and asthenia in both groups. XELOX led to less grade 3/4 paresthesia and neuropathy. One toxic death was reported in each arm. Pts receiving XELOX experienced less grade 3/4 neutropenia and more thrombocytopenia than those on FOLFOX-6.
Conclusions: These data show that XELOX and FOLFOX-6 are well tolerated in first-line MCRC. If the final results from this study confirm this preliminary analysis, XELOX offers benefits to the pt in terms of clinical safety. The planned enrollment of 304 pts is now complete and updated safety results will be reported at the meeting.

	% of pts with Adverse events (NCIC-CTC grade)			
	XELOX (n = 91)		FOLFOX-6 (n = 86)	
	1/2	3/4	1/2	3/4
Diarrhoea	47	9	45	7
Hand–foot syndrome	19	0	12	0
Nausea	54	2	62	2
Vomiting	36	3	36	1
Asthenia	31	9	54	7
Neuropathy	11	1	11	11
Paresthesia	63	3	65	14
Anaemia	13	2	19	5
Neutropenia	21	6	16	49
Thrombocytopenia	12	14	50	6

637 POSTER

CAPOX vs CAPIRI in combination with concomitant boost 3D-conformal radiotherapy in neoadjuvant treatment of locally advanced rectal cancer

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Background: Several randomised trials have demonstrated the role of preoperative chemo-radiotherapy in the treatment of local advanced rectal cancer to reduce the rate of local recurrence, but there is no agreement on the chemotherapy and radiotherapy schedule. The aim of this study is to compare the combination of oral Capecitabine with Oxaliplatin or Irinotecan (CPT-11) in association with high dose radiation therapy.
Patients and methods: Thirty-three patients (21 males/12 females, median age 59 years and ECOG-PS 0–1) with a histologically proved uT3–4 N-/+ or uT2 N+ rectal cancer entered the study, from January 2003 to December 2004. No patient showed systemic disease at the time of diagnosis. They were randomly assigned to receive Oxaliplatin 130 mg/m^2 on days 1, 22 and 43 (17 pts, CAPOX GROUP) or Irinotecan 180 mg/m^2 on days 1, 22 and 43 (16 pts, CAPIRI GROUP) in combination to Capecitabine 1250 mg/m^2 bid days 1–14 and then 825 mg/m^2 bid on days 22–55, concomitant with radiotherapy started on day 22. The radiotherapy was administered to the whole pelvis to a dose of 45 Gy (1.8 Gy/fraction), with a concomitant boost to the CTV to a dose of 9 Gy (1.5 Gy/fraction, during the last 6 days of treatment with a 6-hour inter-fraction interval): the total dose to the primary tumor was 54 Gy with a 3D-conformal technique. Surgery was carried out 6–8 weeks after the completion of chemo-radiation by the same surgical team.
Results: Among all treated patients, in one patient in CAPIRI GROUP the chemo-radiation treatment was discontinued for GI toxicity and the patient came out the study; the other 32 pts received 95% and 92% of the planned chemotherapy dose, respectively 17 pts in CAPOX GROUP and 15 CAPIRI GROUP. The dose-limiting toxicity was grade III-IV diarrhoea, occurring in 1 pt (CAPOX GROUP) and 3 pts (CAPIRI GROUP). Neurotoxicity was very limited, as only 5 patients experienced grade I toxicity in CAPOX GROUP. A clinical and pathological downstaging was detected in 12 pts (70%) in CAPOX GROUP and 11 pts (73%) in CAPIRI GROUP. A complete pathological remission was seen in 4 pts (23%) in CAPOX GROUP and 4 pts (26%) in CAPIRI GROUP. Twenty-three patients (72%) underwent sphincter-saving surgery, 12 (70%) in CAPOX GROUP and 11 (73%) in CAPIRI GROUP; nine patients were treated with Miles abdomino-perineal resection. All patients are alive after a median follow-up of 16 months (range 2–24 months), but 4 of them, equally distributed in the two groups, developed distant metastases.
Conclusions: both CAPOX and CAPIRI are feasible and effective, resulting in excellent results, comparable to those of best series of neoadjuvant treatment. CAPOX was better tolerated than CAPIRI, as diarrhoea was more frequently associated with Irinotecan infusion. Moreover, it was reported an increased radio-chemo induced-fibrosis in CAPIRI GROUP. Further studies are needed to assess the superiority of a particular treatment schedule.

638 POSTER

Distal clearance margin less than 9 mm: a safe margin in rectal cancer patients

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Background: Recent reports suggest that a distal clearance of 10 mm at the lower surgical margin may be considered adequate in the surgical treatment of rectal cancer.
Methods: We report the experience of the National Cancer Institute of Milano (Italy) in the treatment of low rectal cancer with the technique of total rectal and mesorectal resection (TRR) with coloendoanal anastomosis (CEAA). Between March 1990 and December 2002 we performed 557 consecutive TRR and CEAA at our Institute. 178 patients of this series with a minimum follow up of 18 months (mean 61 months) were treated for a primary cancer without preoperative chemoradiotherapy.
There were 94 patients with distal clearance margin (DCM) <9 mm and 84 with DCM >10 mm. Each group was stratificated by pathological stage and nodal status. The local recurrence subsets was stated. All B2 and C1–2 Astler Coller stage patients in this series received post operative chemo-radiotherapy.
Results: see table.
Conclusions: Our data suggest that the distal clearance margin of resection less than 9 mm eventually in combination with post operative chemo-radiotherapy do not affect local recurrence rate in N0 and N+ patients.

Table 1. Number of events by DCM group.

	DCM			
	Negative ⩾1 cm		Negative <1 cm	
	No.	%	No.	%
Total subjects	84	41.4	94	46.3
First event:				
Local relapse	6	7.1	7	7.5
Distant metastasis	*15	17.9	*21	22.3
Second malignancy	3	3.6	–	–
NED death	7	8.3	2	2.1
Deaths	28	33.3	16	17.0

DCM: Distal Clearance Margin; * One distant metastasis was concurrent with local relapse

639 POSTER

Phase I/II study of PTK/ZK, a novel, oral angiogenesis inhibitor in combination with FOLFIRI as first-line treatment for patients with metastatic colorectal cancer

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Background: Vascular endothelial growth factors (VEGFs) and VEGF receptors (VEGFRs) are important mediators of tumor growth and metastasis, and their expression is associated with poor prognosis in