	Grade 3	Grade 4	Hospitalized (grade 3–4)
Nausea/vomiting	13	1	4
Diarrhea	33	5	17
Stomatitis	8	–	–
Mucositis	4	1	3
Dermatitis	63	1	–
Infection	7	4	7
Hemorrhage	2	2	3
Thrombocytopenia	5	1	1
Neutropenia	19	9	8
Aplasia	1	5	4
Fistulae	1	4	5
Ileitis RT	2	–	2
Dysuria	5	–	–
Cystitis	5	–	–
IRA	1	–	1
Femoral Artery Occlusion	1	–	–
Ataxia	1	–	–
Dental Abscess	1	–	–
Dyspnea	1	–	–
Pulmonary Embolism	–	3	2
Infarction	–	1	–
Dehydration	–	1	1
Cachexia	–	1	–
Total	**177 (17.5%)**	**39 (3.9%)**	**56 (5.5%)**

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A randomized phase III study (LARCS) comparing preoperative radiotherapy alone versus chemoradiotherapy in non-resectable rectal cancer

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Background: Preoperative chemoradiotherapy is considered standard treatment for locally advanced rectal cancer, but there is still limited scientific evidence from randomized studies concerning the value of the chemotherapy in addition to the radiotherapy. This trial investigated if chemotherapy as part of a multidisciplinary treatment approach would improve survival and recurrence rates.
Material and methods: A randomized study of 208 patients in Norway, Sweden and Poland between 1997 and 2003 included patients with locally non-resectable (all T4) primary rectal carcinomas or local recurrences from rectal carcinomas. The patients received either preoperative radiotherapy alone (50 Gy) or chemotherapy (5 FU/leucovorin, Nordic regimen) given concurrently with the same radiotherapy schedule and for 16 weeks after surgery. Surgery was performed 6–8 weeks after the last radiation treatment. All analyses were according to intention-to-treat.
Results: 110 patients were randomized to radiotherapy alone versus 98 to chemoradiotherapy. Radical surgery was performed in 79 (72%) and 82 (83%, p = 0.07) patients and pathological CR was 8% versus 21% (p = 0.04). Local recurrences were seen in 16% versus 12% and distant metastases in 39% versus 27%. Local control, i.e. removed primary and no local recurrence was seen in 66 (60%) versus 73 (74%, p = 0.04) patients. Any grade 3–4 toxicity, mainly gastrointestinal, was seen in 5/110 (5%) and 37/98 (38%), respectively. There were no toxic deaths. Postoperative morbidity and mortality did not differ between groups. Disease–free survival (50% versus 65% at 5 years, log-rank p = 0.05), cancer-specific survival (50% versus 70%, p = 0.03) and overall survival (50% versus 63%, p = 0.1) all favoured the chemoradiotherapy group.
Conclusions: Preoperative chemoradiotherapy results in downstaging, improved resectability and local control in non-resectable rectal cancer versus radiotherapy alone. After a minimum follow-up of one year (median approximately 3 years) there is a marked difference in disease-free and cancer-specific survival (70% at 5 years in the combined treatment group). More grade 3–4 toxicity was seen in the chemoradiotherapy group, but the treatment was generally well tolerable.

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Randomized phase III trial in locally advanced rectal cancer: preoperative chemoradiotherapy with oral uracil and tegafur/leucovorin versus intravenous fluorouracil /leucovorin

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Background: Preoperative intravenous fluorouracil (FU) based chemoradiotherapy (CT-RT) is commonly used to treat locally advanced rectal cancer. Oral fluoropyrimidines have been developed as a therapeutic alternative to FU. Based in our previous phase II study report (Int J Radiat Oncol Biol Phys 1999; 45: 629–634), we designed a prospective, multicentric and randomized phase III study to determinate the equivalence of oral uracil & tegafur (UFT)/leucovorin (LV) and FU/LV with concomitant preoperative radiotherapy (RT) in pts with locally advanced rectal cancer.
Material and methods: We randomly assigned pts with cT3-T4 and/or N+ disease to receive either FU (arm A) or UFT (arm B) preoperative CT-RT. Patiens received pelvic RT 45–50.4 Gy (1.8 Gy/day; 25–28 fractions) and concurrent chemotherapy (CT) consisted of bolus FU 350mg/m^2/day and LV 20 mg/m^2/day i.v. days 1–5 and 29–33 (Arm A) or one course of oral UFT 300 mg/m^2/day divided in three doses and oral LV 12.5 mg twice daily days 8–35. Surgery was performed 4–6 weeks after the completion of CT-RT. Adyuvant CT was recommended for N+ pts. The primary end points were pathological response rate and resectability rate. Secondary end points included downstaging rate, toxicity and survival.
Results: Between January 1999 and September 2004, 153 pts from three hospitals were entered in the trial. 77 pts were randomly assigned to arm A and 78 pts to arm B. 76 pts (arm A) and 77 pts (arm B) were included in the analysis of acute toxicity. 71 pts (arm A) and 73 pts (arm B) were included in full analysis. Complete pathological response rate was 13.2% in both arms A and B, and tumor stage downstaging rates were 46.5% and 61.6% respectively (p = 0.07). The resectabilidad rates were 98.6% and 97.3% respectively (p = 0.98). All eligible patients had been followed for a median of 22.7 months (22.1 months-arm A, and 22.7 months-arm B). The 3-year overall survival, disease-free survival and local-relapse free survival was 87% and 74% (p = 0.37), 71.2% and 66.7% (p = 0.33) and 91% and 83% (p = 0.48), respectively. Grade 3 or 4 acute hematological toxicity only occurred in arm A (neutropenia 9.2%, p = 0.023). Grade 3 or 4 diarrhea was 13.2% in arm A and 10.5% in arm B (p = 0.81). Gastrointestinal grade 3 or 4 late toxicity occurred in 2 pts (3%) and 6 pts (8%) respectively (p = 0.27). Treatment related mortality was 5.3% in arm A (2 pts died for acute toxicity, and 2 pts died for gastrointestinal late toxicity) and 1.3% in arm B (1 pts died for post-surgical complications) (p = 0.36).
Conclusions: Preoperative oral UFT/LV based CT-RT in the treatment of locally advanced rectal cancer is at least as effective as i.v. FU/LV based CT-RT, with reduced toxicity. Data from this phase III study support the use or oral fluoropyrimidines with RT in stage II-III rectal cancer.

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Induction chemotherapy (ICT) and dose intensification of the radiation boost in locally advanced anal canal carcinoma (LAACC): Interim analysis of the 101 first randomised patients (pts) in the Intergroup ACCORD 03 trial (Fédération Nationale des Centres de Lutte Contre le Cancer – Fondation Française de Cancérologie Digestive)

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Background: Combined radiochemotherapy is the standard treatment of LAACC. The addition of an ICT (Ann Oncol 2001;12:397) and of a higher