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Initial safety findings from XELOXA: a randomised phase III trial of capecitabine plus oxaliplatin vs. bolus 5-FU/LV as adjuvant therapy for patients (pts) with stage III colon cancer

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Background: Updated efficacy findings from a large phase III study in stage III colon cancer (X-ACT) show that adjuvant capecitabine results in at least equivalent disease-free survival (DFS) to i.v. bolus 5-FU/LV [Twelves et al. 2005]. Early phase III data in 1st-line metastatic colorectal cancer suggest that capecitabine plus oxaliplatin (XELOX) safety is at least comparable to oxaliplatin + infusional 5-FU ± LV [Sastre et al. 2005; Ducreux et al. 2005]. Oxaliplatin + infusional 5-FU/LV (FOLFOX4) leads to superior 3- and 4-year DFS vs. infusional 5-FU/LV (MOSAIC) and the addition of oxaliplatin to bolus 5-FU/LV also results in superior DFS (NSABP C-07). The XELOXA study compared the safety and efficacy of XELOX vs. bolus 5-FU/LV (the standard regimen at study start) as adjuvant therapy for pts with stage III colon cancer.
Materials and methods: Pts with resected stage III colon cancer were randomised to receive either XELOX (capecitabine 1000 mg/m^2 bid d1–14 + oxaliplatin 130 mg/m^2 d1, q3w for 8 cycles) or i.v. bolus 5-FU/LV (Mayo Clinic, LV 20 mg/m^2 + 5-FU 425 mg/m^2 d1–5, q4w for 6 cycles; or Roswell Park [RP], LV 500 mg/m^2 + 5-FU 500 mg/m^2 d1, w1–6 in 8w cycles x4). Centres' preferred 5-FU/LV regimen was selected at study start and used in all patients.
Results: 1861 of the 1886 pts randomised between April 2003 and October 2004 were evaluable for safety. Treatment arms were well balanced (table). The rate of related grade 3/4 adverse events was 54% for XELOX and 45% for 5-FU/LV (table). 60-day all cause mortality rate was 1.0% in both arms. Treatment-related death rates within 28 days from the last dose of treatment were 0.7% for XELOX and 0.5% for 5-FU/LV.
Conclusions: Early safety findings from the largest population of pts treated with XELOX to date indicate that XELOX is feasible in adjuvant colon cancer. XELOX appears to cause less myelosuppression and stomatitis, but more skin and neurosensory toxicity than 5-FU/LV. Cross-study comparison of grade 3/4 adverse events in the current trial and MOSAIC trial suggests that the safety of XELOX is similar to FOLFOX4, with the advantage of an oral fluoropyrimidine-based regimen. Efficacy results from this study are expected in late 2007. XELOX has now been incorporated in the 3-arm AVANT adjuvant trial (FOLFOX4 vs. FOLFOX4 + bevacizumab vs. XELOX + bevacizumab).

Baseline characteristics	5-FU/LV total (n = 942)	Mayo (n = 664)	RP (n = 278)	XELOX (n = 944)	FOLFOX4* (n = 1123)
Median age, yrs (range)	60 (24–82)	60 (24–82)	61 (24–82)	60 (22–83)	61 (19–75)
ECOG PS 0/1, %	78/22	78/22	76/24	75/25	86/14
Male/female, %	53/47	54/46	49/51	54/46	56/44
N0/N1/N2, %	–/65/35	–/64/36	–/67/33	–/64/36	41/44/15
Grade 3/4 AEs, %	(n = 924)	(n = 656)	(n = 268)	(n = 937)	(n = 1108)
Diarrhoea	20	16	29	19	12
Stomatitis	8	12	0	<1	3
Nausea	4	2	9	5	5
Vomiting	3	2	6	6	6
Neurosensory	0	0	0	11	12
Hand–foot syndrome	<1	<1	<1	5	2
Neutropenia	15	19	4	8	41
Febrile neutropenia	4	5	1	<1	2

*MOSAIC [André T, et al. N Engl J Med 2004; 350: 2343–51].

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Lymph node ratio as prognostic factor in node-positive colorectal cancer

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Background: We found in non-colorectal digestive cancers that the lymph node ratio (LNR), defined as the proportion of involved nodes among excised nodes, was a consistent survival prognostic factor in all major anatomical sites. The investigation is now extended to colorectal subsites.
Material and methods: Data was abstracted from the Surveillance, Epidemiology, and End Results (SEER) public use database 2004. Selection was histology confirmed primary invasive colorectal carcinoma, diagnosed between 1988 and 1997, surgically resected. Three LNR groups were defined based on the average LNR quartiles distribution (using the same cutoffs for non-colorectal cancer): low LNR$\leqslant$0.25, intermediate LNR more than 0.25 up to 0.75, and high LNR >0.75. Survival analyses were performed using the product-limit method. End-point was death from any cause. Significance testing used the log-rank test. Survival results were compared with those based on TNM colorectal nodal classification, N1 (1–3 involved nodes) and N2 (>3 involved nodes).
Results: The median follow-up was 92 months (range 1–167). The total number of cases was 26181, and number of events was 18904. LNR-based log-rank test was significant in all subsites (<0.0001). Using the LNR, all subsites showed a wider range of survivals. For cecum, the median survival associated with low-LNR was 54 months, and the median survival associated with high-LNR was 9 months (Table 1). Using the TNM, the corresponding survival associated with a small number of involved nodes, N1, was 42 months, and the survival associated with a large number of involved nodes, N2, was 15 months (Table 1). That is, the N1-N2 categories blurred the distinction between good and poor prognosis cases. Similarly, all other subsites showed that the LNR was able to identify long and short survivals more distinctly than the TNM (Table 1). The LNR-based log-rank chi-square was double that of the TNM-based chi-square in almost all cases, further indicating a better separation between prognostic groups with the LNR.
Conclusions: The lymph node ratio performed consistently in all colorectal subsites. Further investigations on its role for staging are warranted.

Table 1: Comparative listing in colorectal subsites: median survival (months) for patients categorized according to the lymph node ratio (LNR, low, mid and high proportion of involved nodes), or categorized according to the TNM nodal staging (pN1 and pN2).

Site	No. of cases	LNR			LNR Log-rank Chi2	pN1	pN2	pN Log-rank Chi2
		Low	Mid	High				
Cecum	5634	54	20	9	956.5	42	15	425.4
Appendix	59	45	21	12	25.1	35	17	7.4
Ascending colon	3070	55	19	9	500.1	45	17	210.5
Hepatic flexure	1063	51	18	13	97.0	42	17	52.1
Transverse colon	1833	52	20	8	304.5	38	16	105.4
Splenic flexure	818	60	33	13	105.4	48	17	53.9
Descending colon	1086	58	30	15	80.5	46	26	26.6
Sigmoid colon	5862	62	34	17	464.0	49	25	258.1
Large intestine, NOS	236	34	23	8	39.5	28	15	5.3
Rectosigmoid juction	2795	62	36	18	208.4	52	27	109.8
rectum	3725	62	38	20	284.6	56	28	234.4

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Survival analysis of pseudomyxoma peritonei after cytoreduction and intraoperative hyperthermic intraperitoneal chemotherapy

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Background: Pseudomyxoma peritonei (PMP) is a clinical syndrome with progressive intraperitoneal mucus accumulation. At The Netherlands Cancer Institute, the common treatment for PMP is cytoreductive surgery in combination with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC). The aim of this study was to evaluate the survival of this treatment protocol.
Material and methods: One hundred and three patients (34 males/69 females) treated by this treatment protocol between 1996 and 2004 were identified. In case of recurrence or progression a second procedure was performed. Survival was calculated from date of initial treatment and corrected for a second procedure. PMP was pathologically categorized

into adenomucinosis, adenomucinosis/carcinomatosis hybrid or mucinous carcinomatosis. Clinicopathological factors were analyzed to identify their prognostic value for survival.
Results: Median follow-up was 51.5 (0.1–99.5) months. The overall 3-year survival was 70.9% (95% CI 62.0%-81.2%) and the 5-year survival was 59.5% (95% CI 48.7%-72.5%). Recurrence or progression had developed in 45%. The median disease-free survival was 25.6 months (95% CI 14.8–43.6). The 3-year disease-free survival was 43.6% (34.4%-55.2%) and the 5-year disease-free survival was 37.4% (28.2%-49.5%). Prognostic factors for survival were pathological subtype, completeness of cytoreduction and degree of tumor load ($p < 0.05$). The main prognostic factor, independently associated with improved survival, was adenomucinosis by pathology ($p < 0.01$).
Conclusion: Cytoreduction in combination with HIPEC is an efficient treatment for PMP in terms of overall and disease-free survival. Incorporation of prognostic factors, especially the pathological subtype, in the pre-operative work-up improves selection of patients who benefit from this treatment.

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Analysis of 10 prognostic factors in patients having a complete cytoreduction plus perioperative intraperitoneal chemotherapy for carcinomatosis from colorectal cancer

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Background: Although lymph node and liver metastases are recognized as indications for the resection of metastatic disease from colorectal cancer, carcinomatosis has not traditionally been regarded as having surgical treatment options. Recently, numerous reports from USA and Europe have suggested that complete surgical removal of carcinomatosis combined with thorough irrigations of the peritoneal cavity with chemotherapy could result in long-term survival in selected patients. The proper selection factors are important in that elective palliative surgery in these patients is usually not of benefit and is not standard of practice.
Methods: From a database of 156 patients with carcinomatosis from colorectal cancer, 70 had a complete cytoreduction and therefore a possibility for long-term survival. A retrospective analysis of data prospectively recorded in these 70 patients was performed. Ten variables were subjected to a univariant and multivariant analysis using survival as an endpoint.
Results: The peritoneal carcinomatosis index ($\leqslant$20 vs. >20) was significant with a p-value of 0.0012. Also significant was negative vs. positive lymph nodes ($p = 0.03$). Improved but not significant differences in survival were present in moderate and well-differentiated vs. poorly-differentiated cancers, female sex, mucinous vs. intestinal type histology, location within the colon vs. rectum and age >30 years. If an adverse factor such as cancer perforation was present at the time of primary cancer resection, this resulted in a diminished survival with marginal statistical significance ($p = 0.056$).
Conclusions: In patients who have a complete cytoreduction, a limited volume of carcinomatosis and negative lymph nodes suggests an improved prognosis. A trend towards diminished survival was noted in poorly differentiated cancers, male sex, non-mucinous histology, location in the rectum and age <30 years. These data can be interpreted to suggest that the earlier in the natural history of the disease that these treatments are initiated, the more favorable the long-term results; prevention of carcinomatosis in primary colorectal cancer patients at high risk for local-regional recurrence needs to be explored.

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Should the primary tumour be resected in patients with colorectal cancer and non-resectable synchronous metastases?

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Background: Whether the primary tumour should be resected in patients with colorectal cancer (CRC) and non-resectable synchronous metastases remains controversial. In particular, the impact of primary tumour resection on overall survival (OS) and progression-free survival (PFS) is unclear.
Methods: Among the 294 patients (pts) with non-resectable colorectal metastases who participated to the FFCD 9601 study, a multicentric randomized trial which compared 4 first-line chemotherapy regimens (LV5FU2; modified LV5FU2 with low dose folinic acid; continuous infusion 5FU; and raltitrexed), 216 pts (73%) with non resected primary CRC and synchronous metastases were studied. The following baseline variables were collected: gender, age, WHO performance status (0, 1, or 2) (PS), location and resection (if performed) of the primary tumour, number of metastatic sites, carcinoembryonic antigen serum level, chemotherapy regimen, and univariate and multivariate analysis were performed using a Cox model. Survival curves were compared by the Logrank test.
Results: Among the 216 pts, 60 pts (39%) had still their primary tumour (not operated group (NOP)) and 156 pts (61%) had undergone a resection of their primary tumour (operated group (OP)). There were no difference between the two groups for baseline characteristics except for the site of the primary (rectum: 14% in OP group vs 35% in NOP group, $p = 0.0006$). The OS at 2 years was significantly better in OP group than in NOP group (24% vs 10%; adjusted relative risk of death in the NOP group (RR), 2.3; $p < 0.0001$), as well as PFS at 2 years (4% vs 0%; RR, 1.9; $p = 0.0002$). Other independent prognostic variables were: PS (RR, 2.0; $p = 0.0002$), number of metastatic sites (RR, 1.3; $p = 0.05$), and left-sided, or rectal primary cancer (RR, 0.7; $p < 0.05$).
Conclusion: Resection of the primary tumour is a strong independent prognostic factor in pts with CRC and synchronous non-resectable metastases treated with first-line chemotherapy.

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Prognostic factors in patients with colon cancer receiving adjuvant 5-FU-based chemotherapy: analysis of a randomized trial including 855 patients

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Background: The influence of body mass index (BMI) and treatment-related toxicity on the long-term outcome of patients with colon carcinoma receiving adjuvant chemotherapy has not been well characterized. On the other hand several studies revealed that hospital volume is an important prognostic factor for several malignancies with superior outcomes after surgical resection at hospitals where the volume of such surgeries is high. However, many of these studies lack detailed information. In the largest German adjuvant trail in colon cancer conducted so far, we previously demonstrated that addition of FA to 5-FU + LEV for 12-months improved the adjuvant treatment of locally advanced high-risk colon cancer decreasing the recurrence rate by 8.7% and increasing the 5-year overall survival rate by 11.5%. The aim of this study was to investigate the effects of BMI, treatment-related toxicity, hospital volume and other clinico-pathological parameters on the adjuvant treatment benefit of patients with high-risk colon cancer enrolled in this trial.
Patients and Methods: Patients with curatively resected colon cancer (UICC IIb and III) were stratified according to T, N, and participating center and randomized to receive a 12-month treatment using 5-FU + LEV alone or in combination with FA or IFN alpha. Eight hundred fifty-five of 904 randomized patients (94.6%) were included in the analysis. Enrolment started in July 1992 and completed in February 1999. Gender, age, BMI, treatment-related toxicity, pathological TNM stage, tumor grading were recorded for each patient, the number of randomized patients was used as hospital volume.
Results: Age and gender did not influence the outcome. As expected T1/T2 and N1 tumors displayed a significantly better outcome that T3/T4 and N2 tumors, respectively. Patients with higher differentiated cancers also survived longer than patients with lower differentiated cancers. Interestingly, neither hospital volume nor obesity had an impact on survival. Only patients with a BMI <20 displayed a poorer prognosis compared to patients with a BMI $\geqslant$ 20. Independent of the treatment arm, patients with recorded toxicities WHO III and IV survived longer compared to patients with no or only WHO I and II toxicities.
Conclusions: The prospectively recorded data of this randomized multi-center trial suggest that hospital surgical volume and obesity had no significant effect on survival in patients with locally advanced colon cancer receiving 12-month 5-FU based adjuvant chemotherapy. Our data further suggest that treatment related toxicities WHO III and IV are accompanied with a favorable prognosis.