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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