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Baseline WHO PS and quality of life in respect to overall survival. A retrospective analysis of the CAIRO study – a study of the Dutch Colorectal Cancer Group

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Background: In phase III oncology trials WHO Performance status (PS) is often used as a stratification parameter because it is predictive for survival. In patients with advanced colorectal cancer in the CAIRO study we observed discrepancies in patients stratified as WHO 0−1 and their baseline quality of life (QoL) form. We investigated the correlation of WHO PS and PS according to baseline QoL in respect to overall survival (OS).
Material and Methods: All 556 patients of de CAIRO study (Koopman et al. Lancet 2007) who completed a baseline QoL form (EORTC QlQ-C30) were included in this retrospective analysis. The 7 items which basically cover the PS were used to divide the patients with WHO 0−1 or 2 into good and bad QoL PS scores. For this the Physical function and Global health items were used. QoL was defined as good if all scores of the Physical function items were scored as 'not at all' or 'a little' and Global health scales as $\geqslant$4. Bad was defined if at least one item of Physical function was scored as 'quite a bit' or 'very much' or Global health scales scored <4 out of 6. The 3 groups were WHO 0−1 good QoL PS (equivalent to WHO 0−1) (group 1, n = 455), WHO 0−1 and bad QoL PS scores (equivalent to WHO PS 2) (group 2, n = 69) and patients with WHO2 (group 3, n = 27) who all scored their PS in the QoL form bad. OS was estimated using the Kaplan-Meier method and was compared using the log-rank test.
Results: 69 patients (12%), had a PS of 0 or 1 at baseline while results of the QoL PS were bad. OS was 18.7 versus 12.4 versus 9.8 months ($p < 0.001$) for group 1 vs 2 vs 3, respectively, table 1.
Conclusions: In 12% patients scored their QoL bad, which was worse than could be expected based on the WHO PS. OS for these patients was significantly worse compared to those with good QoL scores in the group stratified as WHO PS 0−1. It therefore seems that baseline QoL as scored by the patients may be a better predictor for OS then WHO estimated by the physicians. We suggest the additional use of these QoL questions to assess PS and use their score for stratification.

Table 1

	N	Median (months)	95% CI
WHO 0−1 and good QoL (group 1)	460	18.7	17.2−20.2
WHO 0−1 and bad QoL (group 2)	69	12.2	9.5−14.9
WHO 2 (group 3)	27	9.8	5.3−14.4

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Synchronous peritoneal carcinomatosis of colorectal origin: description of a Dutch population-based series of 811 patients diagnosed between 1995 and 2007

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Introduction: A common site of synchronous metastases in patients presenting with colorectal cancer is the peritoneum, resulting in peritoneal carcinomatosis (PC). The recent introduction of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) as a potential effective treatment is gaining interest. This study provides population-based data on the incidence and prognosis of synchronous PC, and evaluates predictors of the development of synchronous PC.
Methods: From 1995 to 2007 16,783 cases of primary CRC were diagnosed in the area of the Eindhoven Cancer Registry in the Netherlands. Patient and tumour characteristics of patients with different sites of metastases were compared and analysed using a two-sided Chi^2 test. The independent influence of relevant patient and tumour characteristics on the risk of PC was analysed by means of a multivariable logistic regression analysis. Median survival in weeks was calculated by site of metastasis.
Results: In total, 811 patients with CRC were diagnosed with synchronous PC (4.8%). From these patients, 453 patients had at least 1 metastasis elsewhere at time of diagnosis. In patients diagnosed with T3 and T4 colon tumors, PC was the single site of metastasis in 1.8% and 6% of patients, respectively. In patients with rectal carcinomas, these percentages were 0.5% and 6% respectively. The risk of synchronous PC among patients with CRC was related to advanced T and N stage, poor differentiation grade, and right-sided localisation of the primary tumour. Median survival of patients with PC as single site of metastasis was only 34 weeks, and did not improve over time. In patients with at least 1 additional metastasis on another location, median survival was 22 weeks.
Conclusion: Synchronous PC appears to be a relatively frequent condition, especially among patients with poorly differentiated right-sided T4 tumors. The prognosis is poor and has not improved over time. Once the HIPEC-procedure will be more popularized, a substantial part of patients presenting with PC may apply for this treatment.

	Median survival in weeks (95% CL)	
	1995–2000	2001–2006
Peritoneal carcinomatosis only	35 (26−41)	30 (17−42)
Liver metastases only	34 (29−39)	51 (43−57)
Lung metastases only	81 (51–104)	89 (52–132)
Other distant metastases at a single location	33 (24−43)	59 (39−85)
Peritoneal carcinomatosis and at least 1 metastasis at other location	20 (15−27)	24 (19−29)
Other distant metastases at multiple locations	32 (24−38)	38 (30−44)

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Phase II study of two doses of NGR-hTNF, a vascular targeting agent (VTA), combined with capecitabine/oxaliplatin (XELOX) in colorectal cancer (CRC) patients failing standard regimens

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Background: NGR-hTNF is a VTA exploiting a tumor-homing peptide (NGR) that selectively binds an aminopeptidase N expressed on tumor vessels. In preclinical models, NGR-hTNF showed synergism with chemotherapy even at low doses. Two phase I trials previously selected 0.8 $\mu g/m^2$ and 45 $\mu g/m^2$ as optimal-biological and maximum-tolerated dose, respectively.
Methods: Two sequential cohorts of 12 CRC patients (pts) failing standard therapies were planned to receive 2 doses of NGR-hTNF given at 0.8 $\mu g/m^2$ (LD) or 45 $\mu g/m^2$ (HD) as 1-hour intravenous infusion every 3 weeks (q3w). XELOX consisted of oxaliplatin 100 mg/m^2 plus capecitabine 825 mg/m^2 twice-daily for 14 days q3w. Primary study objective was safety ($\leqslant$2/12 pts with grade 3−4 toxicity related to NGR-hTNF). Secondary aims included tolerability and clinical activity. Tumor restaging was done q6w.
Results: From January 2008 to March 2009, 12 pts (median age, 57 years, range 40−74; M/F 7/5; PS 0/1 11/1) were enrolled in the LD cohort and 11 pts (median age, 54 years, range 43−65; M/F 7/4; PS 0/1 8/3) in the HD cohort. All pts had previously received oxaliplatin and fluoropyrimidines. The median number of prior regimens was 3 (range, 1−4) in LD and 2 (range, 2−4) in HD. Globally, 44 cycles (median, 3; range, 2−6) and 24+ cycles (median, 2; range, 1−4+) were delivered in LD and HD, respectively. The combination was well tolerated. No grade 3−4 study drug-related toxicities were observed in both cohorts, most common grade 1−2 toxicity being short-lived, infusion-time related chills (58% in LD and 54% in HD). In the LD cohort, 1 partial response, 5 stable diseases (SD) lasting for a median time of 5.0 months (range, 3.0−8.6), and 6 progressions (PD) were observed. Maximal change in target lesions of SD pts ranged from 0% growth to 46% shrinkage. The median PFS was 3.4 months (range, 1.5−9.4), whereas the median ratio between PFS on current study and on prior therapy was 0.92. In the HD cohort, there are currently 3 SD, 6 PD, and 2 too-early, as best response.
Conclusions: Both NGR-hTNF doses were safely administered in combination with XELOX in heavily pretreated CRC pts, without worsening of chemo-associated toxicity.