Circadian Rhythm in Rest and Activity: A Biological Correlate of Quality of Life and a Predictor of Survival in Patients with Metastatic Colorectal Cancer

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Abstract

The rest-activity circadian rhythm (CircAct) reflects the function of the circadian timing system. In a prior single-institution study, the extent of CircAct perturbation independently predicted for survival and tumor response in 192 patients receiving chemotherapy for metastatic colorectal cancer. Moreover, the main CircAct parameters correlated with several health-related quality of life (HRQoL) scales. In this prospective study, we attempted to extend these results to an independent cohort of chemotherapy-naive metastatic colorectal cancer patients participating in an international randomized phase III trial (European Organisation for Research and Treatment of Cancer 05963). Patients were randomized to receive chronomodulated or conventional infusion of 5-fluorouracil, leucovorin, and oxaliplatin as first-line treatment for metastatic colorectal cancer. Patients from nine institutions completed the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 and wore a wrist accelerometer (actigraph) for 3 days before chemotherapy delivery. Two validated parameters (I<O and r24) were used to estimate CircAct. Of 130 patients with baseline CircAct assessments, 96 had baseline HRQoL data. I<O was confirmed to correlate with global quality of life, physical functioning, social functioning, fatigue, and appetite loss ($r > |0.25|$; $P < 0.01$). I<O further independently predicted for overall survival with a hazard ratio of 0.94 ($P < 0.0001$). The associations between CircAct parameters, HRQoL, and survival, which were shown in this international study involving previously untreated metastatic colorectal cancer patients, confirm prior single-institution findings in mostly pretreated metastatic colorectal cancer patients. The circadian timing system constitutes a novel therapeutic target. Interventions that normalize circadian timing system dysfunction may affect quality of life and survival in cancer patients. [Cancer Res 2009;69(11):4700–7]

Introduction

Most activities of daily living, such as locomotor activity, eating behavior, sleep/wakefulness, psychophysical performance, and mood, are regulated along the 24-h period by the circadian timing system (1–3). This system is constituted of molecular circadian clocks in peripheral tissues, the coordination of which is ensured by the suprachiasmatic nuclei, a central pacemaker located in the anterior hypothalamus (1–3). The alternation of light and darkness, social routine, and feeding schedules calibrate the circadian timing system to precisely 24 h by resetting the central pacemaker and the peripheral clocks, respectively (4). The suprachiasmatic nuclei coordinate the peripheral clocks through polysynaptic neuroanatomic pathways as well as through blood-borne cytokines and hormones (5, 6). The circadian rhythm in locomotor activity (CircAct) is a well-established marker of the function of the central pacemaker (7, 8) and can be continuously and noninvasively assessed in an objective, reliable, and validated manner with wrist actigraphy (9, 10).

The affective and constitutional symptoms, which tend to cluster in cancer patients, may be partly due to circadian disruption (5). Disrupted circadian function, objectively estimated with wrist actigraphy, has been found to correlate with subjective parameters, such as performance status (PS; refs. 11–13) and self-reported symptoms, particularly fatigue, poor sleep, appetite loss, and depression (12–15). Jetlag and shift work are associated with the same symptoms (16–19).

Abnormal circadian rhythms have been associated with higher risk of cancer development and more rapid cancer progression in both rodents and humans. In tumor-bearing rodents, disruption of the circadian rest-activity rhythm resulted in faster tumor growth and shorter survival (20, 21). Shift work, with the associated disruption of the circadian rhythm, is a significant and independent risk factor for the development of breast, colorectal, endometrial, and prostate cancers (22–26).

Abnormal circadian rhythms have been shown in cancer patients (27–29) and associated with poorer outcome. In women with metastatic breast cancer, a disrupted cortisol rhythm was associated with poorer survival (30). In a prior single-institution study, the extent of CircAct perturbation independently predicted for survival and tumor response in 192 patients receiving chemotherapy for metastatic colorectal cancer (31). Moreover, CircAct correlated with several health-related quality of life (HRQoL) scales (31, 32). In the present study, we attempted to extend these previous results to an independent cohort of chemotherapy-naive patients with metastatic colorectal cancer participating in an international randomized phase III trial.

Materials and Methods

Study outline. The focus of this study was to correlate the circadian rest-activity rhythms of patients with advanced colorectal cancer with quality of life and survival. This open prospective study was a companion to an international, multicenter, randomized two-arm phase III trial [European Organisation for Research and Treatment of Cancer (EORTC) 05963] that compared two biweekly schedules of the combination of oxaliplatin, 5-fluorouracil, and leucovorin in 564 chemotherapy-naive patients with metastatic colorectal cancer (33). Patients were randomized to receive either a conventional 2-day regimen (FOLFOX2) or a 4-day chronomodulated schedule (chronoFLO4). Inclusion criteria were PS of ≤2 (WHO scale), ages 18 to 76 years, adequate hematologic, renal, and hepatic functions, no overt brain metastases, and no prior chemotherapy or radiotherapy for metastatic disease. The primary trial registered 564 patients at 36 institutions in 10 countries. The 9 institutions (in Belgium, Canada, France, and Italy) participating in this companion study entered 191 patients on the main trial from August 1999. This group of patients was eligible for the current study that was approved by the local ethics review boards. Clinical outcomes (overall survival, progression-free survival, tumor response, and toxicity grading) were evaluated as described previously (33).

CircAct and HRQoL assessments. To assess individual circadian rest-activity rhythm, a Mini-Motionlogger actigraph (Ambulatory Monitoring) was used. The actigraph is similar to a watch and is worn on the nondominant wrist. It contains a piezoelectric linear accelerometer to detect wrist movements and a memory chip for data storage. The user-defined time interval for the recording and count of activity level was 1 min. The actigraph was worn for at least 72 h continuously before the beginning of the first or second course of chemotherapy (9, 10, 31). All actigraphy time series were analyzed using a specific program (Action 4 version 1.10; Ambulatory Monitoring) by one investigator. Two robust and well-characterized parameters were used to estimate the circadian activity pattern: the dichotomy index (I<O), which integrates the circadian regulation of sleep and takes into account the relative difference in activity between the rest and wakeful spans, and the autocorrelation coefficient at 24 h (r24), a measure of the regularity and reproducibility of the activity pattern over a 24-h period from one day to the next (31). In case of a prominent circadian rhythm, I<O reaches 100% and r24 reaches 1. Average activity (meanAct) was calculated as the average number of wrist movements per minute throughout the recording time. All parameter values were computed for the whole monitoring period (72 continuous hours).

The EORTC Quality of Life Questionnaire-C30 (version 2.0) was completed before the first or second course of chemotherapy (34). All scores were calculated using the standard recommended EORTC procedures.

Statistical analyses. Means, medians, SDs, and interquartile ranges were used as summary statistics for the raw distribution of CircAct parameters. The normality of the CircAct parameters distribution was assessed with the Shapiro-Wilk test. The Wilcoxon two-sample test was used to assess the association between CircAct parameters and binary factors or outcomes. The Jonckheere-Terpstra test was computed to assess the association between

CircAct parameters and ordinal factors. Logistic regression was used to test whether each quantitative CircAct parameters predicted for the occurrence of severe toxic events.

The correlations among CircAct parameters, between CircAct parameters and continuous variables, as well as the correlation between CircAct parameters and baseline HRQoL scores were examined using the Spearman's rank correlation coefficient. Partial correlation coefficients were computed between CircAct parameters and HRQoL scores using age, body mass index, and hemoglobin concentration separately as controlling variables. Correlations were considered as relevant if $r > |0.25|$ and two-sided $P \leq 0.01$. Moreover, CircAct parameters were dichotomized according to their median (above and below median), and the HRQoL indices were compared in these two subgroups with the Mann-Whitney U test.

The effect size of the difference in HRQoL scores between the two CircAct subgroups was calculated as the difference in subgroup means divided by the pooled SDs. The threshold for clinical relevance was set at effect size ≥ 0.4.

Because multiple analyses were done, and because the sample size of the current study was not computed with these endpoints in mind, the threshold for statistically significant differences was set at $P < 0.01$.

Progression-free and overall survival functions were estimated by the Kaplan-Meier's method. The survival curves for each CircAct parameter were drawn in groups of patients defined according to the quartiles of the distribution of the considered parameter. The survival curves were compared using the log-rank test. The association between each CircAct parameter as quantitative variable and progression-free or overall survival was also assessed with a simple Cox's regression model. Each CircAct parameter found significantly prognostic with the simple regression analysis at the 5% significance level was included in a multiple Cox's regression model and adjusted for age, gender, body mass index, study center, primary tumor site, prior adjuvant chemotherapy, and treatment arm together with clinically relevant prognostic factors (31, 35). Stepwise regressions at the 5% significance level were done, and the bootstrap resampling technique was used as an internal validation tool.

Results

Study compliance. A total of 130 patients (23% of the whole trial population) had their CircAct evaluated: 103 patients before treatment onset, 24 patients after the first course, and 3 patients after the second course of treatment. Considering the 191 potential patients available for study, the true baseline compliance was 68%. Of the 130 patients with baseline actigraphy monitoring, 96 (74%) patients also completed the EORTC Quality of Life Questionnaire-C30.

Representativeness of the current study population. The main clinical characteristics of the 130 patients in this companion study were comparable with those of the 564 patients registered in the main trial (Table 1). The current study population had baseline HRQoL scores, overall survival, progression-free survival, response rate, and grade 3 to 4 toxicity rate that did not significantly differ from those of the remaining trial population ($P \geq 0.10$; data not shown).

Distribution of circadian rest-activity rhythm parameters. The 24-h patterns in rest-activity displayed wide interindividual differences. For meanAct and r24, the assumption of a normal distribution was not rejected ($P = 0.20$ and 0.19, respectively). Mean and median meanAct were 105 and 106 counts/min, respectively (SD, 27; interquartile range, 41). For r24, mean and median values were 0.38 and 0.37, respectively (SD, 0.17; interquartile range, 0.24). Conversely, the distribution of I<O was nonnormal ($P < 0.0001$) and skewed. Thus, median I<O was 97.0, whereas mean I<O was 94.3 (SD, 8.6; interquartile range, 6.8). The CircAct parameters I<O and r24 were positively correlated with each other ($r = 0.74$; $P < 0.001$)

Table 1. Main clinical features of the whole EORTC 05963 trial population according to the availability or not of actigraphy assessment at baseline

Variable	CircAct assessment available		Total (33)
	Yes (*n* = 130)*	No (*n* = 434)	*n* = 564
	n (%)	*n* (%)	*n* (%)
Treatment arm			
FOLFOX2	67 (51.5)	215 (49.5)	282 (50)
ChronoFLO4	63 (48.5)	219 (50.5)	282 (50)
WHO PS			
0	70 (53.8)	203 (46.8)	273 (48.4)
1	45 (34.6)	186 (42.9)	231 (41.0)
2	15 (11.5)	45 (10.4)	60 (10.6)
Age (y)			
Median	60	63	62
Range	22-76	24-76	22-76
Gender			
Male	74 (56.9)	264 (60.8)	338 (59.9)
Female	56 (43.1)	170 (39.2)	226 (40.1)
Body mass index (kg/m^2)			
≤18.4 (underweight)	4 (3.1)	19 (4.4)	23 (4.1)
18.5-24.9 (normal)	57 (43.8)	220 (50.7)	277 (49.1)
25.0-29.9 (overweight)	51 (39.2)	134 (30.9)	185 (32.8)
≥30.0 (obese)	17 (13.1)	59 (13.6)	77 (13.7)
Missing	0	2 (0.5)	2 (0.4)
Median	25.2	24.5	24.6
Range	16.7-39.1	14.9-42.9	14.9-42.9
Site of primary tumor			
Colon	96 (73.8)	329 (75.8)	425 (75.4)
Rectum	34 (26.2)	105 (24.2)	139 (24.6)
No. metastatic sites			
0	0 (0.0)	4 (0.9)	4 (0.7)
1	58 (44.6)	224 (51.6)	191 (33.9)
2	52 (40.0)	139 (32.0)	86 (15.2)
≥3	20 (15.4)	66 (15.2)	1 (0.2)
Unknown	0 (0.0)	1 (0.2)	
Organs involved			
Liver	106 (81.5)	377 (86.9)	483 (85.6)
≤25%	62 (47.7)	204 (47.0)	266 (47.2)
>25%	44 (33.8)	173 (39.9)	217 (38.5)
Lung	47 (36.2)	162 (37.3)	209 (37.1)
Analgesics at entry	26 (20.0)	56 (12.9)	82 (14.5)
Previous adjuvant treatment	23 (17.7)	79 (18.2)	102 (18.1)
WBC (10^9 cells/L)			
Median	8.0	8.1	8.1
Range	3.6-25.5	3.1-27.6	3.1-27.6
≥10	30 (23.1)	102 (23.5)	132 (23.4)
Baseline HRQoL available	96 (74)	347 (80)	443 (79)

*Current study population.

and with meanAct ($r = 0.47$; $P < 0.001$ and $r = 0.46$; $P < 0.001$, respectively).

CircAct correlation with patient characteristics. Patients with good PS had significantly more robust CircAct in comparison with patients with poor PS (Fig. 1) for I<O ($P = 0.01$), r24 ($P = 0.0014$), and, to a lesser extent, meanAct ($P = 0.047$). Thus, median I<O and r24, respectively, decreased from 98.2 and 0.44 in the patients with PS = 0 ($n = 70$) to 95.7 and 0.36 in those with

PS = 1 ($n = 45$) and 95.3 and 0.24 in patients with PS = 2 ($n = 15$). Patients receiving analgesic treatment at study entry ($n = 26$) displayed significantly more perturbed CircAct compared with patients without painkillers for I<O ($P = 0.004$), r24 ($P = 0.001$), and, to a lesser extent, meanAct ($P = 0.048$). Indeed, median I<O was 95.3 and median r24 was 0.26 in patients on analgesics, whereas corresponding median values were 97.7 and 0.41, respectively, in patients not requiring analgesics. CircAct parameters did not
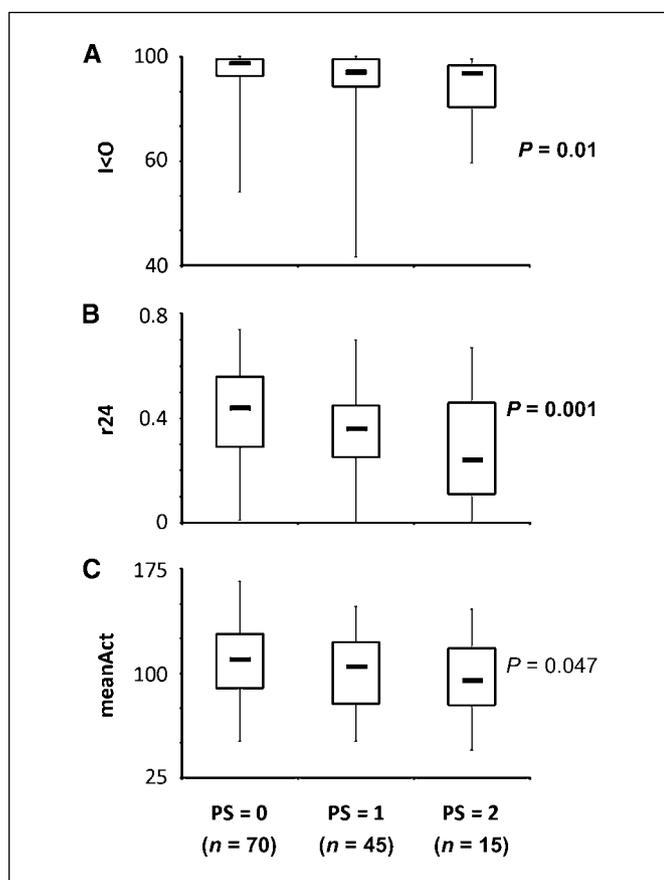
Figure 1. Distribution of the CircAct parameters I<O (*A*), r24 (*B*), and meanAct (*C*) according to the WHO PS. *Box,* median (*middle line*) and first and third quartiles; *thin vertical columns,* range.

associated with less fatigue, whereas higher than median meanAct was associated with better global quality of life, higher role functioning, less fatigue, and better physical functioning.

CircAct correlations with toxicity, response, and survival. Baseline CircAct parameters predicted neither for best objective tumor response ($P \geq 0.14$) nor for the occurrence of at least one moderate or severe toxic event based on the National Cancer Institute of Canada Common Toxicity Criteria version 2.0 grading score ($P \geq 0.31$). No statistically significant association was found between progression-free survival and any CircAct parameter ($P > 0.10$).

For each CircAct parameter, the comparison of the survival functions of the patient groups defined by the quartiles of the parameter showed a significant difference for r24 ($P = 0.002$, log-rank test) and for I<O ($P = 0.008$, log-rank test) but not for meanAct ($P = 0.201$, log-rank test). The corresponding Kaplan-Meier survival estimate curves for r24 and I<O were plotted in Fig. 3*A* and *B*, respectively. No consistent trend in Kaplan-Meier survival estimates was observed as a function of r24 quartiles (Fig. 3A). Conversely, a trend was evident for I<O, with the poorest survival occurring in the lowest quartile group, intermediate and overlapping survival in both middle quartiles, and a slightly better survival in the highest quartile group (Fig. 3B). These observations were confirmed by plotting the log (-log) of the survival curves (data not shown).

A significant positive association was found between overall survival and I<O with a hazard ratio of 0.95 (95% confidence interval, 0.93-0.97; $P < 0.0001$) using a Cox's proportional hazards univariate regression model. A similar relationship was found for overall survival and r24, with a hazard ratio of 0.20 (95% confidence interval, 0.07-0.60; $P = 0.004$). No such association was found for survival and meanAct ($P = 0.15$). The relation between I<O and survival remained roughly similar following adjustment for the

correlate with age, gender, body mass index, percentage of liver involvement with tumor, number of metastatic sites, site of primary tumor, blood test results (blood counts, liver tests, and carcinoembryonic antigen), or previous adjuvant chemotherapy administration ($P > 0.10$).

CircAct correlations with HRQoL. All CircAct parameters (I<O, r24, and meanAct) correlated positively with global quality of life and role functioning but negatively with fatigue and appetite loss. In addition, I<O and r24 correlated positively with social functioning and negatively with pain and dyspnea. Furthermore, I<O correlated positively with physical functioning but negatively with insomnia. MeanAct correlated positively with physical functioning. Conversely, no CircAct parameter correlated with emotional or cognitive functioning, nausea/vomiting, constipation, or diarrhea. These correlations remained statistically significant after adjustment for age, with minimal modifications in coefficient values (range, -0.02 to +0.04) and *P* values (Table 2). Controlling for body mass index or hemoglobin level did not relevantly alter any of the previously listed correlations either (results not shown).

Figure 2 shows the difference in mean HRQoL scores between two subgroups of patients classified by CircAct parameters above median (*black columns*) versus below the median (*gray columns*). Based on the thresholds for clinical relevance (effect size ≥ 0.4; $P < 0.01$), higher than median I<O was associated with better global quality of life, higher role functioning, less fatigue, less appetite loss, and less pain. However, higher than median r24 was only

Table 2. Partial correlation coefficients, adjusted for age, between HRQoL indices, and CircAct parameters at baseline, with significance levels

HRQoL scale ($n = 96$)	CircAct parameter		
	I<O	r24	meanAct
Global quality of life	0.39*	0.32 †	0.37*
Role functioning	0.36*	0.31 †	0.40*
Fatigue	-0.39*	-0.36*	-0.39*
Appetite loss	-0.32 †	-0.30 †	-0.32 †
Social functioning	0.35*	0.33*	‡
Pain	-0.40*	-0.30 †	‡
Dyspnea	-0.29 †	-0.27 †	‡
Physical functioning	0.35*	‡	0.35*
Insomnia	-0.33*	‡	‡
Emotional functioning	‡	‡	‡
Cognitive functioning	‡	‡	‡
Nausea/vomiting	‡	‡	‡
Constipation	‡	‡	‡
Diarrhea	‡	‡	‡

*$P \leq 0.001$.
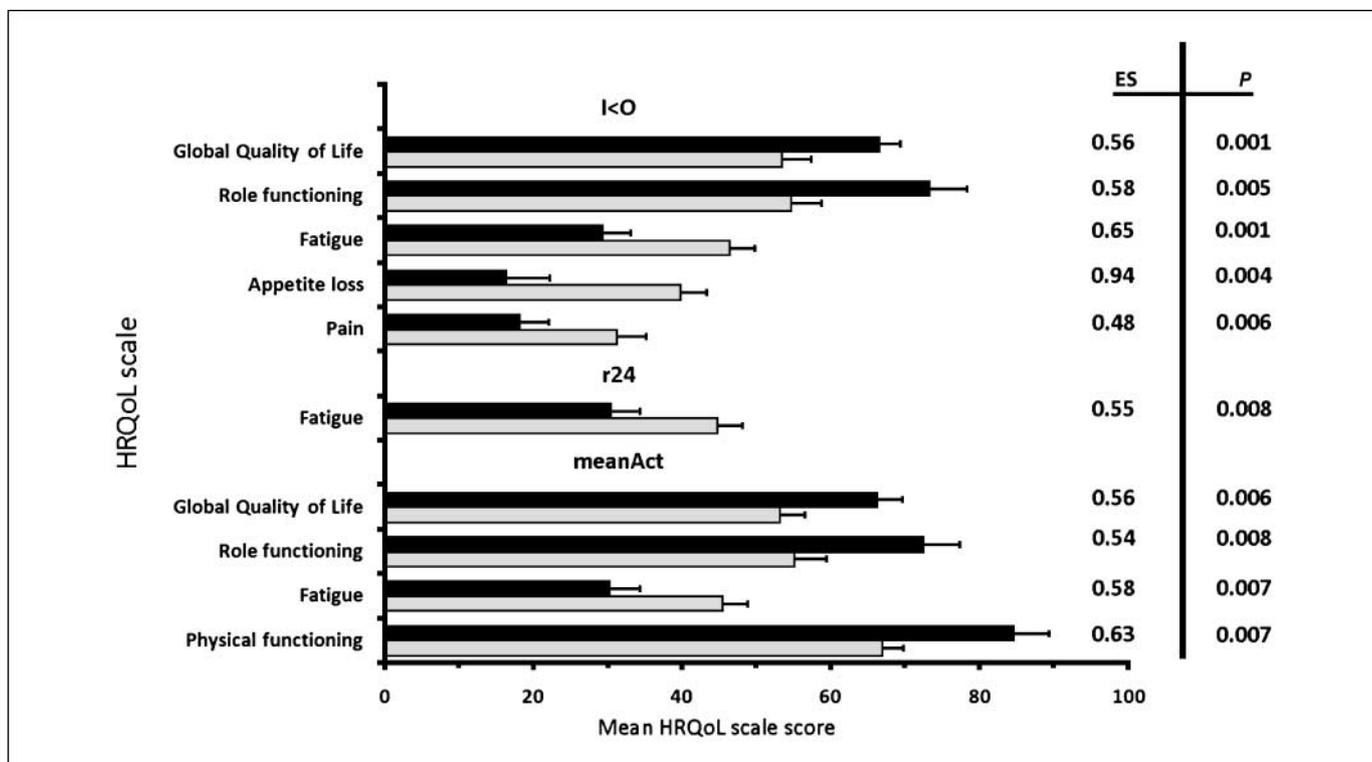† $P \leq 0.01$.
‡ r < |0.25| and/or $P > 0.01$.

Figure 2. Difference in mean ± SE HRQoL scores between two subgroups of patients classified by CircAct parameters above median (*black columns*) versus below the median (*gray columns*) where the clinical relevance (effect size ≥ 0.4) was statistically significant (*P* < 0.01). *Black boxes,* CircAct parameters above median: I<O ≥ 97.0% (*n* = 49), r24 ≥ 0.38 (*n* = 47), and meanAct ≥ 106 counts/min (*n* = 49). *Gray boxes,* CircAct parameters below median: I<O < 97.0% (*n* = 47), r24 < 0.38 (*n* = 49), and meanAct < 106 counts/min (*n* = 47).

main prognostic factors in metastatic colorectal cancer (31, 35) as well as age, gender, body mass index, institution, prior adjuvant chemotherapy, primary tumor site, and treatment arm in a Cox's multivariate regression analysis (hazard ratio, 0.94; 95% confidence interval, 0.92-0.97; *P* < 0.0001). Of those factors, the number of metastatic sites (1 versus >1) and the WBC count (<10 versus ≥10 × 10^9 cells/L) were significantly related to survival (*P* = 0.041 and 0.01, respectively). The bootstrap analysis showed percentages of inclusion in the multiple regression models of 89% for I<O, 74% for PS, and <60% for other parameters. I<O remained independently related to overall survival (hazard ratio, 0.93; 95% confidence interval, 0.90-0.96; *P* < 0.0001) after excluding the 23 patients who had received prior adjuvant chemotherapy. Conversely, r24 did not display an independent prognostic value in a Cox's multivariate regression analysis (*P* = 0.13) after adjustment for the aforementioned factors.

Discussion

The focus of this study was to correlate the circadian rest-activity rhythms of patients with advanced colorectal cancer with quality of life and survival. In this international study involving 130 patients with metastatic colorectal cancer, wrist actigraphy monitoring provided three objective parameters that were selected based on their clinical relevance in a previous study (31). The correlation between CircAct and selected HRQoL scales was confirmed as well as the independent prognostic value of CircAct for survival.

Both r24 and I<O, which quantify different aspects of CircAct, were strongly correlated with each other yet more weakly so with meanAct. The average level of activity, which does not account for

any circadian rhythmicity, was not as clinically relevant, highlighting the clinical importance of circadian physiology as opposed to the mere count of physical activity. Nevertheless, meanAct correlated with the two rhythm parameters, suggesting that a dampened CircAct was associated with reduced average activity. These CircAct parameters do not constitute an objective evaluation of sleep. Other actigraphy parameters, not assessable in the current study, have been reported to correlate with subjective sleep perception as estimated with specific sleep questionnaires (14, 36, 37). A specific assessment of sleep quality and quantity of 95 cancer patients with 42 h continuous ambulatory polysomnography revealed disturbances in sleep and waking states maintenance, with features supporting a blunted sleep drive from the circadian timing system (38).

PS (WHO), a subjective estimate of physical performance, was significantly correlated with I<O and r24. Conversely, the extent of disease involvement did not seem to influence the rhythmic pattern of activity. Damped circadian rhythms have been described in cancer patients with no evidence of disease, for example, in the adjuvant setting (14, 36), suggesting that factors other than tumor burden can account for circadian disruption.

The rest-activity rhythm provides a window on the circadian timing system, which controls hormonal patterns, sleep, food intake, and other rhythmic behaviors (1–3). Disturbances of the circadian timing system are associated with a cluster of symptoms, including fatigue, anorexia, and sleep disturbances (16–18, 39, 40). Damped CircAct was associated with subjective impairment in the physical, role, and social functioning dimensions of HRQoL (with more fatigue, anorexia, pain, dyspnea, and insomnia) as well as with poor global quality of life. These correlations were barely altered by age, body mass index, or hemoglobin concentration

(Table 2), underpinning the hypothesis of an independent role of the circadian timing system on the well-being of patients. These findings further extended and strengthened the relevance of previous results from a single institution study (31, 32). The order of magnitude of the correlation coefficients between CircAct parameters and HRQoL scales ($r \leq 0.4$; Table 2) was comparable with that reported in other studies correlating an objective and unidimensional biological parameter, such as hemoglobin, with the subjective measure of HRQoL (41, 42).

In the current study, CircAct parameters predicted neither for best objective tumor response nor for progression-free survival. In our previous study, the association between CircAct parameters
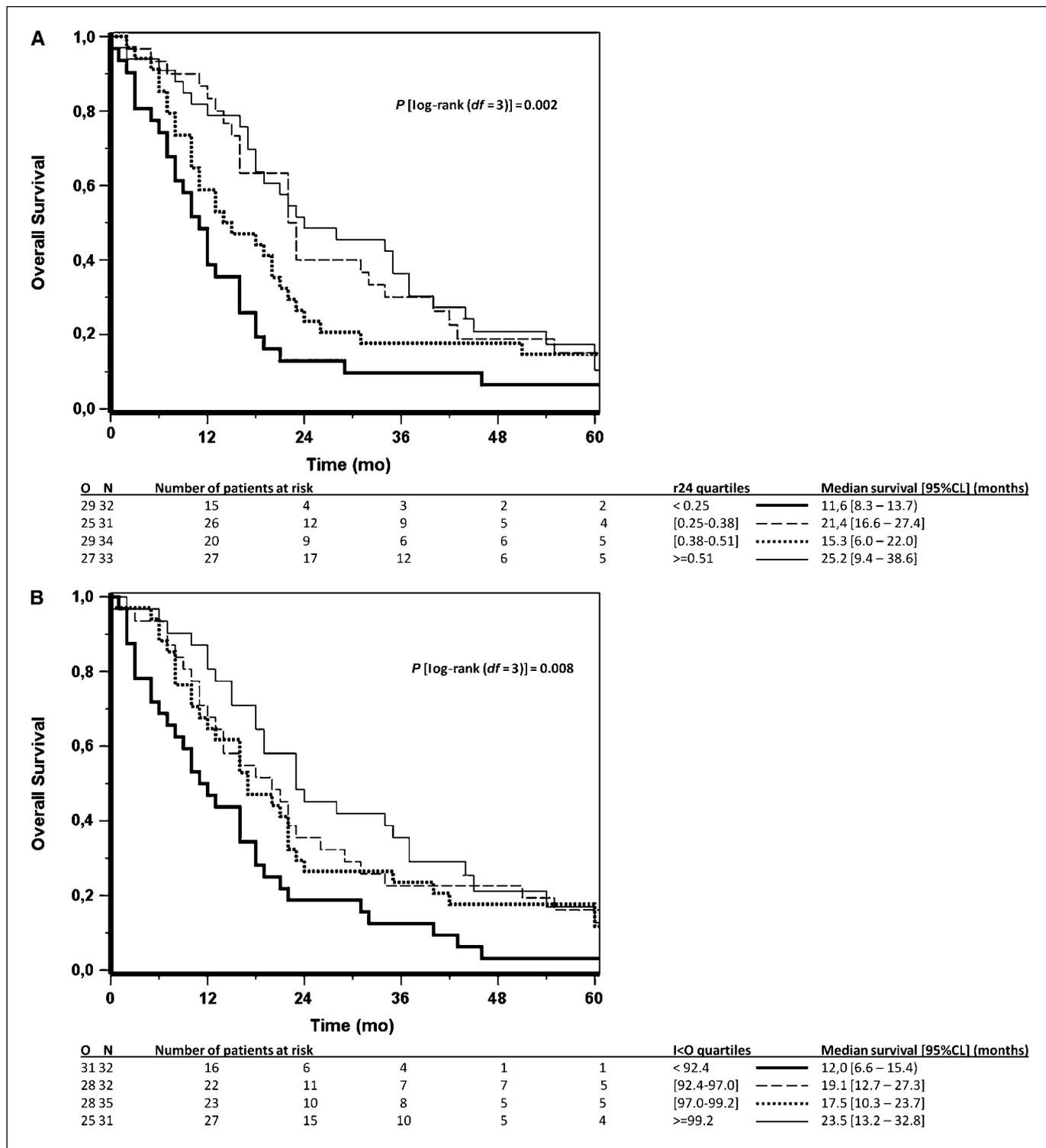
Figure 3. Kaplan-Meier survival curves according to r24 (*A*) and I<O (*B*) split by the quartiles of their distribution. *Thick solid line,* first quartile; *thin dashed line,* second quartile; *thick dotted line,* third quartile; *thin solid line,* fourth quartile. Log-rank test (*df* = 3): *P* = 0.002 for r24 (*A*) and *P* = 0.008 for I<O (*B*).

and progression-free survival was not investigated, but I<O was found to independently predict for tumor response (31). This discrepancy could relate to differences between the two studies regarding the proportion of chemotherapy-naive patients (all versus 39%), the subsequent administration of chronomodulated chemotherapy (48% versus all), and the rate of best objective response (52% versus 35%, respectively; refs. 31, 33).

The peripheral tissue clocks determine the temporal patterns of drug cytotoxicity (1, 43, 44). The CircAct is a marker of the output from the central circadian pacemaker and does not reflect the rhythmicity of molecular clocks in peripheral tissues. Thus, alterations of host CircAct may only marginally affect the time-dependent antitumor activity and normal tissue toxicity. This could account for the lack of correlation between CircAct parameters and tumor response, progression-free survival, or toxicity.

In the present study, I<O was confirmed as an independent prognostic factor for overall survival. The lesser relevance of r24 compared with I<O for HRQoL and survival could indicate that the regular sequence of daytime highly active spans and restful nighttime sleep spans (as measured with I<O) rather than the consistent reproducibility of the activity pattern over exactly 24 h (as estimated by the r24) better reflect the functional status of the circadian timing system.

The trend in overall survival, which differentiated the quartiles of I<O, persisted with time elapsing after CircAct assessment. This observation indicated that the relationship between CircAct and overall survival was independent from immediate premortality disruption in circadian rest-activity cycles (Fig. 3B).

Social synchronization represents an essential time cue for the entrainment of human circadian rhythms (4, 45). A significant correlation between the social functioning dimension of HRQoL and I<O was revealed in both our previous and current studies (32). The independent prognostic value of social functioning for survival has been separately shown in all patients enrolled on the EORTC 05963 trial that completed the EORTC Quality of Life Questionnaire-C30 questionnaire at baseline (46), confirming previous results (47). Impaired social functioning, perceived as interference with family life and social activities, could reflect the patient's self-sensation of cancer-related physiologic disturbances.

Taken together, these data corroborate the hypothesis that the circadian rest-activity rhythm, measured with wrist actigraphy, correlates with several symptoms and domains of well-being as well as with the survival of patients with metastatic colorectal cancer.

The circadian timing system constitutes a novel potential therapeutic target for future multidisciplinary research efforts (44, 48, 49). Interventions that normalize circadian timing system dysfunction should be studied with the aim of relieving symptoms, improving HRQoL and prolonging survival in cancer patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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