Marked 24-h Rest/Activity Rhythms Are Associated with Better Quality of Life, Better Response, and Longer Survival in Patients with Metastatic Colorectal Cancer and Good Performance Status[1]

Marie-Christine Mormont, James Waterhouse, Pascal Bleuzen, Sylvie Giacchetti, Alain Jami, André Bogdan, Joseph Lellouch, Jean-Louis Misset, Yvan Touitou, and Francis Lévi[2]

Laboratoire "Rythmes Biologiques et Chronothérapeutique," Université Paris XI and I.C.I.G., Hopital Paul Brousse, 94800 Villejuif, France [M-C. M., P. B., S. G., A. J., J-L. M., F. L.]; School of Human Sciences, Liverpool John Moores University, Liverpool L3 3AF, United Kingdom [J. W.]; Département de Biochimie Médicale, Hopital de la Pitié-Salpêtrière, 75013 Paris, France [A. B., Y. T.]; and INSERM U 472, 94800 Villejuif, France [J. L.]

ABSTRACT

The rest/activity circadian cycle has been used as a reference for chemotherapy administration at specific times to improve tolerability and efficacy. Because cancer processes may be associated with alterations of circadian rhythms, the rest/activity cycle was monitored noninvasively to assess its relationship with tumor response, survival, and quality of life in 200 patients with metastatic colorectal cancer. Patients wore an actigraph, a wristwatch that records the number of accelerations per minute, for 3 days before receiving chronomodulated chemotherapy. The circadian rhythms in activity were estimated by two robust parameters: the autocorrelation coefficient at 24 h ($r24$), and the dichotomy index (I<O) for comparing amounts of activity when in bed and out of bed. Accurate data for inclusion, quality of life, response, and survival were available for 192 patients. Survival at 2 years was 5-fold higher ($P = 10^{-4}$) in patients with marked activity rhythm (I<O in upper quartile) than in those with rhythm alteration (I<O in lower quartile). These results were supported by the multivariate Cox analysis. Multivariate regression analysis showed that circadian rhythms in activity (I<O; $P = 3 \times 10^{-4}$) and in WBCs ($P = 0.03$) as well as performance status ($P = 0.02$) were jointly prognostic of response. Patients with marked rest/activity rhythms also had better quality of life and reported significantly less fatigue. The individual rest/activity cycle provides a novel independent prognostic factor for cancer patients' survival and tumor response as well as a quantitative indicator for quality of life.

INTRODUCTION

Locomotor activity reliably reflects circadian clock function in several animal species (1). The stereotaxic destruction of the suprachiasmatic nuclei, considered as the hypothalamic circadian clock, suppresses the rest/activity rhythm, whereas their transplantation restores it (2). Mutations in the genes involved in circadian regulation also induce profound alterations of the rest/activity cycle in *Drosophila*, hamsters, or mice (3–5).

In humans, the rest/activity rhythm is considered, and used as, a marker of the endogenous circadian clock function in isolation studies (6–8), in phase-shift studies (9–11), and in psychiatry (12–14) The rest/activity rhythm is a better marker of the human circadian system than cortisol or leukocytes, which interfere with and may be affected by peripheral physiological changes (reviewed in Ref. 15). However, the clinical relevance of the rest/activity rhythm has not yet been addressed in cancer patients.

The administration of anticancer agents at specific stages of the rest/activity cycle improves their therapeutic index in laboratory rodents (16). Time-qualified chemotherapy (chronotherapy) was first successfully used for ovarian cancer (17, 18). An appropriate adjustment of chemotherapy delivery to circadian rhythms became feasible with the advent of multichannel programmable pumps and led to the clinical validation of the chronotherapy principle in Phase I, II, and III clinical trials involving >1500 patients with metastatic colorectal cancer (19–22). More specifically, chronotherapy with 5-fluorouracil, leucovorin, and oxaliplatin reduced by 5-fold the incidence of severe mucositis, halved the incidence of functional impairment from peripheral sensory neuropathy, and nearly doubled the objective response rate compared with constant infusion (21). Nevertheless, interpatient variability was observed, indicating that factors other than the timing of treatment influenced outcome.

Cancer processes can alter circadian function in both experimental tumor models and patients (23). Thus, variability in the outcome of patients receiving chronotherapy may reflect differences in individual circadian rhythms. If so, these rhythms may constitute novel prognostic factors, possibly independent from the clinical factors, which mostly reflect tumor spread

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[2] To whom requests for reprints should be addressed, at Hopital Paul Brousse, 14-16, Avenue Paul Vaillant Couturier, 94800 Villejuif, France. Phone: 33 1 45 59 38 55; Fax: 33 1 45 59 36 02; E-mail: chronbio@club-internet.fr.

(24–26). The status of the circadian system as an estimate of cancer patients' prognosis was first tested in two pilot studies. The first study investigated individual rhythms in relation to clinical predictors for survival in 20 patients with advanced ovarian cancer. Significant correlations were found between well-documented prognostic factors, such as the WHO PS[3] or tumor size, and the circadian amplitude in serum cortisol and leukocyte or neutrophil counts (27). The second study indicated that circadian rhythm alterations were associated with both poor PS and liver metastases in 13 patients with advanced breast cancer (28).

This prospective study was initiated to evaluate the prognostic value of circadian rhythms in patients with metastatic colorectal cancer. The primary hypothesis was that altered rest/activity rhythms would predict for shorter survival. Maximum tumor response and QoL were secondary end points of patient outcome. Additional exploratory analyses were performed to determine whether clinical prognostic factors, other marker circadian rhythms, or QoL factors such as fatigue, sleep disturbances, and pain significantly influenced the relationship between the rest/activity rhythm and survival.

PATIENTS AND METHODS

Patients Selection and Clinical Study

From May 1994 to January 1997, 200 consecutive ambulatory patients with histologically proven metastatic colorectal cancer, referred for chronomodulated chemotherapy, were registered in the study; 52% of the patients had two or more metastatic sites, and 59% had previously failed one to six chemotherapy lines before registration (Table 1). All patients were followed for survival until February 1, 1998, when 126 deaths were recorded. Patients in poor general condition, *i.e.,* with PS, according to WHO, above 2, were not included in the study, as is usual in oncology clinical trials. The initial evaluation included a clinical examination, with PS assessment, thoracic and abdominopelvic computed tomography scan and liver echography. Serum CEA and CA19.9 were determined. Chronomodulated chemotherapy consisted of the association of 5-fluorouracil (3200–3500 mg/m^2/course; peak delivery at 4:00 a.m.) and leucovorin (1200–1500 mg/m^2/course; peak at 4:00 h); oxaliplatin was added to this two-drug regimen in 87% of the patients (100–125 mg/m^2/course; daily maximum at 4 p.m.). Chronotherapy was delivered in fully ambulatory conditions to all patients, using a multichannel time-programmable pump (9–12). Circadian rhythms in serum cortisol and in leukocyte and neutrophil counts as well as the rest/activity cycle were studied before the first cycle of chronotherapy. Maximum tumor response to therapy was assessed every 2 months for the first 6 months by the investigators. Computed tomography scans of the thorax, abdomen, and pelvis were generally complemented with abdominopelvic ultrasonography and underwent extramural review. Complete response was defined as a disappearance of all signs of disease for 4 weeks, and partial response was defined as a reduction of at least 50% in the area of all measurable lesions (20, 21). The Ethical Committee of Kremlin-Bicêtre (France) approved the study, and each patient signed a written informed consent.

Table 1 Characteristics of 192 patients evaluated for circadian rhythms and outcome

Characteristic	No. of patients
Sex (M:F)	128:64
Age (years)	58 (20–75)[a]
Primary tumor site	
Colon	136
Rectum	56
Number of metastatic sites	
1	88
2	74
≥3	30
PS (WHO)	
0	123
1	55
2	14
Liver replacement by tumor	
None	36
<25%	97
≥25%	52
Unknown	8
Chronomodulated chemotherapy regimen	
5-FU[b]/leucovorin/oxaliplatin	166
5-FU/leucovorin	26
Previous chemotherapy for metastases	
Yes:no	118:74

[a] Mean (range).
[b] 5-FU, 5-fluorouracil.

Evaluation of the Rest/Activity Cycle

Individual activity rhythms were measured noninvasively with a small-size wrist-worn piezoelectric accelerometer (Actigraph; Ambulatory Monitoring Inc., New York). The user-defined time interval for the count of wrist accelerations was 1 min. Patients were asked to wear the actigraph for at least three consecutive 24-h spans, which is the recommended duration for evaluating activity circadian rhythm (29). Each patient kept a diary for times of rising and retiring. Data were retrieved and analyzed with specific programs (Ambulatory Monitoring Inc.).

The circadian rhythm in activity (main evaluation criteria) was estimated by two parameters: autocorrelation coefficient at 24 h (*r*24), and a dichotomy index (I<O) comparing amounts of activity when in bed and out of bed. For the autocorrelation, if X_i is the measurement at time *i*, the correlation coefficient r_k, between X_i and X_{i+k} is computed for lags *k*, with $k = 1–4320$ min (72 h); the coefficient at 24:00 h (*r*24) can, in theory, range between −1 and 1. If there is a circadian variation, the correlation coefficient will increase around 24-h lags, and a more pronounced circadian rhythm will result in a higher coefficient at 24:00 h (Fig. 1*a*; Ref. 30). I<O is the percentage of the activity counts measured when the patient is in bed that are inferior to the median of the activity counts measured when the patient is out of bed; thus I<O quantifies the level of activity

[3] The abbreviations used are: PS, performance status, QoL, quality of life; CEA, carcinoembryonic antigen; *r*24, autocorrelation coefficient at 24 h; I<O, dichotomy index; EORTC, European Organization for Research and Treatment of Cancer; HADS, Hospital Anxiety and Depression Scale; CI, confidence interval.

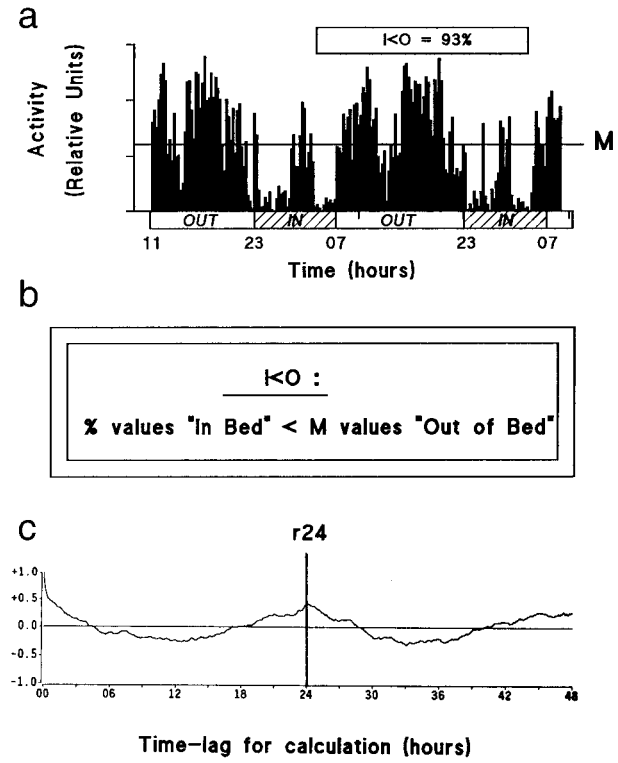

Fig. 1 Example of an actigraphy recording and of the methods for its analysis. *a*, raw data, *i.e.*, activity counts during 48 h as a function of time; *b*, formula for the dichotomy index I<O; *c*, autocorrelation function showing the autocorrelation coefficient (*Y axis*) calculated as a function of successive time lags.

during the rest span, as defined in the patient's diary. This index can theoretically vary between 0 and 100%, and a high I<O reflects a marked rest/activity rhythm (Fig. 1*b*; Ref. 31). Mean activity was calculated for each patient and used as a secondary criteria.

Circadian Rhythm Assessment for Blood-borne Variables

Circadian changes in cortisol and in WBC counts were used as secondary criteria. They were estimated from blood samples collected at 8:00 h and at 16:00 h for 2 consecutive days because the difference between values at these times was shown to be a reliable estimate of the amplitude of circadian rhythm in control subjects and in colorectal cancer patients (32).

QoL Assessment

QoL questionnaires were filled in by the patients before putting on the actigraph. A study investigator was available for questions about the study and how to fill in the forms.

QLQ-C30, from EORTC, is a 30-item questionnaire that incorporates five functional scales, eight symptom scales, and a global QoL scale (33, 34). The questions are formatted with either yes/no answers or with four-answer categories, except for the two questions on general QoL, which are to be answered on a scale numbered from 1 to 7. All calculations were performed after linearly transforming the scores to a 0–100 scale, according to EORTC guidelines (in EORTC QLQ-C30 scoring manual). Higher scores for the global QoL and functional scales represent better functioning, whereas higher scores on the symptom scales indicate a higher level of disturbance.

The HADS consists of seven items that evaluate anxiety and seven that aim at measuring depression; all questions are formatted with four-categories answers. Individual anxiety and depression scores range between 0 and 21 (35–37).

Statistical Analysis

Descriptive Statistics. Mean scores and SEs were calculated for all demographic, clinical rest/activity or other rhythm-related as well as QoL parameters. Normality of distributions was checked.

Primary Hypothesis. Each of the main evaluation criteria (*r*24 and I<O) was assigned to one of four categories according to quartiles, and the survival of patients with very low (<25% quartile), low (>25% and <50% quartile), high (>50% and <75% quartile), or very high (>75% quartile) rhythm parameters was estimated with the Kaplan-Meier method (38), with a comparison of the survival curves by the log-rank test. A regression analysis was conducted on survival time, measured from the date of activity rhythm recording, with the Cox proportional hazard model (39).

Secondary and Exploratory Hypotheses. Parametric or nonparametric (Kruskal-Wallis) ANOVAs were also used to analyze mean rhythm or QoL parameters as a function of categorical demographic and clinical characteristics. Possible associations between rhythm parameters, QoL scores, and continuous clinical parameters were tested with Spearman rank correlations. The influence of each demographic, clinical, or rest/activity-related parameter on maximum tumor response to treatment was assessed by single and multiple factors linear regression. Finally, the multivariate Cox model was used to determine which factors were jointly influential on survival (39).

RESULTS

Analysis of the Rest/Activity Cycle. The pattern of most activity recordings (actograms) ranged between the contrasted examples that are represented in Fig. 2. The three subjects on the left in Fig. 2 had a high mean activity level. The first subject (Fig. 2, *top left-hand panel*) displayed a high activity level during the day, which decreased during the night (rest) period: he had thus high rhythm parameters (I<O and *r*24) The second subject (Fig. 2, *middle left-hand panel*) had a *r*24 above median (*i.e.*, his activity pattern was highly reproducible) but a low I<O (*i.e.*, poor sleep), and the third subject (Fig. 2, *bottom left-hand panel*) had a low *r*24 (*i.e.*, his activity pattern was not reproducible from 1 day to the next) but a high I<O (he slept well when he was in bed). The two subjects on the right in Fig. 2 had a low mean activity level: the first subject (Fig. 2, *top right-hand panel*) maintained a marked circadian rhythm (high I<O and *r*24), whereas the second subject (Fig. 2, *bottom right-hand panel*) had low circadian parameters with apparently altered periods of activity and rest.

The minimum and maximum values of the autocorrelation coefficient were −0.06 and 0.77, respectively, in the 192 eval-

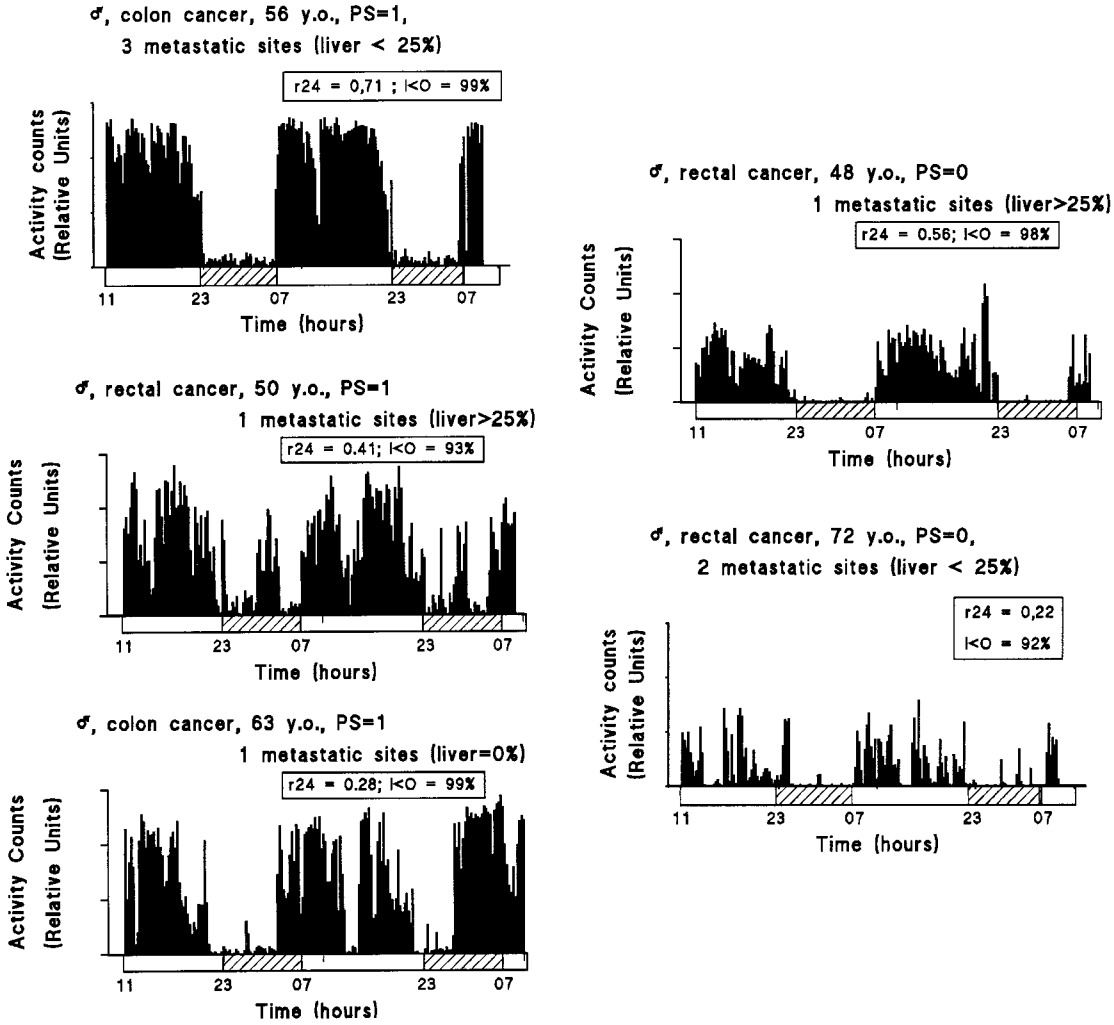

Fig. 2 Recording of the rest/activity cycles of five patients during 48 h.

uated patients, with a median of 0.42 and a normal distribution. I<O ranged from 49 to 100%, with a median at 97%. Mean activity ranged from 6 to 152 cpm; the median value was 96.

Overall Treatment Efficacy. Median survival was 13.2 months, with 31% of the patients alive at 2 years. Sixty-seven patients displayed an objective response (35%), among which 3 were complete. The disease was stabilized in 72 patients (37.5%) and progressed in 53 patients (27.5%).

Influence of Rest/Activity Rhythms on Survival. Marked circadian rhythms in activity, *i.e.*, high $r24$ ($P < 10^{-4}$) and high I<O ($P < 10^{-4}$), predicted for longer survival in the univariate Cox analysis. For graphic purposes, each individual rhythm parameter was assigned to one of four categories according to 25% quartiles. After a 2-year follow-up, survival was 34% (95% CI, 26–43%) for the patients with $r24$ in the three upper quartiles compared with 10% (95% CI, 1–20%) for those whose $r24$ was in the lowest quartile (Fig. 3*a*). Similarly, 2-year survival was nearly 5-fold higher for patients with I<O in both upper quartiles (38%; 95% CI, 27–49%) compared with those with I<O in the lowest quartile (8%; 95% CI, 1–15%; Fig. 3*b*).

Relation of Rest/Activity to Other Rhythm-related Factors. The estimate of cortisol circadian rhythm was positively correlated to $r24$ ($r = 0.16$; $P = 0.04$) but not to I<O or mean activity. The mean cortisol concentration was higher in patients with low values for rest/activity parameters ($r24$: $r = -0.17$; $P = 0.04$, I<O: $r = -0.24$; $P = 0.007$). Mean circadian changes in leukocytes were larger for patients with a high $r24$ ($r = 0.23$; $P = 0.003$) or high I<O ($r = 0.21$; $P = 0.009$). The rhythm estimate of cortisol was not correlated to that of leukocyte count.

Correlations between Rest/Activity and QoL. Global QoL and physical functioning scores, as measured by EORTC QLQ-C30, were positively correlated to circadian rest/activity rhythm but not to the mean activity level. Fatigue and appetite loss were associated with decreased circadian rhythm parameters and with diminished mean activity, whereas pain was correlated with only one of the rest/activity rhythm parameters (I<O). Patients' self-rated sleep difficulties were not significantly correlated to either the rest/activity rhythm or to mean activity. From the HADS questionnaire, depression was associ-

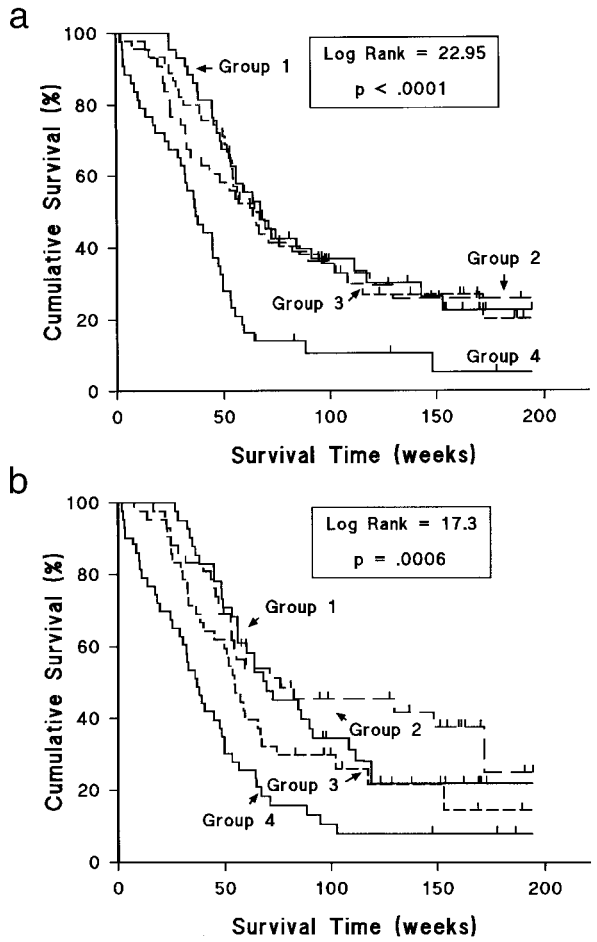

Fig. 3 Kaplan-Meier estimates of survival as a function of the 24-h rhythm parameters, *r*24 (*a*) and I<O (*b*), assigned to one of four categories according to quartiles: *group 1*, very high (>75% quartile); *group 2*, high (>50% and ≤75% quartile); *group 3*, low (>25% and ≤50% quartile); *group 4*, very low (≤25% quartile). Comparison of the survival curves with the log-rank test was statistically significant for either circadian rhythm parameter (*r*24, $P = 10^{-4}$; I<O, $P = 10^{-4}$).

ated with damped circadian rhythms but not to low mean activity (Table 2).

Relationship between Clinical Factors, Activity Rhythms, and QoL. Patients with poor PS had significantly less marked circadian rhythms in activity (*r*24: $P < 10^{-4}$, ANOVA; I<O: $P < 10^{-4}$, Kruskal-Wallis ANOVA); they also had lower mean activity levels ($P = 0.04$, Kruskal-Wallis ANOVA) Mean I<O was also significantly higher in patients who had not been previously treated for metastases ($P = 0.03$). The distributions of I<O, *r*24, and mean activity appeared independent from all other clinical factors. The mean cortisol concentration was higher in patients with poor PS ($P = 5 \times 10^{-4}$) or severe liver involvement ($P < 10^{-4}$).

Increased anxiety ($P = 0.004$), depression ($P = 0.03$), and decreased physical functioning ($P = 0.05$) were associated to rectal tumors. QoL scores did not vary as a function of any other clinical characteristics.

Prognostic Factors of Tumor Response. Objective response rates differed significantly as a function of PS ($P < 10^{-4}$) and previous chemotherapy for metastases ($P = 0.04$) in the univariate analysis. This analysis also showed that the probability for achieving an objective response was significantly influenced by the rest/activity parameters *r*24 ($P = 0.02$) and I<O ($P < 10^{-4}$) as well as the circadian rhythm estimate for leukocyte count ($P = 0.006$). The cortisol rhythm estimate did not influence objective response.

In the multiple regression model, only PS ($P = 0.02$), circadian rhythm in WBC count ($P = 0.03$), and I<O ($P < 10^{-4}$) were jointly influential on maximum response to treatment.

Global Survival Analysis. Univariate survival analysis was performed for all clinical, rhythm-related, and QoL variables. PS, number of metastatic sites, and previous treatment for metastatic disease were strongly related to survival. Patients with <25% liver involvement had a longer survival than those with more extensive liver involvement or those with extrahepatic metastases; the latter patients usually had lung metastases associated with either peritoneal or bone metastases. High levels of CA19.9 or CEA were associated with shorter survival (Table 4). In addition to both rest/activity rhythm parameters (I<O and *r*24), mean activity was significantly related to survival as well as the scores for global QoL physical functioning, fatigue, appetite loss, pain, and depression (Table 3). No significant prognostic value was established for cortisol or leukocyte rhythm estimates with regard to survival.

After univariate analysis, the multivariate Cox model was used to determine which factors were jointly influential on survival. A first multivariate model was built using only well-established clinical factors. When added one by one to this multivariate clinical model, the three parameters from actigraphy maintained independent prognostic value, whereas only four of the QoL scores did (Table 3). Finally, the best fitting clinical prognostic model included liver involvement (>25% *versus* ≤25%), number of metastatic sites, previous treatment for metastases, and PS (2 *versus* 0) jointly with the rest/activity circadian rhythm and mean activity (Table 4). Thus, the circadian rest/activity rhythm added significant prognostic information to the well-established clinical factors related to the tumor or to the patient's general condition (40). This was also the case for mean activity, but to a lesser extent, as documented by the smaller relative risk associated to this parameter.

To further determine whether rest/activity parameters provided additional prognostic information to that already contained in PS, Cox analysis was also performed separately in the subsets of patients with PS = 0 or with PS = 1. Survival was still significantly influenced by I<O in the subgroup of patients with PS = 0 and in patients with PS = 1 (Table 5).

DISCUSSION

By measuring the rest/activity cycle as a major circadian clock output, actigraphy provides a simple tool for evaluating circadian system function in cancer patients. Because wrist monitoring of activity is totally noninvasive, there is no restriction on its use in an ambulatory setting. Dense and reliable individual data could be collected, and a pertinent analysis of the

Table 2 Correlation of QoL and depression with rest/activity rhythm parameters and mean activity

	I < O		*r*24		Mean activity	
	r	*P*	*r*	*P*	*r*	*P*
EORTC QLQ-C30						
Global QoL	0.34	$<10^{-3}$	0.24	0.002	NS[a]	
Physical functioning	0.43	$<10^{-3}$	0.23	0.005	NS	
Fatigue	−0.33	$<10^{-3}$	−0.26	0.001	−0.16	0.05
Appetite loss	−0.29	$<10^{-3}$	−0.23	0.003	−0.20	0.01
Pain	−0.24	0.002	NS		NS	
HADS						
Depression	−0.31	$<10^{-3}$	−0.22	0.01	NS	

[a] NS, not significant.

Table 3 Statistical significance of prognostic factors for the survival of 192 patients with metastatic colorectal cancer in univariate and multivariate Cox analyses

	P	
Variable	Univariate	Multivariate
Clinical		
Previous treatment for metastasis	$<10^{-4}$	10^{-4}
Number of metastatic sites	0.0001	0.0006
PS	$<10^{-4}$	10^{-4}
Liver involvement	0.0003	0.001
Previous surgery for metastasis	0.006	0.003
CA19.9	0.001	NS[a]
CEA	0.01	NS
Rest/activity		
I < O	$<10^{-4}$	10^{-4}
*r*24	$<10^{-4}$	10^{-4}
Mean activity	0.02	0.03
QoL		
Global QoL	0.004	0.02
Physical functioning	10^{-4}	NS
Fatigue	0.0003	0.04
Appetite loss	$<10^{-4}$	0.05
Pain	0.02	NS
Depression	$<10^{-4}$	0.05

[a] NS, not significant.

Table 4 Best fitting multifactorial model for the survival of 192 patients with metastatic colorectal cancer after a 1-year minimum follow-up

Variable	β[a]	SE (β)	*P*
Rest/activity rhythm (I < O)	−0.06	0.01	10^{-4}
Previous treatment for metastasis	1.39	0.32	10^{-4}
PS			10^{-4}
(1 *versus* 0)	0.16	0.21	NS
(2 *versus* 0)	1.82	0.41	10^{-4}
Liver involvement			0.001
(0% *versus* ≥25%)	−0.73	0.29	NS
(<25% *versus* ≥25%)	−0.8	0.23	4×10^{-4}
Number of metastatic sites	0.38	0.11	2×10^{-4}
Previous surgery for metastasis	−0.83	0.28	0.003
Mean activity	−0.007	0.003	0.03

[a] β, regression coefficient; NS, not significant.

rest/activity rhythm was achieved by the robust parameters chosen herein: *r*24 estimated the strength of the circadian periodicity, and I<O quantified abnormal peaks of activity during the rest span. This technique has allowed detection of alterations of the rest/activity circadian pattern, with wide interindividual variations, thus confirming previous observations (23, 31).

The rest/activity rhythm was a strong predictor of both tumor response and survival in patients with metastatic colorectal cancer. Each of the rest/activity-related variables provided additional prognostic information on patients' maximum response to treatment and survival potential to that of well-known clinical factors that reflect tumor burden and patient general condition. The patients with poor circadian rhythmicity, *i.e.*, with I<O in the lowest quartile, had a 5-fold higher risk of dying within 2 years than the patients with a better circadian rhythmicity. Furthermore, the prognostic value of I<O remained statistically significant in the subgroups of patients with PS = 0 or PS = 1 in both univariate and multivariate analysis. This result demonstrated that low rest/activity rhythm parameters did not merely reflect poor PS and further confirmed that the rest/activity rhythm was an independent prognostic factor.

Mean circadian changes in WBC counts were associated with activity rhythms, but the correlation was weak; this might account for the prognostic value of the circadian rhythm in WBC for response but not for survival. The estimate of the circadian rhythm in cortisol, another output variable of the circadian system, was not correlated to patients' outcomes. This suggests that there is an uncoupling between different outputs of the circadian clock in some cancer patients. As documented by the association of cortisol mean concentration with poor-prognosis clinical characteristics, the secretion of cortisol may be directly influenced by tumor burden and spread, whereas the activity rhythm may reflect the global effect of the disease on the circadian clock function.

This study also documented the existence of a link between the rest/activity rhythm and the welfare of cancer patients. Marked rest/activity rhythms are associated with high functional scores and low symptom scores. This is not surprising because several variables evaluated in QoL questionnaires, such as locomotor activity, sleep, and psychomotor performance, are organized along the 24-h time scale. I<O appears to be the parameter that was best correlated to QoL. This circadian index aims at quantifying sleep difficulties by comparing activity values when in bed to the median value of activity when out of bed for each 24-h period. This parameter differs from the usual end points of sleep studies, such as timing of sleep onset, sleep latency, duration, and timing of rapid eye movement (REM)

Table 5 Prognostic multifactorial models of survival in patients with PS = 0 and PS = 1: Statistical significance of the rest/activity cycle parameters and the clinical prognostic factors

	P	
Variable	Subgroup PS = 0 (n = 123)[a]	Subgroup PS = 1 (n = 55)[a]
Rest/activity rhythm (I < O)	0.001	0.03
Previous treatment for metastasis	0.001	3×10^{-4}
Liver involvement	0.01	NS
(0% *versus* ≥25%)	0.02	NS
(<25% *versus* ≥25%)	0.004	NS
Number of metastatic sites	10^{-4}	0.01
Previous surgery for metastasis	0.05	0.01
Mean activity	NS	NS

[a] Number of patients.

sleep; these latter items focus on a description of sleep timing, duration, and structure and do not lead to a global scoring of the sleep phase. In the present study, I<O correlates with the global estimate of QoL, physical functioning, fatigue, appetite loss, and pain scores (Table 2) but not with patients' subjective evaluation of sleep disturbances ($r = -0.14$; $P = 0.07$). The statistical analyses of this study indicate that the rest/activity rhythm does not simply reflect confounding factors such as fatigue or pain: the rest/activity parameters significantly improve the multivariate Cox model for survival, whereas the QoL parameters, even if related to survival, do not increase the significance of the model.

Diagnostic and therapeutic management as well as social or environmental factors exert a major impact on the QoL and outcomes of cancer patients (41–44). Moreover, this study suggests that the individual's circadian system function is associated to some dimensions of a cancer patient's psychological distress and QoL. Likewise, circadian system disturbances were reported in patients with neurological and/or psychological diseases (12–15). Although the issue of causal relationship may not be addressed in this study, these results open novel perspectives toward understanding the impact of cancer-induced circadian system alterations on the host physical and psychological balance.

There were previous indications that circadian rhythms can be altered in severe illness, the degree of abnormality being related to severity, as in cancer patients (27, 28) and in patients in intensive care (44). However, this study is the first to establish that an output rhythm of the circadian clock significantly predicts for survival in a prospective clinical trial. Furthermore, this investigation indicates that individual patients' circadian function may provide a pertinent explanation for interindividual differences in the outcome of patients with colorectal cancer metastases. The scope of application of this concept now needs to be assessed with regard to chemotherapy schedule. The results call for further investigation of the relationship between cancer processes and circadian rhythm alteration, for devising specific therapies to restore the circadian rest/activity rhythm, and for testing the effect of such treatment in combination with chemotherapy on cancer survival.

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