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Sleep-Wake Circadian Activity Rhythm Parameters and Fatigue in Oncology Patients Prior to the Initiation of Radiation Therapy

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Abstract

Background—Little is known about the relationships between sleep parameters and fatigue in patients at the initiation of radiation therapy (RT).

Objectives—In a sample of patients at the initiation of RT, to describe values for nocturnal sleep/rest, daytime wake/activity, and circadian activity rhythm parameters measured using actigraphy and to evaluate the relationships between these objective parameters and subjective ratings of sleep disturbance and fatigue severity.

Methods—Patients (n=185) with breast, prostate, lung, or brain cancer completed self-report measures for sleep disturbance (i.e., Pittsburgh Sleep Quality Index, General Sleep Disturbance Scale) and fatigue (Lee Fatigue Scale) and wore wrist actigraphs for a total of 48 hours prior to beginning RT. Actigraphy data were analyzed using the Cole-Kripke algorithm. Spearman rank correlations were calculated between variables.

Results—Approximately 30% to 50% of patients experienced sleep disturbance depending on whether clinically significant cutoffs for the subjective or objective measures were used to calculate occurrence rates. In addition, these patients reported moderate levels of fatigue. Only a limited number of significant correlations were found between the subjective and objective measures of sleep disturbance. Significant positive correlations were found between the subjective, but not the objective measures of sleep disturbance and fatigue.

Conclusions—A significant percentage of oncology patients experience significant disturbances in sleep-wake circadian activity rhythms at the initiation of RT. The disturbances occur in both sleep initiation and sleep maintenance.

Implications for Practice—Patients need to be assessed at the initiation of RT for sleep disturbance and appropriate treatment initiated.

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INTRODUCTION

Fatigue and Sleep Disturbance in Oncology Patients

For over three decades, studies have demonstrated that fatigue associated with radiation therapy (RT) can have a significant impact on patients' mood, functional status, and quality of life (QOL).¹⁻⁴ In fact, fatigue is the most common and disruptive symptom reported by approximately 80% of patients during RT.⁵⁻⁷

While the exact mechanisms that underlie the development of RT-related fatigue remain to be determined, as noted in the National Comprehensive Cancer Network's (NCCN) Clinical Practice Guideline on Cancer-related Fatigue,⁸ fatigue is rarely an isolated symptom and most commonly occurs with other symptoms including sleep disturbance. However, while several reviews have noted the high prevalence rates of sleep disturbance in cancer patients,⁹⁻¹¹ only a few studies have examined the relationship between fatigue and sleep disturbance in patients who underwent RT.¹²⁻¹⁴ An increased understanding of the relationships between these two symptoms would provide critical information to guide the development and testing of interventions to decrease fatigue and improve sleep.

Subjective and Objective Assessment of Sleep Disturbance

The optimal approaches to assess sleep disturbance in clinical research remain to be determined. Objective measures such as wrist actigraphy and polysomnography can discriminate more precisely between sleep and wake activity which allows for the computation of important sleep parameters (i.e., total sleep time, number of nocturnal awakenings). In contrast, subjective measures help to clarify the effects of sleep disturbance on patients' physical and psychological well-being. Additional information is needed on the relationships between subjective and objective measures of sleep disturbance in oncology patients.^{11,15}

Studies of the Relationship Between Sleep Disturbance and Fatigue

In one of the first studies that used both objective and subjective measures to evaluate the relationship between sleep disturbance and fatigue,¹³ twenty-four patients with bone metastasis who underwent RT completed the Lee Fatigue Scale and wore a wrist actigraph for two consecutive days and nights. Total sleep time ranged from 0.8 to 10.7 hours (mean = 6.7 hours) with an average of 17.4 awakenings per night. Patients' mean sleep efficiency was 70.7% and 75% had sleep efficiency of < 85%. A higher number of total minutes sleep time was associated with decreased levels of morning fatigue ($r = -0.54$, $p = 0.03$). Correlations between other actigraphy parameters and fatigue severity did not reach statistical significance because of the small sample size.

In another study that evaluated the correlates of fatigue in patients undergoing RT ($n=379$),¹² fatigue was assessed using the Fatigue Severity Scale¹⁶ and sleep disturbance was evaluated using a single item on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QOL core 30).¹⁷ At the initiation of RT, a significant positive correlation was found between fatigue severity and sleep disturbance ($r = 0.36$, $p < 0.01$).

The first extensive description of subjective assessments of both fatigue and sleep disturbance, as well as objective assessments of nocturnal sleep/rest, daytime wake/activity, and circadian activity rhythm parameters in oncology patients was reported by Berger and colleagues.¹⁸ In this study, women with breast cancer ($n=219$) completed the Pittsburgh Sleep Quality Index (PSQI)¹⁹ and the Piper Fatigue Scale²⁰ prior to the initiation of adjuvant chemotherapy. Actigraphy was used to obtain objective data on nocturnal sleep,

daytime activity, and circadian rhythm parameters. While patients reported poor sleep, the majority of the actigraphy values were within normal limits established for healthy individuals, except for number and length of night awakenings. A limited number of significant relationships were found between subjective and objective sleep parameters. Higher fatigue severity was associated with higher subjective ratings of sleep disturbance. However, in terms of the various actigraphy parameters, higher fatigue scores were associated with only total wake time per day and acrophase.

Studies of the Relationships Between Various Sleep/Wake and Activity Rhythm Parameters

Only five studies have examined the relationships between various aspects of sleep/wake activity rhythms in patients with lung cancer;²¹ in hospitalized patients with a variety of cancer diagnoses;²² and in patients with breast cancer during chemotherapy.^{9,23, 24} While these studies provide additional information on disruptions in sleep/wake activity rhythms for comparative purposes, no studies were found that provided detailed information on nocturnal sleep/rest, daytime wake/activity, and circadian activity rhythm parameters in patients at the initiation of RT. Detailed information on these parameters is warranted in these patients because of the high prevalence rates and negative consequences of fatigue associated with RT. Therefore, the purposes of this study, in a sample of patients at the initiation of RT, were to describe values for nocturnal sleep/rest, daytime wake/activity, and circadian activity rhythm parameters measured using actigraphy and to evaluate the relationships between these objective parameters and subjective ratings of sleep disturbance and fatigue severity. It was hypothesized that patients at the initiation of RT would report similar levels of sleep disturbance as previously published reports^{18, 21–24} and that significant correlations would be found between objective sleep parameters and subjective ratings of sleep disturbance and fatigue severity.

METHODS

Patients and Settings

This descriptive, correlational study is part of a larger, longitudinal study that evaluated multiple symptoms in oncology outpatients who underwent primary or adjuvant RT.^{7, 25} The patients were recruited from two RT departments located in a Comprehensive Cancer Center and a community-based oncology program. Patients were eligible to participate if they: were ≥ 18 years of age; were scheduled to receive primary or adjuvant RT for one of four common cancer diagnoses (i.e., breast, prostate, lung, brain) that are treated with RT; were able to read, write, and understand English; gave written informed consent; and had a Karnofsky Performance Status (KPS) score of ≥ 60 . Patients were excluded if they had metastatic disease, more than one cancer diagnosis, or a diagnosed sleep disorder.

Theoretical Framework

The theoretical framework for the study was the Theory of Symptom Management, which was developed by faculty members in the Center for Symptom Management at the University of California, San Francisco.^{26–28} As it relates to this analysis, the symptom experience dimension includes an individual's perception of sleep disturbance, physical fatigue and energy, and attentional fatigue, an evaluation of the meaning of the symptoms, and response to the symptoms. The symptom management strategies dimension includes both the self-care strategies that individuals use for themselves and the treatments that clinicians may prescribe. The outcomes dimension specifies that outcomes emerge from symptom management strategies as well as from the symptom experience. The Theory of Symptom Management places the experience of symptom management in the context of the domains of nursing science — namely person, health and illness, and environment. The

focus of this analysis is on the symptom experience dimension of the Theory of Symptom Management, specifically how the experience of sleep disturbance, physical fatigue and energy, and attentional fatigue are related to each other in a sample of oncology patients at the initiation of RT.

Instruments

The study instruments included a demographic questionnaire, the KPS scale,²⁹ the Pittsburgh Sleep Quality Index (PSQI),¹⁹ the General Sleep Disturbance Scale (GSDS),³⁰ the Lee Fatigue Scale (LFS),³¹ and the Attentional Function Index (AFI).³² Objective data on sleep-wake circadian activity rhythms were obtained by continuous noninvasive monitoring of activity over 48 hours using a wrist motion sensor (Mini Motionlogger Actigraph, Ambulatory Monitoring Inc., Ardsley, NY).^{33–35} A minimum of 36 hours of continuous data are necessary to have sufficient data to calculate circadian rhythm parameters for a 24-hour period.¹⁵

The demographic questionnaire obtained information on age, gender, marital status, education, ethnicity, employment status, living arrangements, and the presence of a number of co-morbid conditions.

Subjective ratings of sleep disturbance were evaluated using the PSQI and the GSDS. The PSQI consists of 19 items designed to assess the quality of sleep in the past month. The global PSQI score is the sum of the seven component scores (i.e., subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, daytime dysfunction). Each component score ranges from 0 to 3 and the global PSQI score ranges from 0 to 21. Higher global and component scores indicate more severe complaints and a higher level of sleep disturbance. A global PSQI score of >5 indicates a significant level of sleep disturbance.¹⁹ A cutoff score of 8 was found to discriminate poor sleep quality in oncology patients.³⁶ The PSQI has established internal consistency, test-retest reliability, and construct validity.^{19, 36, 37} In this study, the Cronbach's alpha for the global PSQI score was 0.72.

The GSDS consists of 21-items designed to assess the quality of sleep in the past week. Each item was rated on a 0 (*never*) to 7 (*everyday*) numeric rating scale (NRS). The GSDS total score is the sum of the seven subscale scores (i.e., quality of sleep, quantity of sleep, sleep onset latency, mid-sleep awakenings, early awakenings, medications for sleep, excessive daytime sleepiness) that can range from 0 (*no disturbance*) to 147 (*extreme sleep disturbance*). Each mean subscale score can range from 0 to 7. Because the GSDS items are rated on a scale of 0 (never) to 7 (every day), the subscale scores provide an estimation of the number of days per week that a patient experiences a particular problem. Higher total and subscale scores indicate higher levels of sleep disturbance. Mean subscale scores of ≥ 3 and a GSDS total score of ≥ 43 indicate a significant level of sleep disturbance.³⁸ The GSDS has well-established validity and reliability in shift workers, pregnant women, and patients with cancer and HIV.^{13, 30, 39} In the current study, the Cronbach's alpha for the GSDS total score was .84.

Subjective ratings of physical fatigue and energy were evaluated using the LFS.³¹ The LFS consists of 18 items that are each rated on a 0 to 10 NRS. Total fatigue and energy scores were calculated as the mean of the 13 fatigue items and the 5 energy items, with higher scores indicating greater fatigue severity and higher levels of energy. Respondents were asked to rate each item based on how they felt "right now," within 30 minutes of awakening (morning fatigue, morning energy), and prior to going to bed (evening fatigue, evening energy). The LFS has been used with healthy individuals^{31, 40} and in patients with cancer and HIV.^{7, 13, 41, 42} Cutoff scores of ≥ 3.2 and ≥ 5.6 indicated high levels of morning and

evening fatigue, respectively.³⁸ Cutoff scores of ≤ 6.0 and ≤ 3.5 indicate low levels of morning and evening energy, respectively. The LFS was chosen for this study because it is relatively short, easy to administer, and has well established validity and reliability. In this study, Cronbach alphas for evening and morning fatigue at baseline were .96 and .95, respectively. Cronbach alphas for evening and morning energy were .95 and .95, respectively.

Subjective ratings of attentional fatigue were evaluated using the AFI. The AFI consists of 16 items that are each rated on a 0 to 10 NRS. A mean AFI score was calculated, with higher scores indicating greater capacity to direct attention and, therefore, lower levels of attentional fatigue.³² Based on a previously conducted analysis of the frequency distributions of AFI scores, attentional fatigue can be grouped into categories of functional status (i.e., patients who score < 5.0 functioning poorly and experiencing high levels of attentional fatigue, patients who score 5.0 to 7.5 functioning moderately well and experiencing moderate levels of attentional fatigue, patients who score > 7.5 functioning well and experiencing low levels of attentional fatigue.⁴³ The AFI has established reliability and validity.^{32, 44} In the current study, Cronbach's alpha for the AFI was 0.95.

Objective data on sleep-wake circadian activity rhythms were obtained by continuous noninvasive monitoring of activity over 48 hours using wrist actigraphy. Seven nocturnal sleep/rest, four daytime wake/activity, and six circadian activity rhythm parameters were selected from those identified by a National Cancer Institute sponsored conference,⁴⁵ an expert panel that recommended a standard set of research assessments in insomnia,⁴⁶ and recently published studies.^{18, 47} The definitions and values for each of these parameters are listed in Table 1.

Wrist actigraphy has been validated with EEG measures of sleep and awakenings in men and women with both healthy and disturbed sleep patterns.^{34, 35, 46} It provides continuous motion data using a battery-operated wristwatch-size microprocessor that senses motion with a piezo-electric beam and detects movement in all three axes. The accompanying Action 4® software (Ambulatory Monitoring Inc., Ardsley, NY) allows analysis of activity and nonactivity as well as automatic scoring of sleep and wake episodes in minutes. Actigraphy scores, calculated using specific algorithms, correlate with polysomnography in adults at greater than 90%.³⁵

Patients were asked to use the event marker on the wrist actigraph to indicate "lights out" and "lights on" time. Patients reported no difficulties wearing the wrist actigraph. Since the actual time is important in the calculation of the amount of sleep obtained in the amount of time designated for sleep, having an additional source of information about nap times, bed times, and wake times is important. This information was recorded by patients in a two day diary. Upon awakening, the patients used the diary to indicate the number of awakenings during the night.

Study Procedures

The study was approved by the Committee on Human Research at the University of California, San Francisco and at the second site. At the time of the simulation visit (i.e., approximately one week prior to the initiation of RT), patients were approached by a research nurse to discuss participation in the study. After obtaining written informed consent, they completed the demographic questionnaire, KPS scale,²⁹ PSQI,¹⁹ GSDS,³⁰ and AFI.³² Medical records were reviewed for disease and treatment information.

Patients were taught to complete the LFS³¹ before going to bed each night (i.e., evening fatigue, evening energy) and upon arising each morning (i.e., morning fatigue, morning

energy) for 2 consecutive days. Patients wore the wrist actigraph to monitor nocturnal sleep/rest and daytime wake/activity continuously for two consecutive days and completed the two day diary. Patients returned the questionnaires and actigraphs to the research nurse in the RT department.

Data Analysis

Data were analyzed using SPSS Version 15.48 Descriptive statistics and frequency distributions were generated for the sample characteristics and symptom data. Spearman rank correlations were calculated between variables.

Actigraphy files programmed in zero-crossing mode with 30 second intervals were analyzed using the Cole-Kripke algorithm in the Action 4® software (Ambulatory Monitoring Inc., Ardsley, NY) by two of the researchers (KL and CW). First, the file was scanned for missing data. If more than four hours of day data or two hours of night data were missing, that day's or night's data were not used in the analyses. Time limits were set for the 48-hour period. The file was reviewed and intervals were individually set for each day and night period using, in order of priority as decision guides, the event marker, diary data, channel data, and cascading movement data. Cosinor analysis fit a cosine and sine wave to the wrist actigraphy data using a least-squares regression model. The mesor (24-hour adjusted mean value or y-intercept), amplitude, and acrophase (time of day for peak activity) were the circadian activity rhythm parameters obtained from the regression model.⁴⁹ The autocorrelation coefficient for a 24-hour rhythm was obtained from the Action 4® software program.

All calculations used actual values. Adjustments were not made for missing data. Therefore, the cohort for each analysis was dependent on the largest set of available data across groups. A p-value of <0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

As summarized in Table 2, the majority of the patients (n=185) were male (51.9%), White (72.1%), married/partnered (56.6%), and well educated, with a mean age of 60.6 ($\pm$ 12.0) years. As summarized in Table 3, 42% of the patients had breast cancer and 44% had prostate cancer. Patients reported an average of 4.8 ($\pm$ 2.5) co-morbidities and were diagnosed with cancer for 6.7 ($\pm$ 9.4) months.

Subjective Ratings of Sleep Disturbance

Subjective ratings of sleep over the past month using the PSQI are listed in Table 4. The mean global PSQI score at the initiation of RT was 6.6 which is higher than the cutoff score of > 5. Over 56% of the patients had a global PSQI score of > 5 and 26% had a global score above the proposed cutoff of > 8 for oncology patients. The PSQI sleep disturbance subscale had the highest score with all patients reporting sleep problems 1 to 2 times per week during the past month.

Subjective ratings of sleep over the past week using the GSDS are listed in Table 4. The mean total GSDS score at the initiation of RT was 40.2 which is slightly lower than the cutoff score of $\geq$ 43. However, over 40% of the patients had a total GSDS of $\geq$ 43. The GSDS subscale scores for quantity of sleep and mid-sleep awakenings had the highest scores, indicating that patients perceived fewer hours of sleep than desired and a high number of mid-sleep awakenings on 4 out of 7 nights.

Nocturnal Sleep/Rest, Daytime Wake/Activity, and Circadian Activity Rhythm Parameters

Table 5 summarizes the data on sleep/rest, wake/activity, and circadian activity rhythm parameters obtained using actigraphy. Mean values for the sleep/rest parameters were within normal ranges for all of the variables except percentage of time awake at night, number of awakenings, total sleep time, and sleep efficiency. All of these values indicated that the patients experienced a significant amount of sleep disturbance. On average, patients slept approximately 50 minutes during the day (range 0 to 651 minutes). In this sample, none of the mean values for the circadian rhythm parameters were within normal ranges.

Subjective Ratings of Fatigue and Energy

Table 4 summarizes the data on morning and evening fatigue and energy scores, as well as on attentional fatigue. While the mean morning and evening fatigue scores were below the cutoff values for clinically significant levels of fatigue, 33.7% and 25.4% of the patients reported morning and evening fatigue scores above these cutoff values. In contrast, both morning and evening mean energy levels were below the cutoff scores which indicated low levels of energy in these patients. The majority of patients (54.4%) reported moderate to high levels of attentional fatigue.

Correlations Between Subjective Ratings of Sleep Disturbance and Nocturnal Sleep/Rest, Daytime Wake/Activity, and Circadian Activity Rhythm Parameters

Tables 6 and 7 summarize the significant correlations between PSQI and GSDS subscale and total scores and the various sleep/rest, wake/activity, and circadian activity rhythm parameters obtained with actigraphy. As shown in Table 6, a limited number of significant correlations were found between the PSQI global score and sleep onset latency, total sleep time, sleep period time, mesor, and circadian quotient. Some of the strongest correlations were found between the use of sleep medications subscale and total sleep time, sleep period time, amplitude, and circadian quotient.

As shown in Table 7, a significant correlation was found between the GSDS total score and sleep onset latency. In addition, significant correlations were found between the subscale of excessive daytime sleepiness and all of the wake/activity parameters and the majority of the circadian activity rhythm parameters.

Correlations Between Fatigue and Energy Scores and Subjective Ratings of Sleep Disturbance and Nocturnal Sleep/Rest, Daytime Wake/Activity, and Circadian Activity Rhythm Parameters

As shown in Table 8, significant positive correlations were found between the majority of the subscale and total scores for both the PSQI and the GSDS and patients' ratings of morning and evening fatigue. In addition, significant negative correlations were found between the majority of the subscale and total scores for both the PSQI and the GSDS and patients' ratings of morning and evening energy and attentional fatigue (i.e., indicating higher levels of attentional fatigue). Only four significant correlations were found between fatigue and energy scores and the objective sleep parameters.

DISCUSSION

This study is the first to provide detailed subjective and objective data on sleep/rest, wake/activity, and circadian activity rhythm parameters in a sample of patients prior to the initiation of RT. In addition, this work extends findings on sleep disturbance in patients who underwent a variety of cancer treatments.^{9, 12, 13, 18, 21–24} Based on these patients' subjective responses to the PSQI and the GSDS, approximately 40% to 50% experienced clinically significant levels of sleep disturbance prior to the initiation of RT. This percentage

is consistent with a previous report that used the PSQI to evaluate sleep disturbance in women prior to the initiation of adjuvant chemotherapy for breast cancer¹⁸ but lower than that reported for patients with advanced lung cancer.^{50, 51} Using an actigraphy-sleep efficiency cutoff of < 80%, approximately 30% of the patients had a “bad night’s sleep”. Taken together, the subjective and objective data suggest that a third to a half of the sample were experiencing clinically significant levels of sleep disturbance prior to the initiation of RT. In addition, an evaluation of the subjective and objective data suggests that many of these patients had difficulties with both the initiation of sleep and sleep maintenance.

Relationships between subjective and objective sleep parameters in oncology patients

Consistent with previous studies of oncology patients^{18, 52, 53} and elderly persons,⁵⁴ only a limited number of significant correlations were found between the sleep/rest, wake/activity, and circadian activity rhythm parameters obtained with actigraphy and the subjective ratings of various aspects of sleep disturbance using the PSQI and the GSDS. As shown in Tables 6 and 7, the strength of most of these correlations ranged from small to moderate. As noted in a recent review,³³ numerous methodological challenges exist with actigraphy that may affect the strength of the correlations between objective and subjective measures of sleep disturbance. While the agreement between actigraphy and polysomnography is high in normal sleepers,^{35, 55} it can be lower in persons with poor sleep quality⁵⁶ because these persons tend to lie in bed motionless but awake for long periods of time. In this situation, actigraphy would overestimate sleep duration. However, patients would report decreased sleep quality and quantity of sleep. This finding is confirmed in this study because using previously established cutoff scores for the subjective measures, approximately 40% to 50% of the patients had significant sleep disturbance at the initiation of RT. However, using an actigraphy-based sleep efficiency cutoff of < 80%, only 30% of the patients were classified as having a significant level of sleep disturbance. In addition, in this study sleep period time ranged from 311 to 686 minutes and over 51% of patients spent more than 8 hours in bed each night.

In several studies,^{18, 33, 53, 54} recommendations were made to use both subjective and objective measures to evaluate sleep because these different approaches capture different aspects of disturbed sleep. For example, subjective measures capture the physical and mental aspects of sleep and the impact of sleep on patients’ ability to function. Of note, differences in the number and strength of the correlations were found between the various actigraphy parameters and subjective ratings using the PSQI and the GSDS. This finding suggests that the PSQI and GSDS may capture different dimensions of sleep disturbance. The use of multiple measures to evaluate sleep disturbance in oncology patients warrants investigation in future studies, particularly in terms of which measures are most sensitive to changes in various sleep parameters over time. This information is critical to the evaluation of the efficacy of pharmacologic and nonpharmacologic interventions to reduce sleep disturbance in oncology patients.

Sleep Disturbance in Oncology Patients Compared to Other Populations

The PSQI is one of the most frequently used self-report measures to assess sleep quality in the past month in oncology patients^{18, 36, 37, 50, 51, 57–61} and in a variety of other populations.^{19, 62–65} The PSQI global score for this sample (6.6 ± 3.8) was higher than values reported for healthy controls (range 1.9 to 3.1),^{19, 65} comparable to previous studies of patients with a variety of cancer diagnoses (range 6.0 to 7.0),^{18, 36, 57, 60} but lower than reports from patients with advanced cancer (range 10.6 to 12.0).^{50, 59} All of the PSQI subscale scores followed a similar pattern. Of note, over 25% of the patients in this study had problems with the initiation (sleep latency subscale) and maintenance (sleep duration subscale) of sleep on two to three nights per week.

For the GSDS measure of disturbed sleep in the past week, patients in this study had lower scores (40.2 ± 19.9) than those in other samples of patients with a variety of cancer diagnoses (i.e., 54.7 and 52.1).^{42, 66} However, patients in this study had GSDS total scores comparable to mothers in their third trimester of pregnancy (43.9)⁴⁰ and women before and after hysterectomy (42.3 and 45.7),⁶⁷ but lower than nurses who worked nights (60.5) or rotated shifts (56.6).³⁰ Because the GSDS items are rated on a scale of 0 (never) to 7 (everyday), the subscale scores provide an estimation of the number of days per week that patients experienced a particular problem. As shown in Table 4, over 95% of the patients in this study reported an insufficient amount of sleep on 4 or more days per week. In addition, almost 75% of the sample experienced a clinically significant number of mid-sleep awakenings on almost 5 nights per week. Actigraphy data showed that patients averaged 16.5 brief awakenings per night which is well above healthy adult values. Similar to the PSQI data, the GSDS data suggest that patients in this study had problems with both the initiation and maintenance of sleep prior to the start of RT.

Compared to healthy adult values, patients in this study reported significant disturbances in all of the sleep-wake parameters, except sleep onset latency. When these patients' data were compared, using one sample t-tests, to the findings reported by Berger and colleagues for women with breast cancer at the initiation of adjuvant chemotherapy,⁸ patients in this study reported longer average sleep onset latencies (16.5 minutes versus 11.4 minutes; $p=0.004$), a higher number of awakenings (16.5 versus 9.7; $p<0.0001$), and a lower sleep efficiency (81.8% versus 86.1%; $p<0.0001$). These differences may be partially explained by differences in sample characteristics. While Berger's sample consisted of only women with breast cancer, in this study approximately 44% of the patients were men with prostate cancer and another 13% had lung cancer or a brain tumor. While no studies of objective sleep-wake parameters in patients with prostate cancer were found, findings from two studies of patients with lung cancer suggest that these patients experience significant sleep-wake disturbances evaluated using actigraphy.^{21, 53} Future studies need to evaluate for differences in sleep-wake parameters based on cancer diagnoses, stage of disease, and different treatment regimens (e.g., chemotherapy versus RT), as well as the impact of the side effects of cancer treatment (e.g., nausea and vomiting, menopausal symptoms, increased urinary frequency, diarrhea) on sleep.

Impact of Daytime Sleepiness

The impact of daytime napping^{68–70} and daytime sleepiness (i.e., sleepiness during the day that is sufficient to interfere with daily activities)⁷¹ were the subject of a number of recent reviews. While most of the research on the impact of daytime naps has focused on healthy adults and shift workers,⁶⁹ additional research in elderly persons⁶⁸ suggests that daytime naps of less than 30 minutes duration may have beneficial effects on performance and alertness. However, several studies in elderly individuals suggest that daytime napping may perpetuate a cycle of reduced sleep quality and daytime sleepiness and increase an individual's risk for cardiovascular morbidity and mortality.⁶⁸

Patients in this study slept approximately one hour during the day. This finding is comparable to previous studies of patients with breast cancer^{18, 52, 61} and patients with bone metastasis¹³ but shorter than the amount of daytime sleep reported by patients with lung cancer.²¹ Of note, patients who reported longer sleep times during the day reported higher GSDS excessive daytime sleepiness subscale scores ($r=.26$, $p<.01$). In addition, patients who reported higher PSQI daytime dysfunction and higher levels of excessive daytime sleepiness on the GSDS reported increased levels of morning and evening fatigue, increased levels of attentional fatigue, and decreased levels of morning and evening energy. One limitation of this study is that the timing and duration of the daytime naps was not determined. Additional research is warranted on when, how often, and for how long

oncology patients nap prior to, during, and after the completion of RT. In addition, an evaluation of “power naps” (i.e., naps of less than 30 minutes duration that occur at around 3:00 PM) is warranted because several studies suggest that these types of naps improve an individual’s ability to function throughout the rest of the day.⁶⁹

Circadian Rhythm Parameters

Findings from several studies primarily in patients with breast cancer,^{18, 22, 47, 50, 72–74} suggest that circadian rhythm parameters are significantly disrupted in oncology patients. These disruptions in circadian rhythms were associated with increased levels of fatigue,^{47, 73, 74} increased levels of depressive symptoms,^{47, 75} decreased levels of function,⁵² decreased QOL,^{76, 77} and increased mortality.^{76, 77} In this study, acrophase values were similar to the general population. However, mesor and amplitude were below healthy adult values. In addition, when these patients’ data were compared, using one sample t-tests, to findings reported by Berger and colleagues,¹⁸ all of the values for the various circadian rhythm parameters were worse (all $p < 0.0001$). This finding indicates that these patients had dampened circadian rhythms with low daytime activity and higher nighttime activity.

Relationships Between Sleep Disturbance and Fatigue

Consistent with previous studies of RT,^{78–82} patients in this study reported moderate levels of morning and evening fatigue. In addition, they reported moderate levels of attentional fatigue which were comparable to those of patients prior to and following surgery for breast cancer.^{32, 83, 84} An important finding is that over 30% of the patients in this study reported low levels of morning and evening energy. As expected and consistent with previous reports,^{18, 47} increased levels of fatigue and decreased levels of energy were associated with almost all of the subscale and total scores on the PSQI and the GSDD. However, similar to the findings by Berger and colleagues,¹⁸ fatigue and energy scores were not correlated with the majority of the actigraphy measures.

Study Limitations

A number of limitations need to be acknowledged. While the sample size was relatively small and the patients were heterogeneous in terms of cancer diagnoses, this study provides important information on sleep-wake circadian activity rhythm parameters that can be used for comparative purposes. Ideally, actigraphy data should be collected for a full 72 hours to study circadian rhythms. However, in order to reduce respondent burden and because some patient’s level of acuity limited data collection to 48 hours, data were collected only on weekdays which eliminated changes in the various objective parameters that might occur on weekends. Finally, data were not available on the specific sleep medications that these patients used or on other medications (e.g., opioid analgesics) that could contribute to sleep disturbance.

Implications for Research and Clinical Practice

Despite these limitations, data from this study suggest that a significant percentage of oncology patients experience significant disturbances in sleep-wake circadian activity rhythms. Additional research is warranted on how both subjective and objective parameters change over time, which patients are at greatest risk for these disturbances, which cancer treatments are associated with the most severe levels of sleep disturbance, which side effects of cancer treatment have the greatest impact on sleep disturbance, and the ability of pharmacologic and nonpharmacologic interventions to decrease the levels of disturbance in these patients.

As noted in a number of state-of-the science papers, 11· 45· 85· 86 oncology clinicians need to perform systematic assessments of patients' sleep quality. At a minimum, a sleep assessment should evaluate: bedtime problems (e.g., difficulty falling asleep, difficulty staying asleep), excessive daytime sleepiness, number of awakenings, regularity of sleep (e.g., bedtimes and wake times), and sleep disordered breathing (e.g., snoring, observed pauses in respirations, morning headaches).⁸⁷ Oncology clinicians need to assist patients to follow basic sleep hygiene principles. Patients should be encouraged to establish regular sleep times and wake times, to engage in regular exercise, and to take short naps of 30 minutes or less prior to 4:00 PM. In addition, they should be encouraged to keep sleeping areas dark, turn off the television at night, avoid excessive fluid intake, and restrict caffeinated beverages in the evening.^{11· 88} Implementation of these simple principles may improve patients' sleep quality and decrease fatigue during RT.

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Table 1

Definitions of and values for sleep/wake, activity/rest, and circadian rhythm parameters obtained with actigraphy^a

Variable	Definition	Healthy adult values
Sleep/wake		
Sleep onset latency (SOL)	Number of minutes between when someone lays down to sleep and actually goes to sleep (measure of sleep initiation)	Normal SOL is less than 20 minutes
Percent wake at night	Percentage of time awake after sleep onset during a sleep period (measure of sleep maintenance)	In adults, normally is less than 10% of the total sleep minutes or 42 minutes if a person sleeps 420 minutes
Number of awakenings	Total number of awakenings during a sleep period	Adults normally awaken 2 to 6 times during a typical night's sleep of 420 minutes
Wake duration	Number of minutes per awakening	Unknown
Total sleep time	Total sleep time while in bed; number of minutes of sleep while in bed	7 to 9 hours (420–540 minutes) in 24 hours
Sleep period time	Total number of minutes in bed	Unknown
Sleep efficiency (SE)	The number of minutes of sleep divided by the total number of minutes in bed, multiplied by 100	95% SE indicates a good night's sleep; less than 80% indicates a bad night's sleep in an night's sleep of 420 minutes
Activity/rest		
Total sleep time/day	Number of minutes asleep during the day from 9:00 to 20:59	Unknown
Total wake time/day	Number of minutes awake during the day from 9:00 to 20:59	Unknown
Sleep percent of day	Percentage of time asleep during the day from 9:00 to 20:59	Unknown
Wake percent of day	Percentage of time awake during the day from 9:00 to 20:59	Unknown
Circadian rhythm		
Mesor	24 hour rhythm adjusted mean of activity counts; higher values represent more robust activity	138.2 (8.4) to 150.3 (17.7)
Amplitude	Peak (or trough) value of the cosine curve minus the mesor; represents the rhythmic change of an individual activity during the 24-hour period	109.0 (23.4) to 112.4 (4.9)
Peak activity	Sum of the mesor and amplitude values; it represents more robust circadian activity rhythms	Approximately 250 to 260
Acrophase	Actual clock time of the peak amplitude	Early afternoon between 14:00 and 15:00
Circadian quotient	Strength of the circadian rhythm, calculated by dividing the amplitude by the mesor.	Closer to 1.00
Autocorrelation	Comparison of the regularity and consistency of the rhythm from one day to the next day	Range -1 to +1; optimal = +1.0

^a Adapted from reference 18

Abbreviations: SE, sleep efficiency; SOL, sleep onset latency

Table 2

Demographic Characteristics of the Patients Prior to Radiation Therapy (n=185)

Characteristic	Mean (standard deviation) and range
Age (years)	60.56 (12.04) – 24 to 85
Education (years)	16.02 (2.93) – 9 to 26
	%
Gender	
Male	51.9
Female	48.1
Ethnicity	
White	72.1
Nonwhite	27.9
Married/partnered	56.6
Lives alone	30.3
Employed	44.1
Children living at home	17.8
Parent living at home	4.3

Table 3

Clinical Characteristics of Patients Prior to Radiation Therapy (n=185)

Characteristic	Total sample	Breast cancer	Prostate cancer	Brain cancer	Lung cancer
Percentage of patients (%)	100	42.2	44.3	7.0	6.5
Karnofsky Performance Status score (Mean (SD))	90.8 (11.7) Range = 50 to 100	88.9 (11.1) Range = 60 to 100	95.6 (6.9) Range = 60 to 100	82.3 (17.9) Range = 50 to 100	79.2(16.2) Range = 50 to 100
Number of comorbidities (Mean (SD))	4.8 (2.5) Range 0 to 14	5.2 (2.6) Range 1 to 14	4.6 (2.5) Range 0 to 11	3.7 (2.1) Range 1 to 7	4.8 (1.8) Range 1 to 8
Length of time since diagnosis (months) (Mean (SD))	6.7 (9.4) Range = 0.2 to 87.1	5.2 (2.7) Range = 0.5 to 13.3	8.9 (12.7) Range = 12.7 to 87.1	2.1 (1.6) Range = 0.7 to 5.7	6.7 (12.2) Range = 0.2 to 44.5
Stage of disease (%)		0 = 9.2 I = 44.7 II = 10.5 IIA = 13.2 IIB = 11.8 IIIA = 5.3 IIIB = 5.3	T1 = 48.8 T2 = 42.5 T3 = 8.8	Meningioma = 23.1 Astrocytoma = 15.4 Anaplastic astrocytoma = 7.7 Glioblastoma = 53.8	Small cell = 18.2 Non-small cell = 81.8
Surgery prior to radiation therapy (%)	-----	100	9.8	100.0	8.3
Chemotherapy prior to radiation therapy (%)	-----	55.8	-----	-----	58.3%
Hormonal therapy prior to radiation therapy (%)	-----	43.8	52.5	-----	-----

Abbreviations: SD, standard deviation.

Table 4
Pittsburgh Sleep Quality Index, General Sleep Disturbance, and Fatigue, and Energy Scores Prior to Radiation Therapy (n=185)

Pittsburgh sleep quality index						
Subscale and Global PSQI scores (range of possible scores)	Mean	Standard deviation	Subscale score range 0 to 0.9 n (%)	Subscale score range 1.0 to 1.9 n (%)	Subscale score range 2.0 to 3.0 n (%)	
Sleep quality (0 to 3)	0.99	0.74	45 (24.5)	102 (55.4)	37 (20.1)	
Sleep latency (0 to 3)	1.02	0.96	67 (36.4)	62 (33.7)	55 (29.9)	
Sleep duration (0 to 3)	0.98	0.93	67 (37.0)	63 (34.8)	51 (28.1)	
Habitual sleep efficiency (0 to 3)	0.69	0.98	106 (58.9)	38 (21.1)	36 (20.0)	
Sleep disturbances (0 to 3)	1.43	0.56	3 (1.6)	101 (54.9)	80 (43.4)	
Use of sleep medications (0 to 3)	0.72	1.17	126 (69.2)	12 (6.6)	44 (24.1)	
Daytime dysfunction (0 to 3)	0.83	0.69	57 (31.0)	106 (57.6)	21 (11.4)	
			Global score < 5	Global score between 5 and 8	Global score > 8	
Global PSQI Score (0 to 21)	6.63	3.77	81 (44.0)	54 (29.4)	49 (26.6)	
General sleep disturbance score						
Subscale and Total GSDD scores (range of possible scores)	Mean	Standard deviation	Range	<3 n (%)	≥ 3 n (%)	
Quality of sleep (0 to 7)	2.46	1.96	0.00 – 7.00	108 (58.4)	77 (41.6)	
Quantity of sleep (0 to 7)	4.39	1.27	0.00 – 7.00	8 (4.3)	176 (95.7)	
Sleep onset latency (0 to 7)	1.72	2.12	0.00 – 7.00	134 (72.8)	50 (27.2)	
Mid-sleep awakenings (0 to 7)	4.62	2.54	0.00 – 7.00	46 (25.3)	136 (74.7)	
Early awakenings (0 to 7)	2.45	2.26	0.00 – 7.00	109 (59.9)	73 (40.1)	
Medications for sleep (0 to 7)	0.32	0.58	0.00 – 4.33	182 (99.5)	1 (0.5)	
Excessive daytime sleepiness (0 to 7)	1.91	1.38	0.00 – 6.00	143 (77.3)	42 (22.7)	
				Total score < 43	Total score ≥ 43	
Total score (0 to 147)	40.17	19.86	8.00 – 110.00	107 (58.2)	77 (41.8)	
Physical fatigue and energy and attentional fatigue						
Variable	Mean	Standard Deviation	Range	n (%) below the cutoff score	n (%) above the cutoff score	

Pittsburgh sleep quality index					
Subscale and Global PSQI scores (range of possible scores)	Mean	Standard deviation	Subscale score range 0 to 0.9 n (%)	Subscale score range 1.0 to 1.9 n (%)	Subscale score range 2.0 to 3.0 n (%)
Morning fatigue ^a	2.38	1.98	0.00 – 7.50	124 (66.3)	61 (33.7)
Evening fatigue ^b	4.23	2.05	0.00 – 9.65	139 (74.6)	46 (25.4)
Morning energy ^c	5.73	1.97	0.30 – 10.00	106 (58.6)	79 (41.4)
Evening energy ^d	4.48	1.85	0.00 – 10.00	59 (32.6)	126 (67.4)
Attentional fatigue ^e	7.02	1.79	2.13 – 9.88	98 (54.4)	87 (45.6)

^a Cutoff for high level of morning fatigue = ≥ 3.2;

^b Cutoff for high level of evening fatigue = ≥ 5.6,

^c Cutoff for low level of morning energy = ≤ 6.0,

^d Cutoff for low level of evening energy = ≤ 3.5;

^e Cutoff for moderate to severe attentional fatigue - ≤ 7.5

Abbreviations: GSDS, General Sleep Disturbance Scale; PSQI, Pittsburgh Sleep Quality Index.

Table 5

Nocturnal Sleep/Rest, Daytime Wake/Activity, and Circadian Activity Rhythm Parameters in Patients Prior to Radiation Therapy (n = 185)^a

Parameters	Mean	Standard deviation	Median	Range
Nocturnal sleep/rest				
Sleep onset latency (minutes)	16.54	23.14	11.00	1.00 – 226.00
Percent wake at night (% of total sleep time)	14.32	12.54	11.21	0.30 – 91.98
Number of awakenings	16.54	8.6	15.50	1.00 – 48.00
Wake duration (minutes)	4.27	5.44	3.17	0.75 – 65.00
Total sleep time (minutes)	397.59	84.14	408.00	17.00 – 617.00
Sleep period time (minutes)	485.36	69.66	482.50	311.50 – 686.50
Sleep efficiency (%)	81.82	13.60	84.72	3.77 – 98.01
Daytime wake/activity				
Total sleep time (minutes/day)	52.52	90.80	22.97	0.00 – 651.60
Total wake time (minutes/day)	667.48	90.80	697.003	68.40 – 720.00
Sleep percent day (% 720 minutes 9:00 – 20:59)	7.29	12.61	3.19	0.00 – 90.50
Wake percent of day	92.71	12.61	96.81	9.50 – 100.00
Circadian activity rhythm				
Mesor	64.93	11.77	65.94	13.78 – 88.51
Amplitude	49.62	10.79	52.18	10.09 – 68.67
Peak activity	114.55	20.17	118.48	23.87 – 147.57
Acrophase	14:49	1:25	14:37	10:58 – 19:45
Circadian quotient	0.77	0.14	0.78	0.36 – 1.11
Autocorrelation	0.46	0.18	0.46	0.20 – 0.84

^aParameters are defined in Table 1

Table 6

Significant Correlations between Pittsburgh Sleep Quality Index Scores and Nocturnal Sleep/Rest, Daytime Wake/Activity, and Circadian Activity Rhythm Parameters in Patients Prior to Radiation Therapy (n=185)

Parameter	PSQI Global score	Sleep quality	Sleep latency	Sleep duration	Habitual sleep efficiency	Sleep disturbances	Use of sleep medications	Daytime dysfunction
Nocturnal sleep/rest								
Sleep onset latency	.22 ^b	.16 ^a	.19 ^a	.19 ^a				
Percent wake at night							-.17 ^a	
Number of awakenings								-.20 ^a
Wake duration								
Total sleep time	.20 ^b		.18 ^a	-.15 ^a			.29 ^c	
Sleep period time	.17 ^a				.24 ^b		.26 ^b	
Sleep efficiency (%)								
Daytime wake/activity								
Total sleep time								
Total wake time								
Sleep percent day								
Wake percent of day								
Circadian activity rhythm								
Mesor	-.20 ^a							
Amplitude							.20 ^d	
Peak activity								
Acrophase			.20 ^d					
Circadian quotient	.29 ^b	.23 ^a	.20 ^d				.42 ^c	
Autocorrelation								

^a p<.05,

^b p<.01,

^c p<.0001

Table 7

Significant Correlations Between General Sleep Disturbance Scores and Nocturnal Sleep/Rest, Daytime Wake/Activity, and Circadian Activity Rhythm Parameters in Patients Prior to Radiation Therapy (n=185)

Parameters	GSDS total score	Quality of Sleep	Quantity of sleep	Sleep onset latency	Mid-sleep awakenings	Early awakenings	Medications for sleep	Excessive daytime sleepiness
Nocturnal sleep/rest								
Sleep onset latency	.20 ^b	.18 ^a						
Percent wake at night								
Number of awakenings			-.17 ^a					
Wake duration								
Total sleep time							.19 ^a	
Sleep period time							.16 ^a	
Sleep efficiency								
Daytime wake/activity								
Total sleep time								.26 ^b
Total wake time								-.26 ^b
Sleep percent day								.26 ^b
Wake percent of day								-.26 ^b
Circadian activity rhythm								
Mesor								-.19 ^a
Amplitude		.19 ^a						-.22 ^a
Peak activity								-.24 ^a
Acrophase			.28 ^b	.22 ^a				
Circadian quotient							.29 ^b	
Autocorrelation								-.24 ^a

^a p<.05,

^b p<.01

Table 8

Significant Correlations Between Morning and Evening Fatigue and Energy Scores and Attentional Fatigue and Nocturnal Sleep/Rest, Daytime Wake/Activity, and Circadian Activity Rhythm Parameters in Patients Prior to Radiation Therapy (N=185)

Variable	Morning fatigue	Evening fatigue	Morning energy	Evening energy	Attentional fatigue
Pittsburgh Sleep Quality Index					
Total score	.57 ^c	.44 ^c	-.42 ^c	-.30 ^c	-.42 ^c
Sleep quality	.42 ^c	.34 ^c	-.24 ^b	-.29 ^c	-.31 ^c
Sleep latency	.42 ^c	.32 ^c	-.28 ^a	-.22 ^b	-.35 ^c
Sleep duration	.37 ^c		-.28 ^a		-.26 ^b
Habitual sleep efficiency	.26 ^b		-.18 ^a		-.28 ^c
Sleep disturbances	.37 ^c	.31 ^c	-.24 ^b	-.27 ^c	-.24 ^b
Use of sleep medications	.26 ^c	.26 ^b	-.22 ^b		
Daytime dysfunction	.43 ^c	.44 ^c	-.46 ^a	-.32 ^c	-.50 ^c
General Sleep Disturbance Scale					
Total score	.56 ^c	.49 ^c	-.41 ^a	-.31 ^c	-.51 ^c
Quality of sleep	.47 ^c	.36 ^c	-.34 ^a	-.26 ^c	-.43 ^c
Quantity of sleep	.50 ^c	.40 ^c	-.36 ^a	-.23 ^b	-.28 ^c
Sleep onset latency	.42 ^c	.29 ^c	-.22 ^b		-.31 ^c
Mid-sleep awakenings					
Early awakenings	.42 ^c	.30 ^c	-.32 ^a	-.16 ^a	-.34 ^c
Medications for sleep	.27 ^c	.25 ^b	-.28 ^b		
Excessive daytime sleepiness	.47 ^c	.40 ^c	-.37 ^c	-.27 ^c	-.52 ^c
Nocturnal sleep/rest					
Sleep onset latency					-.16 ^a
Percent wake at night					
Number of awakenings					
Wake duration					

Variable	Morning fatigue	Evening fatigue	Morning energy	Evening energy	Attentional fatigue
Total sleep time		.17 ^a			
Sleep period time					
Sleep efficiency					
Daytime wake/activity					
Total sleep time					
Total wake time					
Sleep percent day					
Wake percent of day					
Circadian activity rhythm					
Mesor					
Amplitude					
Peak activity					
Acrophase	.26 ^b	.20 ^a	.26 ^b		
Circadian quotient					
Autocorrelation					

^a p<.05,

^b p<.01,

^c p<.0001