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Relationship between fatigue, sleep quality and inflammatory cytokines during external beam radiation therapy for prostate cancer: A prospective study

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Abstract

Background and purpose—Mechanisms of fatigue reported during radiotherapy are poorly defined but may include inflammatory cytokines and/or sleep disturbances. This prospective, longitudinal, phase II study assessed fatigue, sleep, and serum cytokine levels during radiotherapy for early-stage prostate cancer (PCa).

Material and methods—Twenty-eight men undergoing radiotherapy for early-stage PCa wore an Actiwatch Score to record fatigue level, sleep time, onset latency, efficiency and wake after sleep onset. Serum levels of IL-1α, IL-1β, TNF-α, IL-6, IL-8, IL-10 and VEGF were measured weekly during radiotherapy. Patient reported quality of life (QOL) metrics were collected before and after treatment. Linear mixed effects models examined trajectories across treatment weeks.

Results—Fatigue increased across treatment weeks ($P < .01$), and fatigue was associated with decreased patient-reported QOL. Sleep efficiency increased across treatment weeks (rate of change over time = .29, $P = .03$), and sleep onset latency decreased (rate of change over time = .86, $P = .06$). IL-6 tended to increase during treatment ($P = 0.09$), but none of the cytokine levels or sleep variables were significantly related to fatigue trajectories.

Conclusions—Despite increased sleep efficiency across treatment weeks, fatigue significantly increased. Although IL-6 increased during the course of radiotherapy, cytokines levels were not associated with fatigue scores or sleep disturbance. Further studies are needed to define the mechanisms for fatigue during radiotherapy.

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Conflicts of interest statement

The authors have no conflicts of interest to disclose.

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Keywords

Radiotherapy; Cancer treatment related fatigue; Prosate Cancer; Cytokines; Sleep disturbance

Patients with cancer can experience debilitating fatigue that significantly interferes with their quality of life (QOL). Fatigue is the most common symptom experienced by cancer patients with an estimated incidence range of 60–90% [1]. The National Comprehensive Cancer Network defines cancer-related fatigue as “a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning” [2].

Patients undergoing surgery [3], chemotherapy [4], radiotherapy (RT) or chemoradiotherapy (CRT) [5] experience significant cancer treatment-related fatigue (CTRF) that begins during treatment and declines following treatment. A growing body of evidence suggests that fatigue is not only the most prevalent symptom associated with cancer and its treatment, it is also the most distressing, and one that has a profoundly negative effect on physical functioning and QOL [6]. Besides having a negative impact on QOL, CTRF can also impact a patient’s ability to complete the prescribed treatment [7] For patients undergoing potentially curative RT, such unscheduled breaks can also contribute to tumor re-growth and compromise outcome [8].

Despite much investigation, the molecular mechanisms underlying the initiation and perpetuation of CTRF are not well established [9], but fatigue intensity seems to increase over the course of treatment and gradually decline over time [10]. One proposed etiologic factor is increased inflammatory cytokine production which is a normal physiological response to treatment-induced tissue injury [11]. Cancer patients undergoing chemotherapy, RT or CRT produce high levels of IL-1β [12], TNF-α [13], and IL-6 [14].

Further complicating the elusive molecular mechanism of CTRF are the many other contributing factors including depression [15], sleep disturbance [16]. There also are treatment- and site-specific symptoms that can affect fatigue. Patients undergoing RT for prostate cancer (PCa), for example, can experience bowel and urinary symptoms during treatment including loose and/or frequent stools, dysuria, polyuria and nocturia [17] Androgen-deprivation therapy (ADT), which is often given prior to and during RT for PCa, has also been shown to increase fatigue [18]. The hot flashes and night sweats associated with ADT can also lead to sleep disturbance and CTRF [19].

In order to best diagnose and treat CTRF in patients with PCa, we first must better understand the contributing factors. Therefore, to better elucidate the mechanism of CTRF in men with early-stage PCa, we performed a prospective, longitudinal, phase II study to assess fatigue, sleep quality, QOL and serum cytokine levels during external beam RT (EBRT). Ultimately, we sought to gain better understanding of whether CTRF is initiated by the production of inflammatory cytokines with the future goal of developing new treatment strategies to improve patients’ physical functioning, QOL and ability to complete the prescribed treatment.

Methods

After approval by the Institutional Review Board, patients were screened for study eligibility at their initial RT consultation. The target population was men who were scheduled to undergo definitive EBRT for early-stage PCa. Exclusion criteria included: (1) patients who were receiving concurrent ADT; (2) patients who received brachytherapy; (3) patients who were unable to complete the surveys and/or operate the Actiwatch Score (AW-S) (Respironics Inc.); (4) current psychiatric disorders or major depression, based on a score of 31 or greater on the Beck depression scale; (5) baseline fatigue level as a 10 on a 1–10 scale where 1 = “no fatigue” and 10 = “very severe fatigue” and (6) patients who had received treatment for any cancer, except skin cancer, within the past 12 months. Informed consent was obtained. Each participant underwent depression screening using the Beck Depression Inventory (BDI) [20]. Any person who was ineligible based on his BDI score (total score > 31) or reported thoughts of suicide was referred to a mental health professional.

Demographics and clinical data

A demographic form was used to obtain information on each subject’s age, ethnicity, gender, education, marital status, occupation, living situation, income and medical comorbidities. Patients were categorized has having medical comorbidities if they took medication for any of the following medical diagnoses: diabetes, asthma/COPD, hyperlipidemia or hypertension, otherwise they were categorized as having no medical comorbidities. These medical comorbidities were chosen for evaluation in particular because of their potential to affect sleep. A medical record chart audit form was used to obtain data regarding type and stage of cancer, levels of prostate specific antigen (PSA), height and weight, comorbidities, smoking status, and history of previous cancer treatment(s).

Patient-reported metrics

Eligible participants completed baseline demographic and two patient reported outcomes (PRO) tools, the Short Form 36 (SF-36 v 1.0) and International Prostate Symptom Score (IPSS) questionnaires [21]. The multi-item SF-36 (distributed by Quality Metric, Lincoln, RI) was used to evaluate QOL prior to and at the end of treatment. Higher scores (possible 0–100) indicate higher QOL [22]. The IPSS was used to evaluate urinary symptoms prior to and at the end of treatment, and increasing scores (possible 0–35) indicate increasing urinary symptoms [21].

Real-time monitoring of fatigue and sleep quality

Patients were given the AW-S [23] to put on their non-dominant wrist each Monday when they arrived in the department for radiation therapy. The goal was to capture four full nights of sleep data and three whole days of fatigue data per week. They returned the AW-S to study staff each Friday after they completed treatment. This occurred during week 0 (before the start of treatment), and during each week of treatment (weeks 1–8). Each AW-S device had an electronic keypad that allowed for the rating of fatigue on a scale of 1–10 in real-time (1 = no fatigue, and 10 = worst fatigue defined as the highest fatigue ever experienced). Participants were instructed to enter their self-reported fatigue levels manually four times

each day (after waking in the morning, at lunch time, at dinner time and before bed). For each week, the recorded fatigue scores were averaged.

Patients were also instructed to wear the AW-S during the night in order to capture sleep data. The AW-S contains very sensitive omnidirectional accelerometers that count wrist movements to estimate sleep duration [23], and wrist actigraphy has been validated against polysomnography and demonstrated a total sleep duration correlation of >0.9 [24]. Participants were also instructed to mark their sleep and their wake times by pressing an indicator on the AW-S. Patient-reported 'onset of sleep' was defined as when the participant is in bed and turns off their light and patient-reported 'wake' defined as when the participant wakes and before they step out of their bed. Patient-reported sleep and wake times as well as AW-S manufacturer software calculated sleep duration were used to determine sleep metrics such as sleep latency (time required for full transition from wakefulness to sleep), sleep efficiency (total time spent asleep after turning off the lights) and wake after sleep onset (WASO, time spent awake after falling asleep but before final awakening). Participants needed to meet the following criteria to have their AW-S data included in the final analysis: to wear the watch for at least three nights during each week of the study (i.e. week 0 through week 8) and to enter at least six fatigue scores during a three-day period.

Blood collection and serum cytokine measurement

Peripheral blood was collected five times throughout the study; immediately before the first radiation treatment as well as 1 h after the 5th, 15th (end of week 3), 25th (end of week 5), and 39th (final) radiation treatment. Serum levels of IL-1α, IL-1β, TNF-α, IL-6, IL-8, IL-10, and VEGF were measured using bead-based immunofluorescence assays commercially available from Millipore Inc. Assays were run in duplicate according to the manufacturers' protocol. A five-parameter regression formula was used to calculate the sample concentrations from the standard curves. Data were collected and analyzed using the Luminex-100 system Version IS (Luminex, Austin, TX).

Statistical analysis

Paired *t*-tests were used to examine changes in SF-36 and IPSS subscores from pre-treatment to the last treatment day. A Bonferroni adjustment was performed due to the large number of variables tested. As 19 variables were tested, the *P*-value below which differences were considered statistically significant was 0.05 divided by 19, which is equal to 0.003. Actigraphy data were analyzed using the Actiware 5.0 software (Respironics Inc.). Average daily fatigue level was calculated for baseline (week 0) and each treatment week (weeks 1–8). Sleep efficiency, wake after sleep onset (WASO), total sleep time (at night) and number of sleep bouts were calculated for weeks 0–9. Cytokine values were log transformed to correct for skewness. Changes in outcomes were examined across the study time course with a linear mixed effects modeling approach implemented in the lme package for the R statistical computing environment (R Core Team, Vienna, Austria, 2015). Model testing was used to determine the random effects structure for each outcome (i.e., intercepts and slopes as random or fixed). Multivariate models were then fit to determine whether changes in cytokines and sleep variables predicted changes in fatigue across time. Body mass index (BMI), smoking status, age, and the presence or absence of medical comorbidities were

included as time invariant covariates as appropriate. A final set of models was used to determine the relation between changes in fatigue and changes in the SF-36 subscale scores.

Results

Twenty-nine eligible men were approached to participate in the study and all consented. One decided to continue treatment elsewhere and as a result withdrew from the study. Of the 28 men who ultimately enrolled and participated in this prospective, longitudinal trial, the majority of patients were Caucasian (96%), married/partnered (64%), and retired or disabled (79%). The mean ± SD age of participants was 66.9 ± 5.6 years. All participants were diagnosed with stage T1 or T2 prostate cancer. Prior to treatment the mean Gleason score was 6.5 ± 0.5 and mean prostate specific antigen (PSA) level was 7.7 ± 4 ng/mL. Demographic and clinical characteristics of the cohort are presented in Table 1.

Patient-reported metrics

QOL data were complete for all patients except for one who missed the end of treatment measurement. There were significant differences in the QOL and urinary symptom scores reported by participants before and after treatment, and the vitality and social functioning sub-scores both significantly decreased. Total IPSS score increased from 12.1 ± 9.0 to 20.7 ± 7.0 ($P = .001$) indicating increased bother, and incomplete emptying, urgency, weak stream, nocturia and IPSS QOL scores also increased. Pre- and post-EBRT scores are presented in Table 2.

Change in fatigue and sleep quality over treatment weeks

Sixteen patients recorded at least six fatigue values per week for all nine weeks of the study. Six patients had one or two weeks where they did not record at least six fatigue values, and six patients did not record at least fatigue values per week for three or more weeks in the study and were therefore excluded from this analysis. For the 22 men included in the fatigue trajectory analysis, the mean ± SD number of fatigue entries per week was 11 ± 4.4 (median [range] was 11 [0–25]). Fatigue, significantly increased across treatment weeks (rate of change over time = .18, $P < .01$). Fig. 1 shows the trends for fatigue across time for each patient and the average trend with 95% CI's.

Four patients did not provide usable data for the sleep variables. There was a trend toward decreased sleep onset latency across treatment weeks (rate of change over time = −.86, $P = .06$), suggesting patients fell asleep faster as treatment progressed. However, there were two subjects with exceptionally high sleep latencies which may have influenced the results. When these two outliers were excluded, the $P = .20$. Sleep efficiency also increased across treatment weeks (rate of change over time = .29, $P = .03$), indicating patients spent a greater percentage of time in bed actually sleeping. There was no significant change found in sleep duration (rate of change over time = −.92, $P = .43$) or WASO (rate of change over time = −.72, $P = .26$) across treatment weeks.

Change in serum cytokine levels over treatment weeks

One patient provided cytokine measures at only two time points (weeks 1 and 3) and a second patient provided cytokine data at four of five time points. All other patients provided complete cytokine data. There were no significant changes in IL-1α, IL-1β, IL-8, IL-10, TNF-α or VEGF across treatment weeks (Table 3). However, IL-6 values tended to increase across treatment weeks ($P = .09$) (Fig. 2).

Predictors of fatigue trajectory

None of the cytokine variables or sleep variables were significantly related to fatigue trajectories with or without controlling for demographic characteristics (age, BMI, smoking, diabetes, respiratory medications, cholesterol medications, and hypertension medications) or treatment-related nocturia.

Relationship between fatigue and QOL

Increasing fatigue was significantly associated with a decreased patient-reported mental health sub-score on the SF-36 (rate of change over time = −6.62; $P < .01$). Increasing fatigue was also significantly associated with decreased emotional role limits (rate of change over time = −11.26; $P < .01$), decreased emotional well-being (rate of change over time = −5.39; $P < .01$) and decreased physical role limits (rate of change over time = −5.63; $P = .05$) sub-scores.

Discussion

The results of this prospective, longitudinal, phase II study show that, although fatigue levels do increase significantly throughout the course of EBRT for early-stage PCa, this could not be easily explained by changes in sleep metrics or cytokine levels. Patients had similar sleep duration, sleep latency, wake after sleep onset as the treatment weeks progressed and actually developed increased sleep efficiency. IL-6 was the only cytokine evaluated that tended to increase during the course of radiotherapy, and none of the cytokines studied were significantly associated with fatigue scores or sleep disturbance.

In our cohort, QOL scores were lower at the end of EBRT compared to pretreatment baseline. There is some evidence to suggest EBRT for early stage PCa is not associated with a decrement in global QOL [25], but several studies have described and quantified the urinary, bowel, and sexual function symptoms that affect men after EBRT for PCa [26]. Fatigue also increased across treatment weeks in our cohort, and increasing fatigue was significantly associated with decreased QOL in several physical, emotional and mental health categories. The effect of CTRF on QOL is widely accepted, and several multidisciplinary programs including nutrition, psychosocial support, and physical activity have been developed to improve both fatigue and QOL for cancer patients [27].

Although sleepiness and fatigue are distinct entities and the NCCN definition of fatigue requires that the symptom be out of proportion to recent activity [2], the effect of cancer-treatment-related sleep disturbance has been shown to contribute to CTRF [28]. Additionally, sleep disturbance in cancer patients have also independently been shown to

negatively impact QOL [29]. In our cohort, we did not see an association with increasing sleep disturbance across EBRT treatment weeks. In fact, though most sleep metrics did not change during EBRT, sleep efficiency actually increased across treatment weeks. One potential reason for increased sleep efficiency as the course of EBRT progressed is that patients did have increasing fatigue, and therefore slept a greater percentage of the time they were in bed. Another contributing factor could be that patients adjust and adapt to their schedule of daily radiotherapy and frequent medical visits and can sleep more efficiently as the treatment course progresses.

The physiologic mechanism of CTRF is unclear, but many have hypothesized that increased cytokine projection may play a role [30]. Several lines of evidence support this hypothesis. First, in addition to fatigue, cancer patients undergoing treatment often experience several other symptoms including anorexia, cachexia, pain, sleep disturbance, depression, and anemia, which can impact the subjective sensation of fatigue [7]. Considerable evidence generated in animal models and in clinical populations implicate inflammatory cytokines like IL-1β, TNF-α, and IL-6 in the etiology of these symptoms [31]. In this regard, CTRF may be homologous to sickness behavior, a normal response to infection or tissue injury [32]. Total body and localized radiation have been shown to induce the production of inflammatory cytokines both in experimental systems and in clinical populations [33].

Although there is much evidence to implicate a role for these cytokines in CTRF, older studies plotting weekly cytokine levels and symptoms of fatigue during radiotherapy for uterine [34], breast [35] and prostate [36] cancer have also failed to find a correlation. Although we demonstrated a trend toward increasing IL-6 during the course of radiotherapy, we did not find any significant correlation between cytokine levels, sleep characteristics or fatigue levels. However, recent studies evaluating cytokine levels and fatigue in other cancer sites were able to demonstrate a positive correlation. A prospective, longitudinal study was performed at MD Anderson in which cytokine levels were measured weekly during chemoradiotherapy for gastrointestinal cancers; this showed increasing TNF-R1 and IL-6 were positively associated with increasing fatigue severity during treatment [31]. The same group also evaluated cytokine levels in patients undergoing chemoradiotherapy for non-small cell lung cancer and found IL-6 to be positively associated with increasing fatigue as well as increasing severity of pain, disturbed sleep, lack of appetite and sore throat [12]. Investigators from the University of California San Diego reported a positive association between IL-6 and the Multidimensional Fatigue Symptom Inventory-Short form score and between IL-6 and IL-1RA and the Pittsburg Sleep Quality Index score in patients undergoing chemotherapy for breast cancer [13].

The strengths of this study include its prospective, longitudinal design as well as the rigorous collection of several metrics of sleep and fatigue using both patient-reported qualitative scales and the AW-S. This is not the first study to attempt to correlate serum cytokine levels with fatigue in patients receiving cancer therapy [37], but the timing of serum collection in this study reflected a better understanding of cytokine kinetics. Older studies measured cytokine concentrations once a week on a set day, regardless of when the patient actually received EBRT [38]. This is problematic because peak serum levels of IL-1β, TNF-α and IL-6 occur at 1–3 h post immune challenge [39]. The persistence of

cytokine-related symptoms in animal models is thought to be due to expression of inflammatory cytokines in the brain, which cannot be measured by serum tests [40]. In an effort to record peak post-radiotherapy cytokine levels for each patient, we took serum samples 1 h after radiotherapy. As fatigue is certainly multifactorial, we attempted to control for as many confounding factors as we could. We collected information regarding demographic information and medical comorbidities and did not find them to be significantly associated with differences in fatigue trajectories. The exclusion of patients receiving ADT and patients with baseline depression was also helpful in focusing in on the effects of EBRT on sleep and fatigue.

One limitation of the study design the failure to detect other factors potentially contributing to fatigue including change in work routine or other activities, daily travel to and from the radiotherapy center, and the development of anxiety and/or depression not present at the baseline evaluation. Additionally, the sample size was small in this pilot study. It is possible that type II error was introduced, and a significant correlation exists between the sleep metrics and cytokines studied and fatigue in PCa patients that went undetected. These results will be used in the power analysis for the forthcoming trial. Nonetheless, these data suggest the mechanism of CTRF in patients undergoing ERBT for PCa is complicated and cannot be explained by sleep disturbance and cytokine levels alone. Radiation-induced gene expression changes associated with CTRF are one area of promising ongoing research [41].

In conclusion, patients undergoing EBRT for early-stage PCa reported significantly increased fatigue across treatment weeks despite similar sleep duration, similar rates of sleep disturbances and increased sleep efficiency. IL-6 tended to increase during the course of radiotherapy, but none of the cytokines studied were significantly associated with fatigue scores or sleep disturbance. Further studies are needed to define the mechanisms more clearly for fatigue during radiotherapy.

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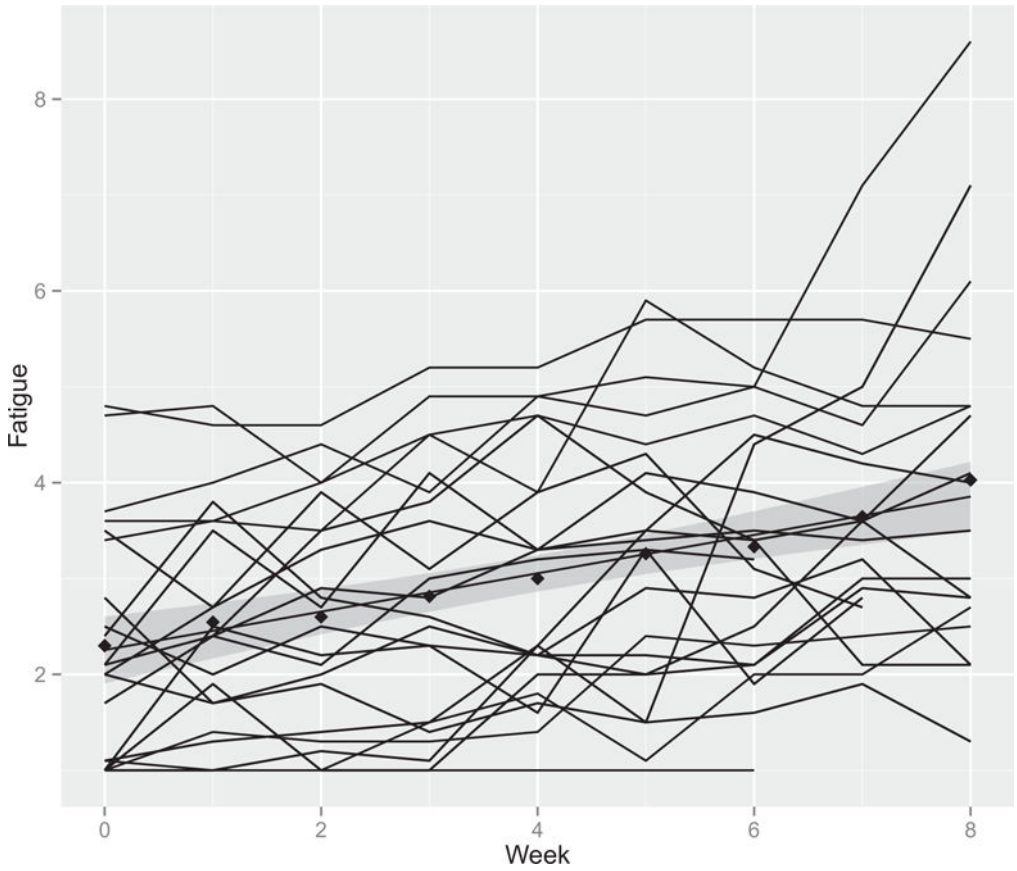

Fig. 1.

Fatigue and sleep quality measures across time for each subject. The shaded region around the slope represents the 95% confidence interval.

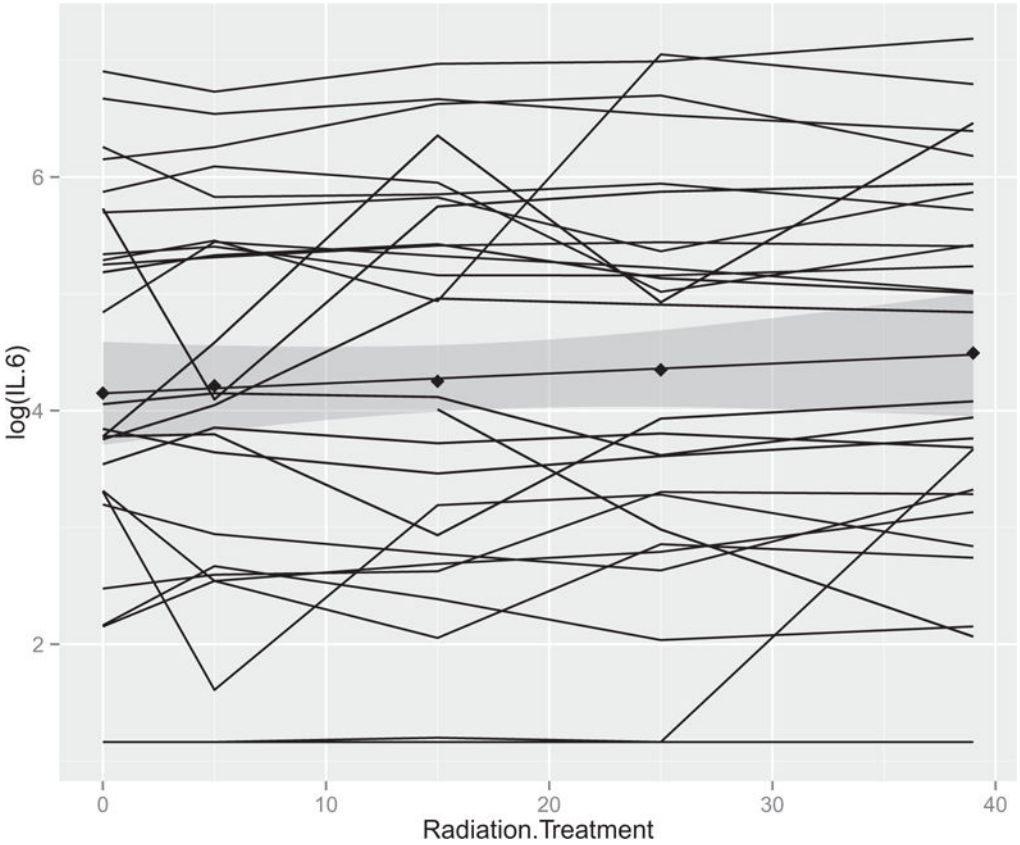

Fig. 2.

IL-6 measure across time for each subject. The shaded region around the slope represents the 95% confidence interval.

Table 1

Demographic information and tumor characteristics.

N* = 28	
Age; mean ± SD	66.9 ± 5.6
BMI; mean ± SD	31.5 ± 5.8
Smoking status; *n* (%)	
Current smoker	7 (25%)
Past smoker	14 (50%)
Never smoked	7 (25%)
Medical comorbidities§; *n* (%)	
Yes	19 (67.9%)
No	7 (25%)
Missing	2 (7.1%)
Marital status; *n* (%)	
Single (never married)	1 (3%)
Separated or divorced	8 (29%)
Widowed	1 (3%)
Married	18 (64%)
People living in household; mean (range)	2 (1–4)
Education; *n* (%)	
High school or technical school	13 (47%)
Some college or college graduate	15 (54%)
Employment status; *n* (%)	
Retired or disabled	22 (79%)
Full time or part time	6 (21%)
Annual income; *n* (%)	
</=$25,000	9 (32%)
$25,000–75,000	18 (64%)
>$75,000	1 (3%)
Clinical stage; *n* (%)	
T1c	16 (57%)
T2a	10 (36%)
T2b	2 (7%)
Gleason score; *n* (%)	
6	15 (54%)
7	13 (46%)
PSA at diagnosis; mean ± SD	7.7 ± 4

SD = standard deviation, BMI = body mass index, PSA = prostate specific antigen in ng/mL.

*Demographic data were obtained for all 28 participants except for two patients who did not provide information regarding their medical comorbidities.

§Patients were categorized as having medical comorbidities if they took medication for any of the following medical diagnoses: diabetes, asthma/COPD, hyperlipidemia or hypertension.

Table 2

Patient reported quality of life and urinary symptom scores before and after radiation therapy for prostate cancer.

	Pre-RT Mean ± SD	Post-RT Mean ± SD	*p*§
N = 28 *			
QOL (SF-36) (possible 0–100)			
Physical function	70.9 ± 24.5	68.1 ± 23.3	.464
Role limits physical	65.3 ± 26.9	55.7 ± 29.1	.146
Role limits emotional	84.8 ±19.1	78.4 ± 27.6	.180
Vitality	62.5 ± 22.4	51.3 ± 24.7	.005
Emotional well being	76.3 ± 16.9	78.5 ± 18.5	.429
Social functioning	86.7 ± 16.5	73.8 ± 23.8	.008
Bodily pain	68.1 ± 24.0	73.8 ± 20.4	.117
General health	64.8 ± 19.9	70.6 ± 22.3	.117
PCS	65.3 ± 19.0	65.6 ± 20.4	.907
MCS	77.1 ± 15.4	70.0 ± 20.3	.028
Urinary symptoms (IPSS) (possible 0–35 for total, 0–5 for each subset)			
IPSS total	12.9 ± 9.2	20.7 ± 7.0	**.001**
Incomplete emptying	1.6 ± 1.6	2.5 ± 1.3	.040
Frequency	2.3 ± 2.0	3.3 ± 1.5	.011
Intermittency	1.5 ± 1.7	2.0 ± 1.5	.170
Urgency	1.6 ± 1.8	3.4 ± 1.4	**<.001**
Weak stream	2.0 ± 1.8	2.8 ± 1.5	.042
Straining	0.8 ± 1.4	1.4 ± 1.2	.143
Nocturia	1.8 ± 1.3	2.7 ± 1.4	**<.001**
IPSS quality of life	1.8 ± 1.4	3.2 ± 1.3	**<.001**

* Complete data were available for 27 participants. One patient failed to complete his end of treatment questionnaire.

§ A Bonferroni adjustment was performed due to the large number of variables tested. As 19 variables were tested, the *P*-value below which differences were considered statistically significant was 0.05 divided by 19, which is equal to 0.003. Bold type indicates a *P*-value <0.003. SD = standard deviation, QOL = quality of life, IPSS = International Prostate Symptom Score, PCS = Physical Component Score, MCS = Mental Component Score.

Table 3

Levels of six cytokines during radiation therapy for prostate cancer.

Analyte*	Pre-treatment Mean ± SD	Day 5 Mean ± SD	Day 15 Mean ± SD	Day 25 Mean ± SD	Last treatment Mean ± SD
IL-1α	439.1 ± 707.4	441.5 ± 738.0	452.7 ± 734.0	480.0 ± 854.9	424.6 ± 637.5
IL-1β	30.1 ± 73.2	32.0 ± 65.9	36.2 ± 86.6	42.9 ± 96.1	24.1 ± 45.3
TNF-α	23.7 ± 25.4	25.2 ± 27.9	26.9 ± 33.2	41.0 ± 104.0	41.8 ± 84.5
IL-6	188.5 ± 251.5	177.4 ± 221.9	221.3 ±279.4	228.6 ± 325.6	236.9 ± 315.8
IL-8	82.4 ± 91.4	169.7 ±314.9	84.6 ± 93.5	150.6 ± 378.5	92.5 ± 103.6
IL-10	63.3 ± 205.1	55.8 ± 179.0	60.4 ± 190.4	86.3 ± 231.3	68.6 ± 159.9
VEGF	690.1 ± 656.2	661.3 ± 653.0	749.7 ± 777.6	729.3 ± 802.4	795.3 ± 871.1

*Cytokine levels in pictograms per milliliter.

SD = standard deviation, analyte levels in picograms per milliliter (pg/mL).