

Basic Original Report

Factors associated with fatigue in prostate cancer (PC) patients undergoing external beam radiation therapy (EBRT)



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Abstract

Purpose: Fatigue is a common adverse effect among cancer patients undergoing external beam radiation therapy (EBRT), yet the underlying disease- and treatment-related factors influencing its development are poorly understood. We hypothesized that clinical, demographic, and treatment-related factors differentially affect fatigue and aimed to better characterize variables related to fatigue development in prostate cancer (PC) patients during EBRT.

Methods and materials: We identified a cohort of 681 patients with nonmetastatic PC undergoing a 6- to 9-week EBRT course. Patient fatigue scores (range, 0-3) were prospectively recorded by providers during treatment visits using standardized criteria. Clinical and demographic factors including age, race, EBRT details, disease staging, smoking status, comorbidities, urinary symptoms, employment status, weight, and concurrent medication use were assessed for their relationship to fatigue levels. Significant differences in fatigue severity by each variable at the beginning and end of EBRT were assessed by nonparametric means testing, and differences in the level of fatigue increase over the treatment course were assessed using an ordered logistic regression model.

Results: Significant increases in reported fatigue severity were seen in patients with age <60 years ($P = .006$), depressive symptoms ($P < .001$), and use of androgen deprivation therapy before radiation start ($P = .04$). In addition, the prescription of antiemetics before radiation start was associated with reduced fatigue severity ($P = .03$).

Conclusions: We identify factors associated with increased (young age, depressive symptoms, androgen deprivation therapy) and decreased (antiemetic prescription) fatigue in a large cohort of

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PC patients receiving EBRT. Continued investigation is needed to further elucidate clinical drivers and biological underpinnings of increased fatigue to guide potential interventions.

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Introduction

Fatigue is a common but poorly understood symptom experienced by cancer patients undergoing external beam radiation treatment (EBRT).^{1,2} Prior reports have demonstrated increases in patient-reported fatigue during EBRT,^{3–8} with fatigue severity increasing as treatment progresses. Certain disease sites, including the pulmonary, gastrointestinal, and central nervous systems, may contribute to fatigue through debilitating adverse events such as pneumonitis (respiratory compromise),⁸ gastrointestinal toxicity (diarrhea),³ and neurotoxicity⁹; however, radiation-induced fatigue seems to occur regardless of the primary site,⁵ even without measurable toxicity.

Despite frequent patient reports of increased fatigue and its adverse impact on quality of life,¹⁰ the biology of radiation-related fatigue and the underlying disease- and treatment-related factors influencing its development remain poorly understood.¹¹ Prior attempts to prospectively characterize fatigue symptoms in radiation patients are illustrative but have been limited by low patient totals⁶ or confounded by the inclusion of several anatomic sites.⁵

In this study, we perform an assessment of clinical-, demographic-, and treatment-related factors that may contribute to fatigue during EBRT for nonmetastatic prostate cancer (PC). Our study focuses on PC because it is a common, relatively curable disease and involves a site distant from the chest and brain so as to minimize confounding fatigue contributors such as EBRT-induced neurotoxicity and pneumonitis. Additionally, compared with other cancer patients, PC patients are generally healthier and unlikely to be on concurrent systemic immunosuppressive drugs and thus have fewer potential non-EBRT contributors to fatigue complaints.

Here, we examine a population of 681 PC patients enrolled in institutional patient registries/clinical protocols and receiving curative radiation therapy (RT) at our institution between 2010 and 2016. Medical providers recorded patient fatigue scores at weekly intervals throughout the EBRT course. This retrospective analysis of prospectively collected data encompasses, to our knowledge, the largest analyzed population of its kind and identifies factors affecting fatigue scores in patients undergoing EBRT for PC.

Methods and materials

Patient inclusion

This study was performed in accordance with the institutional review board at our institution. Using PC

patients previously enrolled on our institutional review board–approved prospective registry or clinical protocols who received EBRT, we identified a convenience sample of 681 adult male PC patients who initiated treatment between January 2010 and June 2016 for analysis.

Fatigue assessment

An assessment of patient-reported fatigue as part of a larger symptom inventory was prospectively collected and recorded at the initial consultation and at each subsequent week during on-treatment visits by providers using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0 definitions as part of routine clinical care using standardized questionnaires. The fatigue question uses a 4-point scale, ranging from 0 to 3 (0 = no fatigue, 1 = fatigue relieved by rest; 2 = fatigue not relieved by rest, limiting instrumental activities of daily living; 3 = fatigue unrelieved by rest, limiting self-care activities of daily living).

Potential fatigue contributor identification

Clinical-, demographic-, and treatment-related factors potentially contributing to the development of fatigue were identified from the medical record for each patient. The list of factors assessed were age (<60 or ≥60 years), race (white, black, Asian, other), treatment modality (photon vs proton beam), American Joint Committee on Cancer (AJCC) stage, Gleason score, baseline prostate-specific antigen level, time of radiation treatment delivery (defined as a categorical variable of majority of treatments delivered before 5 PM vs after 5 PM), total dose delivered (in centigray), total fractions delivered, treatment volume (whole pelvis vs prostate only), smoking status, depression by CTCAE reporting (present vs absent), depression by International Classification of Diseases-9 diagnosis code, urinary urgency and urinary frequency by CTCAE criteria (present vs absent), nocturia, Charlson-Deyo comorbidity score (<3, 4-7, 8-11, >11),¹² employment status, body mass index (BMI), and medications prescribed by class. The medication classes evaluated in this analysis were analyzed by whether they were initiated before or during RT and included narcotic analgesics, anabolic androgens, antidepressants, antiemetics, antihistamines, androgen deprivation therapies (ADT), beta blockers, miscellaneous endocrine agents, miscellaneous genitourinary products, prescription stimulants, and urinary antispasmodics.

EBRT

Patients in this analysis underwent definitive EBRT using either intensity modulated RT, proton beam

therapy, or a combination of the 2 modalities. Treatment was delivered using Varian TrueBeam linear accelerators (Varian Inc., Palo Alto, CA) or the IBA proton delivery system (IBA Inc., Louvain-La-Neuve, Belgium). Patients were treated with standard fractionation in 1.8-Gy fractions or moderate hypofractionation in 2.5-Gy fractions daily per clinical protocol over the course of 6 to 9 weeks. ADT was administered based on provider judgment as dictated by disease presentation.

Statistical analysis

Fatigue scores during each week of treatment (weeks 1-9) were compared within each treatment variable by category. Given the ordinal nature of the reported fatigue scores, nonparametric means testing was used to compare fatigue scores by category within each week. Wilcoxon rank sum tests and Kruskal-Wallis tests were performed to assess for statistical significant differences in level of reported fatigue at each week of treatment based on number of classification factors (2 or >2, respectively). A χ^2 test was used to evaluate the association of increased fatigue with increased severity of reported urinary symptoms. Benjamini-Hochberg correction was used to control for false discovery rate from multiple comparisons testing.¹³ Significance threshold was set at P values $\leq .05$.

Patient-reported fatigue scores during week 1 of treatment were assessed as discussed previously to identify factors associated with differences in baseline fatigue level. Fatigue scores reported during weeks 6 through 9 were analyzed to determine potential contributors to higher fatigue at the end of radiation. The range of weeks used in this analysis was chosen to accommodate differences in length of the radiation courses given different fractionation schemes used.

In addition to our analysis at static time points, we also analyzed factors contributing to the change in fatigue over the treatment courses. We calculated this by using the maximum reported fatigue score at any point during treatment and then subtracting the baseline fatigue score. The Wilcoxon rank sum and Kruskal Wallis tests were again used to identify factors associated with differential levels of fatigue increase during radiation. To adjust for multiple comparisons, a multivariate analysis by ordered logistic regression was performed to determine the effect of each potential fatigue variable. The ordered logistic regression model was constructed with selected variables previously found to be statistically significant on our univariate analysis. The model was built using the variables of age, BMI, urinary urgency symptoms, depression symptoms, and concurrent prescription of antiemetics, ADT, urinary antispasmodics, or miscellaneous genitourinary products. All analyses were performed using R 3.2.1.¹⁴

Results

Patient characteristics

Details of the 681 patients in our study regarding demographic variables, smoking status, employment status, medical comorbidities, disease stage, and EBRT details are summarized in Table 1. The median age was 68 (range, 43-86) years. Of patients with recorded data, 387 (57%) were Caucasian, 134 (20%) were African American, 10 (1%) were Asian, and the remaining 160 (23%) were other ethnicity/unknown, which is representative of the patient population at our facility. A total of 490 patients (72%) received treatment with proton beam therapy or a mixture of proton and photon therapy, whereas 181 patients (28%) were treated using photon therapy only, reflective of the clinical protocol and registry populations.

Baseline fatigue and trends

The mean patient-reported fatigue score was 0.15 at the start of EBRT, indicating essentially no fatigue at the initiation of treatment. Mean patient-reported fatigue scores increased weekly and reached a peak of 0.59 during week 9 of EBRT. Three months after EBRT completion, fatigue scores fell dramatically and returned to near baseline levels by the end of the first year after treatment completion (Fig 1).

Disease stage and concurrent use of certain medication classes were associated with significant differences in baseline fatigue severity (Table 2). For AJCC overall disease stage, average mean fatigue scores at week 1 significantly increased with higher stage disease ($P = .02$). Patients using antidepressant therapy (89% of patients) before EBRT had higher mean week 1 fatigue scores (0.22) compared with those not using antidepressants (0.13; $P = .03$). Patients endorsing depression by NCI-CTCAE criteria also had higher week 1 fatigue scores (0.29) versus those not endorsing these symptoms (0.12; $P < .001$). ADT use was also associated with higher baseline fatigue, because patients receiving ADT (50% of patients) had week 1 mean fatigue scores of 0.18 versus 0.11 for those not receiving ADT ($P = .02$). A similar association was also seen with patients using urinary antispasmodics medications, with a mean week 1 fatigue score of 0.29 for medication users compared with 0.13 for nonusers (0.004). No other demographic, clinical, or treatment variable was associated with a significant difference in fatigue by patient class at baseline.

Fatigue contributors at end of radiation

Variables associated with higher levels of reported fatigue at the end of treatment were similarly analyzed using nonparametric means testing. Clinical variables associated with significantly greater levels of reported fatigue were higher disease stage ($P = .006$), Gleason score

Table 1 Clinical and demographic characteristics for patient cohort

		No. of patients	Result ^a
Median age, years (range)		68	43-86
Ethnicity	White	387	57
	Black	134	20%
	Asian	10	1%
	Other/unknown	150	22%
Smoking status	Current	58	9%
	Former	327	48%
	Never	278	41%
	Data unavailable	18	3%
Median BMI (range)		27.98	17.37-48.12
Weight category	Not overweight (BMI <25)	121	18%
	Overweight (BMI 25-30)	298	30%
	Obese (BMI >30)	207	44%
	Data unavailable	55	8%
	Employment status	Actively working	184
	Not working	293	43%
	Data unavailable	204	30%
Charlson-Deyo Comorbidity Score, age-adjusted median (range)		6	2-16
	<4	11	2%
	4-7	559	82%
	8-11	97	14%
	> 11	14	2%
Dose delivered range, cGy		2520-8100	
Fractions delivered, range		18-45	
Surgical status	Postprostatectomy	23	3%
	No prostatectomy	658	97%
AJCC disease stage	I	173	25%
	II	397	58%
	III	82	12%
	IV	28	4%
T stage	T1	469	69%
	T2	116	17%
	T3	89	13%
	T4	5	1%
	Data unavailable	2	0%
N stage	N0	651	96%
	N1	27	4%
	Data unavailable	3	0%
Gleason score	6	196	29%
	7	333	49%
	>= 8	150	22%
	Not recorded	2	0%
PSA median (range)		6.25	0.2-370

(Continued)

Table 1 (continued)

		No. of patients	Result ^a
Risk grouping	Low	162	24%
	Intermediate	303	44%
	High	215	32%
Radiation modality	Photon	181	28%
	Proton	417	61%
	Photon/proton mix	73	11%
Time of treatment delivery, median (range)	11 AM	6	6 AM-8 PM
	Majority delivered before 5 PM	613	90%
	Majority delivered after 5 PM	48	7%
	Data unavailable	20	3%

AJCC, American Joint Committee on Cancer; BMI, body mass index; PSA, prostate-specific antigen.

^a Percentage not summing to 100% attributable to rounding error.

($P = .02$), and tumor stage ($P = .03$) (Table 3). Concurrent use of antidepressants ($P = .001$), depression by NCI-CTCAE criteria ($P < .001$), depression by diagnosis code ($P = .006$), ADT ($P = .01$), urinary antispasmodics ($P = .0495$), miscellaneous genitourinary products ($P = .001$), and narcotic analgesics ($P = .01$) were also associated with significantly higher levels of reported fatigue. Likewise, higher BMI ($P = .03$) and greater proportion of radiation treatments delivered in the evening hours ($P = .02$) were associated with higher levels of reported fatigue at end of EBRT. Concurrent antiemetic prescription (primarily ondansetron, 94% of patients receiving antiemetics) had the opposite effect and was associated with lower levels of reported fatigue at end of EBRT ($P = .03$) (Table 3).

Factors influencing severity of fatigue increase

To control for differences in baseline fatigue, the maximal difference in patient-reported fatigue over the entire treatment course was calculated for each patient. This metric was used to assess for factors contributing to differential increases in fatigue levels over the EBRT course. With these data, we assessed which of the 28 variables in our analysis were associated with higher rates of fatigue increase over radiation treatment. We found that age <60 years ($P = .03$), advanced AJCC overall disease stage ($P = .04$), use of ADT ($P = .03$), depression by NCI-CTCAE score and diagnosis code ($P < .001$ and $P = .002$, respectively), and use of miscellaneous genitourinary products ($P = .04$) were factors associated with higher levels of fatigue increase during EBRT (Table 4). We evaluated urinary symptoms specifically in addition to medication use and found that greater reported urinary

Treatment/ Follow-Up Visit	Mean Fatigue Score (95% Confidence Interval)
RT Week 1	0.15 (0.1 - 0.2)
RT Week 2	0.21 (0.15 - 0.27)
RT Week 3	0.29 (0.22 - 0.36)
RT Week 4	0.38 (0.3 - 0.45)
RT Week 5	0.44 (0.36 - 0.52)
RT Week 6	0.48 (0.4 - 0.57)
RT Week 7	0.53 (0.44 - 0.62)
RT Week 8	0.58 (0.48 - 0.68)
RT Week 9	0.59 (0.48 - 0.71)
3 Month FU	0.32 (0.28 - 0.36)
6 Month FU	0.29 (0.24 - 0.33)
9 Month FU	0.24 (0.19 - 0.29)
12 Month FU	0.22 (0.16 - 0.28)

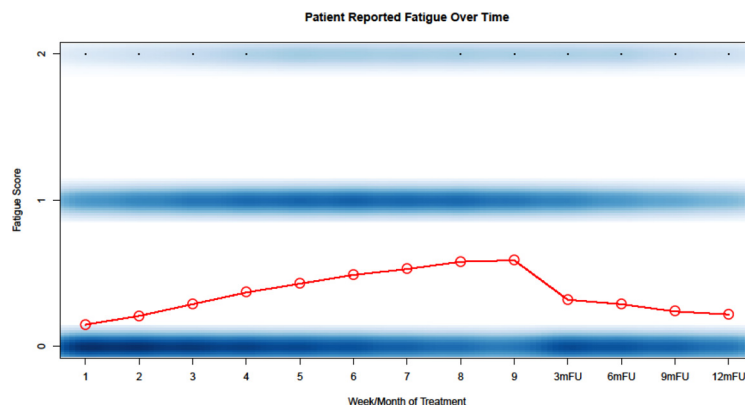


Figure 1 Patient-reported fatigue over time. Weighted scatterplot showing individual reported fatigue scores for the patient cohort (n = 681) by time point. The darkness of the blue gradient is proportional to the fraction of patients reporting the specific fatigue score (0, 1, or 2). No fatigue scores of 3 were reported by patients. The mean patient-reported fatigue score is plotted over the scatterplot and in tabular format with the 95% confidence interval. Additional time points for FU visit at 3, 6, 9, and 12 months after the end of RT are also shown. FU, follow-up; RT, radiation therapy

Table 2 Variables showing significant differences in week 1 reported fatigue

	Patient category	Mean (95% CI)	P value
AJCC disease stage	I (n = 173)	0.09 (0.05-0.14)	.02 ^a
	II (n = 397)	0.13 (0.09-0.18)	
	III (n = 82)	0.16 (0.6-0.25)	
	IV (n = 28)	0.32 (0.12-0.52)	
Depression-CTCAE score	Present (n = 92)	0.29 (0.17-0.43)	<.0001 ^a
	Absent (n = 589)	0.12 (0.09-0.14)	
Concurrent medications Antidepressant initiated before RT	Yes (n = 73)	0.22 (0.12-0.32)	.03 ^b
	No (n = 608)	0.13 (0.1-0.16)	
ADT initiated before RT	Yes (n = 301)	0.18 (0.13-0.22)	.02 ^b
	No (n = 380)	0.11 (0.08-0.15)	
Urinary antispasmodics initiated before RT	Yes (n = 55)	0.29 (0.15-0.43)	.004 ^b
	No (n = 626)	0.13 (0.1-0.16)	

Variables that demonstrated significantly higher fatigue scores at the start of radiation treatment are reported with total patient number by group, mean fatigue score by group with 95% (CI). Two-tailed P values determined by univariate nonparametric means testing are displayed.

ADT, androgen deprivation therapy; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; RT, radiation therapy.

Other abbreviation as in Table 1.

^a P value based on Kruskal-Wallis test.

^b P value based on Wilcoxon rank sum test.

urgency (χ^2 P value = .02), but not greater reported urinary frequency (χ^2 P value = .41) or increased frequency of nocturia (χ^2 P value = .06), was associated with greater fatigue increase during EBRT (Table 5). Additionally, we found a strong association between the presence of urinary urgency and frequency and the prescription of urinary antispasmodics (eg, oxybutynin) and miscellaneous genitourinary products (eg, tamsulosin, finasteride) (χ^2 P value < .001 for all associations). Prescription of antiemetics (P = .005) was associated with lower level fatigue increase during EBRT (Table 4). We then performed a multivariate analysis, with our model incorporating selected factors we found to be significant in

our univariate analysis. Our ordered logistic regression model found that age <60 years (P = .006) years, depressive symptoms (P < .001), and concurrent use of ADT (P = .04) were significant factors associated with higher levels of fatigue increase during EBRT, whereas concurrent use of antiemetics (P = .03) was associated with significantly lower levels of fatigue increase during EBRT (Table 6).

Discussion

Despite high rates of reported fatigue seen in oncology patients, and more specifically in patients receiving

Table 3 Variables showing significant differences at end of treatment

	Patient category	Mean (95% CI)	<i>P</i> value
AJCC disease stage	I (n = 173)	0.52 (0.42-0.64)	.006 ^a
	II (n = 397)	0.57 (0.48-0.66)	
	III (n = 82)	0.86 (0.69-1.1)	
	IV (n = 28)	0.88 (0.45-1.3)	
Gleason score	6 (n = 196)	0.49 (0.40-0.57)	.02 ^a
	7 (n = 333)	0.51 (0.44-0.59)	
	≥8 (n = 150)	0.65 (0.56-0.75)	
BMI	<25 (n = 121)	0.46 (0.34-0.57)	.03 ^a
	25-30 (n = 298)	0.5 (0.43-0.57)	
	>30 (n = 207)	0.65 (0.56-0.74)	
Tumor stage	T1 (n = 469)	0.5 (0.44-0.56)	.006 ^a
	T2 (n = 116)	0.55 (0.43-0.67)	
	T3 (n = 89)	0.68 (0.55-0.81)	
	T4 (n = 5)	1.25 (0.45-2.0)	
Treatments delivered after 5 PM	>50% (n = 48)	0.79 (0.6-0.98)	.02 ^b
	≤50% (n = 613)	0.57 (0.51-0.62)	
Depression CTCAE score	Present (n = 92)	0.84 (0.68-1.0)	<.0001 ^a
	Absent (n = 589)	0.49 (0.43-0.54)	
Depression diagnosis code	Present (n = 17)	0.92 (0.76-1.09)	.006 ^a
	Absent (n = 664)	0.53 (0.48-0.58)	
Concurrent medications			
Antidepressant initiated before RT	Yes (n = 73)	0.92 (0.71-1.13)	.001 ^b
	No (n = 608)	0.56 (0.5-0.62)	
ADT initiated before RT	Yes (n = 301)	0.67 (0.59-0.76)	.01 ^b
	No (n = 380)	0.52 (0.45-0.6)	
Urinary antispasmodics initiated before RT	Yes (n = 55)	0.79 (0.58-1.0)	.0495 ^b
	No (n = 626)	0.57 (0.52-0.63)	
Antiemetic initiated before RT	Yes (n = 42)	0.37 (0.18-0.55)	.03 ^b
	No (n = 639)	0.60 (0.55-0.65)	
Miscellaneous genitourinary products initiated before RT	Yes (n = 428)	0.67 (0.6-0.74)	.001 ^b
	No (n = 253)	0.46 (0.37-0.55)	
Narcotic analgesics initiated during RT	Yes (n = 28)	1.07 (0.62-1.51)	.01 ^b
	No (n = 652)	0.58 (0.52-0.63)	

Variables that demonstrated significantly higher fatigue scores at the end of radiation treatment are reported with total patient number by group, mean fatigue score by group with 95% CI. Two-tailed *P* values determined by univariate non-parametric means testing are displayed.

Abbreviations as in Table 2.

^a *P* value based on Kruskal-Wallis test.

^b *P* value based on Wilcoxon rank sum test.

radiation,^{1,2,8,15,16} our understanding of biologic and clinical contributors to cancer-related fatigue is poor. This study uses a cohort of 681 PC patients enrolled in our institution's radiation oncology patient registry to assess factors related to differences in patient-reported fatigue throughout EBRT. To our knowledge, this represents the largest reported dataset of its kind to date. Prior attempts to address the question of fatigue in patients receiving RT have been performed, including a small, prospective study in a PC cohort using clinically tested fatigue reporting instruments,⁶ analyses examining large patient cohorts across multiple disease sites,⁸ and other studies analyzing potential contributors to increased fatigue within a single anatomic site.^{3,6-8} The strength and unique contribution of our work lies in the large size of our study cohort of PC patients receiving EBRT; the wealth of prospectively collected patient-

reported fatigue scores; and the ability to assess multiple clinical-, demographic-, and treatment-related variables simultaneously.

Our study reveals some common clinical themes associated with higher grades of patient-reported fatigue throughout radiation. The association with depression or antidepressant use (Tables 2-5) highlights the potential impact of mood on fatigue. Alternatively, patients who report fatigue may be more likely to be diagnosed with depression. Higher AJCC overall disease stage was associated with increased fatigue throughout all phases of radiation (Tables 2-5). Features related to aggressive disease, such as higher Gleason score, were associated with significantly higher rates of fatigue at the end of RT (Table 3), likely because of their correlation with the overall AJCC disease stage and likelihood of ADT usage (data not shown).

Table 4 Univariate analysis of factors contributing to fatigue increase over radiation treatment course

Variable	Class	Univariate analysis P value ^a
Age, y	<60	.03 ^b
	≥60	
Race	Caucasian	.4
	African American	
	Asian	
	Other/unknown	
Patient residence	Greater Philadelphia	.14
	Outside greater Philadelphia	
Surgery status	Postprostatectomy	.53
	Intact prostate	
Disease stage	I	.04 ^b
	II	
	III	
	IV	
T stage	1	.27
	2	
	3	
	4	
N stage	0	.3
	1	
Gleason score	6	.16
	7	
	≥8	
PSA score	≤10	.6
	10-20	
	>20	
Risk classification	Low	.23
	Intermediate	
	High	
Working status	Actively working	.77
	Not working	
Smoking status	Current	.75
	Former	
	Never	
BMI	Normal (BMI < 25)	.32
	Overweight (BMI 25-30)	
	Obese (BMI > 30)	
Charlson-Deyo comorbidity score (age-adjusted)	<4	.59
	4-7	
	8-11	
	>11	
Depression-CTCAE score	Present	<.001 ^b
	Absent	
Depression-diagnosis code	Present	.002 ^b
	Absent	
Treatment modality	Photon	.5
	Proton	
	Proton/photon mixture	
Time of treatment delivery	Majority before 5 PM	

(Continued)

Table 4 (continued)

Variable	Class	Univariate analysis P value ^a
Fractions delivered	Majority after 5 PM	.09
	<20	
	20-30	
Dose delivered (cGy)	35-42	.18
	>43	
	<5000	
	5000-6999	
Volume of treatment	7000-7020	.13
	7020-7100	
	7100-7500	
	7560-7920	
Concurrent medications initiated at any point before or during RT	Whole pelvis	.65
	Prostate only	
Analgesic narcotics	Prescribed	.11
	Not prescribed	
ADT	Prescribed	.03 ^b
	Not prescribed	
Antidepressants	Prescribed	.1
	Not prescribed	
Antiemetics	Prescribed	.005 ^b
	Not prescribed	
Antihistamines	Prescribed	.95
	Not prescribed	
Beta blockers	Prescribed	.61
	Not prescribed	
Miscellaneous endocrine agents	Prescribed	.45
	Not prescribed	
Miscellaneous genitourinary products	Prescribed	.04 ^b
	Not prescribed	
Stimulants	Prescribed	.31
	Not prescribed	
Urinary antispasmodics	Prescribed	.18
	Not prescribed	

Abbreviations as in Tables 1 and 3.

^a Variables with 2 categories tested using Wilcoxon rank sum test and those with 3 or more categories assess using Kruskal Wallis test.

^b Significant at .05 level.

Unsurprisingly, use of ADT tracked with increased fatigue because fatigue is a well-described side effect of this therapy.^{17,18} We found an increasing percentage of ADT use with higher overall disease stage in our dataset, in keeping with evidence from large randomized control trials supporting a survival advantage in advanced stage or higher risk subgroups of PC.¹⁹⁻²² Given the high correlation among ADT, Gleason score, and AJCC disease stage, ADT alone of these 3 variables was included in our multivariate model and was significantly associated with increased fatigue (Table 6).

Despite the known impact of ADT on increased fatigue and potential for overwhelming or obscuring other fatigue

Table 5 Urinary symptoms fatigue association

Urinary urgency	Fatigue		
	Grade 0	Grade 1	Grade 2
Grade 0	73	69	2
Grade 1	187	230	16
Grade 2	24	51	0
		χ^2 P value	.02
Urinary frequency			
Grade 0	29	30	1
Grade 1	229	274	19
Grade 2	26	46	4
		χ^2 P value	.4
Nocturia			
0-2 episodes/night	115	113	9
>2 episodes/night	165	237	15
		χ^2 P value	.06

contributors, our analysis was able to uncover other potential factors associated with increased fatigue. In particular, we found that certain medication classes were associated with higher levels of reported fatigue. Use of urinary antispasmodics (eg, oxybutynin) was associated with higher levels of fatigue on our univariate analysis (Table 4). One explanation for this association is the central nervous system sedative effects of these anticholinergic agents. An alternative explanation is that antispasmodic use is explained by symptoms of nocturia, which may disrupt sleep and contribute to fatigue.

Antiemetic prescription, on the other hand, was surprisingly associated with decreased levels of fatigue over the EBRT course. The primary antiemetic used was ondansetron, a serotonin 5HT₃ receptor antagonist that may affect fatigue by acting centrally on the area postrema in the brain stem or peripherally on vagal nerve terminals.²³ Alternatively, because we know that ondansetron was prescribed but cannot be certain whether the patients took the medication, it is possible that the patient complaint of nausea, rather than the medication use, is associated with reduced fatigue.

A particular strength of our patient registry data was the ability to more thoroughly assess demographic and social factors than what has been reported in prior studies examining RT-related fatigue. This allows us to examine multiple proposed nonclinical contributors to increased fatigue and report on their potential importance or lack thereof. One potential explanation for fatigue in patients undergoing EBRT is the need for daily travel to our facility. We attempted to account for distance traveled for EBRT by analyzing the ZIP codes of patients' home residences and did not find this to be a contributor to increased fatigue (Table 4). We did find that age was a predictor of fatigue, although, perhaps surprisingly, we observed that advanced age was associated with lower rather than elevated levels of patient-reported fatigue (Tables 2, 4, and 6). Increased fatigue in younger patients

receiving EBRT may be explained by multiple factors, including increased sleep needs in younger patients or increased activity requirements related to employment or home life demands. Regardless of the explanation, the effect of age must be controlled for in future analyses.

We also examined the potential contribution of radiation treatment-related parameters to differential levels of fatigue. We compared patient groups across different treatment modalities, fractionation schemes, and time of day of treatment. Our analysis did not show significantly different levels of fatigue between those patients receiving photon treatments versus those receiving proton treatments, between different dose and fraction levels, or by volume of disease treated (Table 4). Regarding the lack of difference in fatigue between proton and photon treatments, it is possible that a difference may only manifest in a different anatomic site or with larger fields where relative differences in tissues irradiated and integral dose may have a greater impact. We did observe higher reported fatigue at the end of EBRT for those patients receiving evening treatments (defined as treatment delivered after 5 PM Eastern Standard Time) (Table 3). This did not translate to a significant difference in the magnitude of fatigue increase when taking into account baseline fatigue, but there was a trend toward higher levels of increase in fatigue for the evening cohort ($P = .09$) (Table 4), which may reflect circadian variation in the inflammatory response to radiation or simply sleep schedule disruption.

One potential fatigue contributor not directly assessed in our study was sleepiness. Monga et al performed assessments using the Epworth Sleepiness Scale in their PC patient cohort and reported no increase in sleepiness at the conclusion of radiation despite higher levels of fatigue.^{6,24} To our knowledge, however, objective assessments of sleepiness and vigilance in patients undergoing RT have not been reported. Future studies assessing the contribution of drowsiness to radiation-related fatigue are worth considering.

Despite our efforts to comprehensively assess fatigue predictors, there are limitations to our findings. Our focus on male patients with localized disease limits our ability to generalize our observations to other cancer treatment populations (eg, women or those also receiving systemic chemotherapy). Although the emphasis on a single disease entity was designed to reduce confounding across disease sites, it does highlight the role for future efforts to address the impact of factors such as gender. Our fatigue analysis was also based on the CTCAE fatigue score, which is an inherently 1-dimensional fatigue metric. This measure was chosen based on availability and simplicity, but in any future prospective study, we would incorporate a multidimensional fatigue instrument (eg, Multidimensional Fatigue Inventory or the Brief Fatigue Inventory),^{25,26} especially in light of the associations with depression noted in this study. This work is also limited in its inability to identify the mechanistic aspects of how EBRT contributes to fatigue or the biologic basis for radiation-induced fatigue, but it does highlight

Table 6 Multivariate analysis of factors contributing to fatigue increase over radiation treatment course

Variable	Class	OR (95% CI)	Multivariate analysis P value ^a
Age	<60		
	≥60	0.57 (0.38- 0.88)	.006 ^b
Urinary urgency	Grade 0		
	Grade ≥1	1.21 (0.99-1.48)	.05
Depression symptoms	Grade 0		
	Grade ≥1	3.54 (2.15-5.94)	<.001 ^b
BMI	Not overweight (BMI <25)		
	Overweight (BMI 25-30)	0.82 (0.44-1.49)	.5
	Obese (BMI >30)	1.03 (0.55-1.93)	.9
Concurrent medications initiated before RT			
	Antiemetics	Prescribed Not prescribed	0.44 (0.21-0.89)
ADT	Prescribed	1.41 (1.01-1.95)	
	Not prescribed		.04 ^b
Urinary antispasmodics	Prescribed	1.31 (0.71-2.44)	
	Not prescribed		.4
Miscellaneous genitourinary agents	Prescribed	1.24 (0.90-1.73)	
	Not prescribed		.2

Ordered logistic regression model to identify variables associated with greater magnitude of fatigue increase during radiation controlled for baseline fatigue. The OR for each variable is reported along with the 95% CI.

OR, odds ratio. Other abbreviations as in Tables 1 and 2.

^a Significance testing performed by ordered logistic regression model.

^b Significant at .05 level.

important areas for future investigation and has been incorporated into our own ongoing prospective protocol assessing objective measures of sleepiness during EBRT in PC patients, to be reported in a future publication.

Conclusions

We observed increased fatigue levels over the course of EBRT for PC patients, as expected, and found that age, depressive symptoms, concurrent ADT, and concurrent antiemetic use were the most significant variables affecting fatigue levels during radiation. Additionally, we report on numerous factors intrinsic to the delivery of radiation itself and other nonclinical factors and show no association with increased fatigue. This knowledge on potential contributors and noncontributors to increased fatigue can assist the practicing clinician in appropriate fatigue counseling. Future studies to explain the fatigue associations observed here are necessary to develop preventative and therapeutic measures that will mitigate the impact of this commonly seen side effect of RT.

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