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Research Article

Physical Activity and its Association with Fatigue in Men with Prostate Cancer

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Abstract

Fatigue negatively impacts health outcomes leading to decreased physical activity, increased depression, and decreased health-related quality of life. This study aimed to determine level/intensity of physical activity (PA) and its associations with cancer-related fatigue (CRF) in prostate cancer patients receiving radiotherapy (RT), compared to those without RT but under active surveillance (AS). A prospective, correlational design with repeated measures was used to determine changes in PA and association of PA with CRF in men with prostate cancer. Fifty-four subjects were recruited (RT=36, AS=18). PA was measured using *The International Physical Activity Questionnaire (*IPAQ*)*, a well-validated, self-report questionnaire. CRF was evaluated by *the revised Piper Fatigue Scale* (r-PFS) and Patient Reported Outcomes Measurement Information System for Fatigue (PROMIS-F), and *Hamilton Depression Rating Scale* (HAM-D) was used to assess depression symptoms. The metabolic equivalent of task (MET) was calculated following the IPAQ analysis guidelines to reflect the intensity/level of PA. Data were collected at 3 times and analyzed using Chi-square/ Fisher's exact tests, t-testes, and Spearman correlation. All tests were two-sided, and p-values < 0.05 were considered statistically significant. Level of IPAQ (low, moderate, high) at the endpoint were significantly different between the two groups (p = 0.03). IPAQ was associated with PROMIS-F (p = 0.014), r-PFS (p = 0.001), and HAM-D (p = 0.01) at midpoint and endpoint in the RT group. Patients with RT reported decreased PA, compared to their baseline and to those with AS. Levels/intensity of PA was associated with CRF severity and depression in patients receiving RT. Assessment of PA and symptoms prior to the treatment may enable clinicians to identify patients who need early and aggressive intervention to prevent worsening symptoms through a decline in PA during and after RT.

Keywords: Physical activity; Radiotherapy-related fatigue; Prostate cancer; Radiation therapy

Introduction

Prostate cancer is a highly prevalent carcinoma, the second most common malignancy, and the third leading cause of cancer mortality in the United States [1]. Radiation therapy (RT) using an intensity-modulated radiation technique, is a standard treatment option for non-metastatic prostate cancer [2]. Although RT has increased survival rates for men with this disease, fatigue is highly prevalent during and at the completion of treatment [3] and causes long-lasting distress even in disease-free stages [4-6] . Up to 71% of men with prostate cancer receiving RT experience significant fatigue related to its therapy [7,8].

Fatigue is one of the cancer symptoms most often reported to nurses by patients receiving RT [9]. Cancer-related fatigue (CRF) is described as pervasive, a whole body excessive tiredness that is unrelated to activity or exertion, and not relieved by rest or sleep [10]. CRF negatively impacts health outcomes leading to increased depression, impaired cognitive function, increased sleep disturbance, decreased physical activity and decreased health-related quality of life [11-14]. CRF is the most common adverse effect of cancer and cancer treatment [15] and typically increases during RT [8,16]. CRF in men treated for prostate cancer has been

found to increase slightly beginning at Week 3 of RT, increasing significantly by Week 6 [8], remaining elevated at the completion of RT,[17] and can last months to years afterward [8,18-21]. CRF is reported as a distressing, persistent sense of tiredness or exhaustion related to cancer or cancer treatment [22]. This symptom is associated with negative health outcomes including depression, impaired cognitive function, sleep disturbance, and decreased physical activity [11-13].

CRF is one of the most burdensome with the greatest adverse effect on quality of life, but arguably the least understood [18, 23]. While a limited number of interventions have been suggested to address CRF, the only one that has an adequate evidence base to date is exercise [24]. Physical activity (PA) is defined as any movement that uses skeletal muscles and requires more energy than resting, including walking, running, exercising [25]. Previous studies have shown levels and changes of PA in cancer patients during chemotherapy [26-29], the association of PA with CRF in patients with breast cancer [30-32], and the impact of PA on CRF and quality of life in patients with cancer [33-35]. However, there is very limited literature/evidence on PA and CRF in patients with prostate cancer. The purpose of this study was to describe level/intensity and changes of physical activity (PA) and its associations with CRF and depression symptoms in patients with prostate cancer receiving radiotherapy (RT), compared to those without RT but under active surveillance (AS). Understanding level/intensity and changes of PA overtime, and how these correlates with CRF is a key for healthcare providers to provide individual prescription of PA for CRF precision management.

Materials and Methods

This was a prospective, correlational design with repeated measures. This study was reviewed and approved by the Institutional Review Board of the Case Comprehensive Cancer Center. Two groups of subjects were recruited in this study: prostate cancer patients with RT and prostate cancer patients without any treatment, but undergoing AS.

Sample, Setting, and Procedures

The study sample was drawn from a population of localized prostate cancer patients scheduled for RT or AS at a National Cancer Institute designated Comprehensive Cancer Center in Northern Ohio. Inclusion criteria were: 1. Clinically localized prostate cancer. 2. Scheduled to receive RT (e.g., external beam radiation therapy either by 3D conformal or IMRT techniques) or undergoing AS. 3. Able to provide written informed consent. 4. ≥18 years of age. Research subjects were excluded from the study if they had any one of the following: 1. Progressive or unstable disease other than cancer of any body system causing clinically significant fatigue (e.g., class IV congestive heart failure, end-stage renal disease, stage IV chronic obstructive pulmonary disease) including patients with systemic infections (e.g., human immunodeficiency virus [HIV], active hepatitis); documented recent (<3 years) history of major depression, bipolar disease, psychosis, or alcohol/drug dependence/abuse; uncorrected hypothyroidism, untreated anemia; and those with chronic inflammatory disease (e.g. rheumatoid arthritis, systemic lupus erythematosus). 2. Patients regularly taking antipsychotics and anticonvulsants, since these medications cause significant fatigue. 3. Patients who have second malignancies or those receiving chemotherapy with their RT. 4. Taking medication for fatigue (e.g., methylphenidate, moldafinil).

Localized RT for prostate cancer is usually administered 5 days a week for 7-9 weeks, depending on the type of treatment delivery and dose used. Data were collected at baseline (before RT), midpoint (21 days of RT), and endpoint (completion of RT, 42 days of RT). After obtaining written informed consent, we collected demographic information and medical history *via* interviews and from the medical records. Study variables included CRF, depression, and PA (Figure 1).

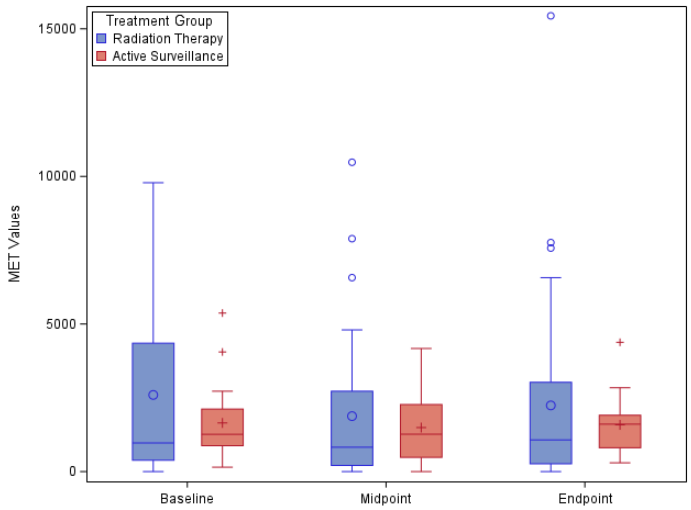

Figure 1: Boxplots of Physical Activity (PA) at each time point; PA was measured by The International Physical Activity Questionnaire and calculated using metabolic equivalent of task (MET). A significant change of PA from baseline to midpoint in RT group ($p = 0.041$).

Study Measures

Cancer-related fatigue (CRF): CRF is a subjective experience, a complex phenomenon with multiple dimensions [36,37], so the revised Piper Fatigue Scale (r-PFS) and Patient-Reported Outcomes Measurement Information System for Fatigue (PROMIS-F) were used to assess the subjective dimensions of fatigue experienced by men treated for prostate cancer. The r-PFS is a 22-item paper/pencil questionnaire that measures 4 fatigue dimensions including

behavioral/severity, sensory, cognitive/mood, and affective. The r-PFS shows good reliability and validity with internal consistency ranging from 0.7-0.9 across 4 fatigue dimensions from cancer patients undergoing RT [36]. The PROMIS-F was developed from multiple disease populations including cancer. It consists of 7-item and showed internal consistency reliability coefficient of 0.80 [38].

Depression: Hamilton Depression Rating Scale (HAM-D) was used to assess depression symptom because depression was a known covariance of CRF. The HAM-D is a 21-item scale with good internal reliability (α = 0.8-0.9), completed by study staff through subject interviews. Scores can range from 0 to 78; higher scores (>17) indicate higher symptoms of depression [39].

Physical Activity (PA): The International Physical Activity Questionnaire (IPAQ) was used to evaluate physical activity levels for each participant. The IPAQ is a well validated, 7-item self-report questionnaire, and asks subjects to recall the amount of physical activity undertaken for the pass 7 days [40].

Statistical Analysis

Descriptive statistics were calculated for the mean, standard deviation, median, and range for the participants' demographic characteristics. Two sample comparisons were conducted using a two-sample t-test for continuous variables and Chi-square/Fisher's exact tests for categorical variables. To test mean changes in PA from baseline (T1) to midpoint (T2) and T1 to endpoint (T3) in patients with RT and AS, the paired t-test for within group and two-sample t-test/Wilcoxon rank sum test was used. To examine the associations among PA, fatigue, and depression at each time point, Spearman correlation was used. All tests were two-sided, and p-values < 0.05 were considered statistically significant. All statistical analyses were conducted using SPSS 25.0 (IBM Corporation, Armonk, NY), and SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

A total of 54 patients diagnosed with localized prostate cancer were enrolled in this study. The demographic characteristics of the two groups (RT = 36 subjects, AS = 18 subjects) are summarized in (Table 1). There was no significant difference in demographics between RT and AS groups; however, we found that race (p = 0.026) and education (p = 0.005) were significantly different within group. A majority of subjects were White, married, with a bachelor's or advanced degree.

Variable		RT (n=36)	AS (n=18)	Total (N=54)	p-value[a]
		Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)		67.78 (8.37)	63.67 (6.72)	66.41 (8.04)	0.076*
Race	White	22 (61.11%)	15 (83.33%)	37 (68.52%)	**0.026**
	Black	14 (38.89%)	2 (11.11%)	16 (29.63%)	
	Asian	0 (0.00%)	1 (5.56%)	1 (1.85%)	
Education	8th grade	1 (2.78%)	0 (0.00%)	1 (1.85%)	**0.005**
	9-12th grade	6 (16.67%)	1 (5.56%)	7 (12.96%)	
	High School Grad	3 (8.33%)	2 (11.11%)	5 (9.26%)	
	Technical	2 (5.56%)	0 (0.00%)	2 (3.70%)	
	Assoc Degree	10 (27.78%)	0 (0.00%)	10 (18.52%)	
	Bachelor's	9 (25.00%)	5 (27.78%)	14 (25.93%)	
	Advanced	4 (11.11%)	10 (55.56%)	14 (25.93%)	
	Other	1 (2.78%)	0 (0.00%)	1 (1.85%)	
Marital Status	Married	23 (63.89%)	15 (83.33%)	38 (70.37%)	0.305
	Widowed	6 (16.67%)	0 (0.00%)	6 (11.11%)	
	Single	3 (8.33%)	1 (5.56%)	4 (7.41%)	
	Divorced	4 (11.11%)	2 (11.11%)	6 (11.11%)	

Variable		RT (n=36)	AS (n=18)	Total (N=54)	p-value[a]
		Mean (SD)	Mean (SD)	Mean (SD)	
Employment Status	Full time	11 (30.56%)	11 (61.11%)	22 (40.74%)	0.073
	Part time	3 (8.33%)	3 (16.67%)	6 (11.11%)	
	Retired	19 (52.78%)	4 (22.22%)	23 (42.59%)	
	Disabled	2 (5.56%)	0 (0.00%)	2 (3.70%)	
	Unknown	1 (2.78%)	0 (0.00%)	1 (1.85%)	
Annual Income	<$8,000	1 (2.78%)	0 (0.00%)	1 (1.85%)	0.134
	$8,000-$14,000	2 (5.56%)	0 (0.00%)	2 (3.70%)	
	$15,000-$24,000	6 (16.67%)	0 (0.00%)	6 (11.11%)	

Table 1: Demographic characteristics in men with prostate cancer; ap-value from Fisher's exact test; *p-value from two sample t-test; Median (IQR) ages for RT, AS, and Total were 68 (63,74), 64.5 (58,68), and 67 (62,70), respectively. IQR = interquartile range; SD = standard deviation; RT = radiation therapy; AS = active surveillance.

Physical activity (PA): The metabolic equivalent of task (MET) is a common measure of PA, reflecting the intensity of PA. One MET is the rate of energy expended by a person sitting at rest. According to the 2018 Physical Activity Guidelines Advisory Committee Scientific Report, expending 1.5 or fewer METs is sedentary, expending more than 1.5 but less than 3 METs is low/light level intensity of PA, expending 3 to 6 METs is moderate level intensity of PA, while expending 6 or more METs is high/vigorous level intensity of PA [41]. Based on the guidelines for data processing and analysis of the IPAQ, the Total MET-minute/week was calculated and categorized into three levels (low, moderate, and high) of PA. The frequencies of PA in each time point and the results of comparisons between two groups using the Chi-square test are presented in (Table 2a). The level of PA at the endpoint was significantly different between the two groups ($p = 0.03$). Table 2b depicts changes in PA over time and comparisons of changes in PA between and within groups. There was a significant change in PA from baseline to midpoint in RT group ($p = 0.041$); However, there was no significant change of PA over time in the AS group, neither significant change in PA over time between the two groups (Table 2b).

Time	Level/Intensity	RT (n = 36)	AS (n = 18)	Total (N = 54)	p-value*
		N (%)	N (%)	N (%)	
Baseline	Low	14 (38.89)	5 (27.78)	19 (35.19)	0.242
	Moderate	8 (22.22)	8 (44.44)	16 (29.63)	
	High	14 (38.89)	5 (27.78)	19 (35.19)	
Midpoint	Low	17 (47.22)	7 (38.89)	24 (44.44)	0.804
	Moderate	8 (22.22)	4 (22.22)	12 (22.22)	
	High	11 (30.56)	7 (38.89)	18 (33.33)	
Endpoint	Low	19 (52.78)	3 (16.67)	22 (40.74)	**0.030**
	Moderate	7 (19.44)	8 (44.44)	15 (27.78)	
	High	10 (27.78)	7 (38.89)	17 (31.48)	

Table 2a: Level/Intensity of PA at each time point in men with prostate cancer;*p-values from Chi-Square test; RT = radiation therapy; AS = active surveillance; PA = physical activity.

Time	Group	N	Mean	SD	Median	Min	Max	p-value[a] (within)	p-value[b] (between)
Change T2-T1	RT	36	-718.28	2026.93	-192.00	-6786.00	3102.00	**0.041**	0.161
	AS	18	-156.72	864.58	-229.50	-1569.00	1390.50	0.452	
Change T3-T1	RT	36	-355.64	1841.88	-132.00	-4800.00	5653.50	0.2545	0.433
	AS	18	-65.61	857.64	-18.75	-1984.50	1588.50	0.7495	

Table 2b: Changes of PA and comparisons of changes in PA between and within groups; [a]p-values from paired t-test; [b]p-values from two-sample t-test; RT = radiation therapy; AS = active surveillance; PA = physical activity.

CRF and Depression: (Table 3) describes the mean, SD, and median scores of r-PFS and PROMIS-F, and HAM-D. The severity of CRF was increased in midpoint and end point in RT group, compared to AS group. The changes in CRF and comparison of changes in CRF between and within groups have been previously published [42]. None of the 54 subjects reached the cutoff score for clinical depression. In addition, Spearman correlations between PA and CRF and depression at each time point in patients with RT and AS are presented in (Table 4) In patients with RT, we found that PA showed significant correlations with r-PFS (r = -0.515, p = 0.001), PROMIS-F (r = -0.326, p = 0.05), and HAM-D (r = 0.411, p = 0.013) at the completion of RT. In the AS group, PA was associated with PROMIS-F at the midpoint (r = -0.567, p = 0.014).

	Time	Group	N	Mean	SD	Median (Min-Max)
r-PFS	Baseline	Total	54	1.37	1.53	0.89 (0-5.36)
		RT	36	1.42	1.68	0.75 (0-5.36)
		AS	18	1.25	1.22	0.93 (0-4.64)
	Midpoint	Total	53	2.27	2.06	1.41 (0-6.77)
		RT	36	2.74	2.13	2.57 (0-6.77)
		AS	17	1.26	1.49	0.64 (0-4.73)
	Endpoint	Total	53	2.74	2.69	1.41 (0-9.64)
		RT	36	3.42	2.86	2.57 (0-9.64)
		AS	17	1.31	1.53	0.82 (0-5.05)
PROMIS-F	Baseline	Total	54	46.71	9.33	46.70 (10-67.8)
		RT	36	48.44	8.03	47.60 (33.4-67.8)
		AS	18	43.26	10.95	45.80 (10-56.4)
	Midpoint	Total	54	47.91	8.92	47.60 (29.4-66.3)
		RT	36	49.48	9.39	50.00 (29.4-66.3)
		AS	18	44.77	7.11	43.90 (29.4-59.2)
	Endpoint	Total	53	47.74	10.18	47.60 (25-72.9)
		RT	36	49.97	10.78	52.20 (25-72.9)
		AS	17	43.03	6.92	43.90 (29.4-53.7)

HAM-D	Baseline	Total	54	1.00	1.68	0.00 (0-8)
		RT	36	1.22	1.82	0.50 (0-8)
		AS	18	0.56	1.29	0.00 (0-5)
	Midpoint	Total	53	0.98	1.80	0.00 (0-9)
		RT	36	1.31	2.05	0.00 (0-9)
		AS	17	0.29	0.77	0.00 (0-3)
	Endpoint	Total	53	0.87	1.69	0.00 (0-8)
		RT	36	1.19	1.94	0.00 (0-8)
		AS	17	0.18	0.53	0.00 (0-8)

Table 3: Severity of CRF and depression at each time point in men with prostate cancer; r-PFS = revised Piper Fatigue Scale; PROMIS-F = Patient-Reported Outcomes Measurement Information System for Fatigue; HAM-D = Hamilton Depression Rating Scale; RT = radiation therapy; AS = active surveillance; CRF = cancer-related fatigue.

		Physical Activities					
	Group	**Baseline**		**Midpoint**		**Endpoint**	
		N	Coefficient (p-value)	N	Coefficient (p-value)	N	Coefficient (p-value)
r-PFS	RT	36	0.028 (0.871)	36	-0.070 (0.685)	36	**-0.515 (0.001)**
	AS	18	-0.196 (0.435)	17	-0.342 (0.178)	17	-0.007 (0.977)
PROMIS-F	RT	36	-0.229 (0.178)	36	0.009 (0.956)	36	**-0.326 (0.05)**
	AS	18	-0.251 (0.313)	18	**-0.567 (0.014)**	17	-0.1394 (0.5936)
HAM-D	RT	36	-0.056 (0.742)	36	0.207 (0.223)	36	**-0.411 (0.013)**
	AS	18	-0.378 (0.121)	17	-0.293 (0.253)	17	-0.4551 (0.0664)

Table 4: Correlations among PA, CRF, and depression at each time point in men with prostate cancer; r-PFS = revised Piper Fatigue Scale; PROMIS-F = Patient-Reported Outcomes Measurement Information System for Fatigue; HAM-D = Hamilton Depression Rating Scale; RT = radiation therapy; AS = active surveillance; PA = physical activity; CRF = cancer-related fatigue.

Discussion

Our major findings include: (1) a significant difference in level/intensity of PA between the two groups ($p = 0.03$); (2) compared to AS group, there was a significant difference in changes of PA from midpoint to baseline in patients receiving RT; (3) there were significantly decreased level/intensity of PA associated with increased CRF and depression at the endpoint of RT in patients receiving RT. Manneville et al (2018) described that women with breast cancer receiving chemotherapy showed low and insufficient frequency of PA, which associated with increased fatigue and decreased quality of life [33]. In men treated with RT for their prostate cancer, we found an increased number/percentage of patients reported low level/intensity of PA during RT (n=17, 47%) and at the completion of RT (n=19, 53%), compared to those prior to the treatment (n=14, 38%). In addition, a significantly decreased intensity/level of PA from baseline (moderate and high levels) to endpoint (low level) was reported by men receiving RT. In contrast, patients without RT (AS group) reported similar level of PA at each time point (Table 2a) with an insignificant change of PA overtime (Table 2b). Decreased level/intensity of PA is significantly associated with the severity of CRF and depression symptom at the completion of RT in patients with prostate cancer receiving RT, which is consistent with previous studies with different cancer patients [30-32, 43]. This suggest that PA can have a positive impact on CRF and depression to enhance health-related quality of life. It is challenge for clinicians to prescribe an individualized, feasible PA regimen with precision, and applicable strategies without evidence-based research. Further investigations using a larger sample to predict trajectories and influential factors of PA for CRF are warranted. Limitations of this study have been recognized, including a small sample size and homogenous sample which limit the study generalizability.

In conclusion, the study findings provide information on changes of PA intensity and the association of PA with CRF and depression in men with clinically localized prostate cancer. Men treated with RT for their prostate cancer experienced a decrease of PA intensity, an increase of CRF and depression symptoms during and after RT, compared to those without RT. Therefore, assessment of PA and symptoms (e.g., CRF and depression) prior to the treatment may enable healthcare providers to identify patients who need early and aggressive intervention to prevent worsening symptoms through a decline in PA during and after the treatment.

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