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Original article

Patient-reported fatigue in breast cancer patients receiving radiation therapy

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ABSTRACT

Purpose: Fatigue or tiredness is one of the most commonly reported symptoms in breast cancer patients treated with radiation therapy (RT). This study aimed to identify characteristics associated with fatigue in breast cancer patients receiving adjuvant RT.

Methods: Patients with non-metastatic breast cancer receiving RT at the Odette Cancer Centre from 2011 to 2017 were included in our study if they completed at least one ESAS pre- and post-RT. Information regarding patient, disease and treatment characteristics was retrieved from chart review. To identify variables associated with fatigue scores pre-RT, post-RT and changes in fatigue scores, a univariate and multivariate general linear regression analysis was conducted; $p < 0.05$ was considered statistically significant.

Results: Our study included 1223 female patients (mean age 59 years old) who completed ESAS on average 28 days before, and 142 days after RT. In multivariate analysis, higher baseline fatigue scores were found in women with higher disease stages ($p = 0.001$), and those who receive locoregional radiation ($p < 0.001$). No variables were significantly associated with post-RT fatigue scores. While adjuvant chemotherapy and locoregional RT were associated with higher baseline scores in univariate analysis, in multivariate analysis, they were associated with significant reduction in fatigue post-RT ($p = 0.01$, $p = 0.007$ respectively).

Conclusions: Fatigue is associated with higher disease stage and receipt of locoregional radiation. While the relationship between anxiety or depressive symptoms and fatigue is well-established, a major gap exists in our understanding of its etiology and treatment; further investigation to address this can better improve patient quality of life.

1. Introduction

Breast cancer patients undergoing radiation therapy (RT) commonly report tiredness or fatigue with incidences up to 80% during treatment [1]. Studies have suggested that fatigue increases during the course of radiation therapy, and can last for over 3 months after treatment completion [2]. Although fatigue is not a dose-limiting side effect of radiation [3], it has a significant impact on patients' perceived quality of life (QoL), with some studies suggesting that it may be the symptom that most influences global QoL, even more so than pain [1,4]. Moreover, fatigue is associated with psychological symptoms of depression, anxiety, and drowsiness [5,6].

The pathophysiology and origin of radiation-associated fatigue in breast cancer is unclear. There have been studies that suggested fatigue in the breast cancer setting is due to the physical and psychosocial distress rather than a biological effect from either the cancer or the treatment [7]; several studies have determined that psychological factors are associated with more adverse fatigue trajectories throughout treatment for breast cancer [8], and are strongly correlated with fatigue in breast cancer survivors [9]. Studies have also found that the intensity of fatigue is correlated with the number of treatment modalities; patients with

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combination therapies of surgery, chemotherapy, and radiation therapy had higher scores than patients who received radiation therapy alone [10].

The Edmonton Symptom Assessment Scale used in cancer centres across Ontario, Canada to prospectively assess nine symptoms pertinent to cancer at every patient visit. These symptoms include anxiety, depression, drowsiness, lack of appetite, nausea, pain, dyspnea, tiredness and overall well-being, assessed on a scale from 0 (no symptom) to 10 (most severe symptom) [11]. A recently published observational study of ESAS that aimed to evaluate symptom burden in Ontario breast cancer patients identified tiredness as the most commonly reported symptom overall (60%) as well as the most commonly reported moderate to severe symptom with 59.7% and 27.0% of scores being ≥ 4 and ≥ 7 respectively [12].

Our study aimed to evaluate fatigue experienced by breast cancer patients by comparing ESAS scores before and after RT and correlating severities and changes with patient, disease, and treatment characteristics.

2. Materials and methods

Approval to conduct the study was obtained from the Sunnybrook Health Sciences Centre research ethics board. Patient population was defined as all non-metastatic breast cancer patients who were treated at the Odette Cancer Centre between January 2011 and June 2017, with at least one baseline ESAS completed no earlier than 3 months before RT, as well as one ESAS completed after RT. Patients who received additional chemotherapy, radiation, or cancer surgery for their cancer initiated before the second ESAS were excluded.

The following information was collected: patient age at start of RT, gender, disease characteristics, and treatment characteristics. Disease characteristics consisted of laterality and pathological cancer stages of 0, 1, II, III, or IVd (inflammatory breast cancer); clinical stage was used in the absence of pathological stage. Treatment characteristics included RT fractionation (hypofractionation defined as 16 or less treatments), dates, locations (breast or chest wall), boost, boost type (simultaneous or subsequent) and locoregional RT. Systemic treatment information included chemotherapy, hormonal therapy and treatment dates, but did not include specific regimens. Chemotherapy was grouped according to when it was completed before or ongoing during the baseline ESAS date. Hormonal therapy was categorised as being prescribed concurrently with RT, or subsequent to RT completion. Surgical information was not available.

2.1. Data analysis

Descriptive statistics were used to summarise patient, disease, and treatment characteristics where proportions were reported for categorical variables, means ± standard deviation (SD), and minimum to maximum values for normally distributed numerical variables, and medians with interquartiles, and minimum to maximum values for non-normally distributed numerical variables. FREQ and MEANS procedures in SAS were applied for calculating these statistic summaries. To compare paired pain scores before and after RT, the two-tailed paired *t*-test test was used after applying a natural log transformation. A univariate general linear regression analysis was conducted to identify variables associated with: 1) fatigue score at baseline, 2) fatigue score after RT, and 3) changes in fatigue (post-RT score subtracted by baseline score). To normalize the distribution for fatigue scores after RT, natural log-transformations were applied. All variables with $p < 0.10$ from univariate analysis were included in multivariable analysis, which then used a backward selection procedure to search for the final model. The coefficient, standard error (SE) of the coefficient, p-value and the coefficient of determination (R^2) were calculated. Higher R^2 values represented a better model fit. To determine whether bilateral synchronous patients should be included with unilateral breast cancer patients in the analysis, the two-tailed Wilcoxon rank-sum test was utilised. Since no significant difference was identified, bilateral synchronous patients were included. Statistical Analysis Software (SAS version 9.4 for Windows, Cary, NC) and R package (version 3.2.0) were used for data analysis, and a p-value of <0.05 was considered statistically significant.

Table 1
Patient, treatment, and disease characteristics.

Variable	Total (N = 1223)
Age at RT start in years	
Mean ± SD	58.6 ± 12.1
Min, Max	25, 94
Age groups at RT start in years (%)	
<30	0.41
30-<40	4.25
40-<50	21.67
50-<60	28.95
60-<70	25.51
70-<80	14.72
≥80	4.50
Stage (%)	
0	11.20
1	43.99
2	34.67
3	9.32
4d	0.82
Laterality (%)	
Left	49.88
Right	47.51
Bilateral	2.53
Unknown	0.08
ESAS Fatigue score at baseline	
Median (Inter-quartiles)	2 (0, 4)
Min, Max	0, 10
ESAS Fatigue score after RT	
Median (Inter-quartiles)	2 (1, 5)
Min, Max	0, 10
Fatigue increase from baseline (%)	
No	61.82
Yes	38.18
RT Site (%)	
Chest	27.80
Breast	71.79
Other (both or unknown)	0.41
Radiation fractionation (%)	
>16 (conventional fractionation)	63.29
≤16 (hypofractionation)	36.71
Boost radiation (%)	
No	64.1
Yes	35.9
Subsequent boost (Sub)	74.72
Concurrent (simultaneous) boost (Sim)	25.28
Regional RT (%)	
No	59.69
Yes	40.31
Receiving adjuvant chemotherapy	83.77
Not receiving adjuvant chemotherapy	16.23
Adjuvant chemotherapy in all patients (%)	
No	51.51
Yes	48.49
Finished before first ESAS	63.74
First ESAS during chemotherapy	36.26
Hormone therapy (%)	
No	21.10
Yes	76.04
Initiated after RT completion	29.35
Initiated concurrently with RT	61.40
Unknown start	9.25
Unknown	2.86

3. Results

There were 1223 patients in this study, with an average age of 58.6 years old. All patients were female. Table 1 summarises patient, disease, and treatment information. On average, the ESAS was completed 28 days before RT with a median fatigue score of 2 (inter quartile range (IQR) 0, 4), and 143 days after RT with a median fatigue score of 2 (IQR 1, 5). Although the average overall fatigue scores increased from 2.71 to 2.86, the change was not considered statistically significant ($p = 0.15$). As there was no statistical significance between fatigue scores in patients with bilateral synchronous breast cancer and unilateral breast cancer (baseline: $p = 0.78$; post-RT: $p = 0.79$), these patients were included in subsequent analysis (Appendix A).

3.1. Baseline fatigue scores

Eight predictive factors were significantly related to fatigue scores before RT (Table 2). Patients who eventually received chest wall radiation, locoregional RT, conventionally fractionated dose schedules (>16 fractions), longer duration of radiation course, and adjuvant chemotherapy were more likely to have higher fatigue scores before start of RT. In addition, stage was also significantly correlated with fatigue score before RT ($p < 0.0001$). Patients with more advanced disease (Stage 2 or 3) had higher fatigue scores when compared to those with ductal carcinoma in situ (Stage 0) or early disease (Stage 1). When the timing of chemotherapy relative to ESAS completion was compared, those who completed chemotherapy before the baseline ESAS were more likely to have lower fatigue scores compared to those who completed the baseline ESAS during receipt of chemotherapy ($p = 0.009$). Patients with fewer days in between completion of chemotherapy and completion of the baseline ESAS were more likely to have higher fatigue scores ($p = 0.004$). In multivariable analysis (Table 3), only locoregional RT (coefficient = 0.16, SE = 0.05, $p = 0.0007$) and stage (overall $p = 0.001$) remained significant. The overall R^2 of the multivariable model was 3.3%.

3.2. Post-radiation fatigue scores

No variables were significantly associated with post-radiation fatigue scores in the univariate analysis (Appendix B).

3.3. Change in fatigue scores

Six predictive factors were significantly associated with changes in fatigue scores (Table 4). Negative coefficients indicate reductions in fatigue (better QOL), and positive coefficients indicate increases in fatigue (worse QOL). Locoregional radiation, longer duration of radiation course (in days), and receipt of adjuvant chemotherapy were more likely to experience reductions in fatigue scores. Patients who received radiation to the breast and those with hypofractionated regimens tended to experience increases in fatigue. Moreover, a larger time gap between completion of chemotherapy and completion of the baseline ESAS was associated with increased fatigue scores after RT. Disease stage overall was not significantly associated with changes in fatigue, although certain comparisons made between individual stages were significant.

In the final multivariable model, adjuvant chemotherapy (coefficient = −0.46, SE = 0.18, $p = 0.01$) and locoregional radiation (coefficient = −0.45, SE = 0.17, $p = 0.007$) remained significant predictors of change in fatigue. Both variables were associated with negative changes in fatigue scores from baseline, indicating fatigue reduction after RT. The overall model had a R^2 of 2.2%.

4. Discussion

Our results found that fatigue scores were slightly higher after RT, but this difference was not significant. Patients at a higher disease stage and who received locoregional RT tended to have higher baseline fatigue scores. However, patients with locoregional RT, in addition to patients who received adjuvant chemotherapy, experienced significant reductions in fatigue scores after completion of RT despite having higher baseline fatigue. This suggests that disease and treatment related factors may influence the severity and development of fatigue during breast RT.

Table 2
Predictors of baseline ESAS fatigue scores (before radiation therapy).

Univariate Predictive factors for baseline fatigue	Coefficient	Standard Error	p-value	R^2 (%)
Age at start of RT (Years)	−0.0026	0.0018	0.138	0.18
Stage (overall effect)			**<.0001**	**2.41**
1 vs. 0	0.0532	0.0715	0.4571	
2 vs. 0	**0.226**	**0.0735**	**0.0021**	
3 vs. 0	**0.3784**	**0.0948**	**<.0001**	
4d vs. 0	−0.0699	0.2448	0.7753	
1 vs. 2	**-**	**-**	**0.0004**	
1 vs. 3	**-**	**-**	**<.0001**	
1 vs. 4d	–	–	0.6059	
2 vs. 3	**-**	**-**	0.0536	
2 vs. 4d	–	–	0.2161	
3 vs. 4d	–	–	0.0692	
Radiation				
RT Site (Breast vs. Chest wall)	**−0.1858**	**0.048**	**0.0001**	**1.22**
Hypofractionation (≤16) vs. Conventional fractionation (>16)	**−0.177**	**0.0445**	**<.0001**	**1.28**
Boost radiation (Yes vs. No)	0.001	0.045	0.9828	0
Simultaneous vs. Subsequent boost	0.0947	0.0811	0.2438	0.31
Locoregional RT (Yes vs. No)	**0.2125**	**0.0436**	**<.0001**	**1.91**
Duration of radiation course in days (log)	**0.2827**	**0.0902**	**0.0018**	**0.8**
Chemotherapy				
Adjuvant Chemotherapy (Yes vs. No)	**0.1564**	**0.0466**	**0.0008**	**0.91**
Chemo completed prior to vs. Ongoing during baseline ESAS	**−0.1607**	**0.0613**	**0.0090**	**1.15**
No. of days since chemotherapy completion before completing ESAS (log)	**−0.1015**	**0.0354**	**0.0044**	**2.17**
Hormonal therapy (Yes vs. No)	−0.0116	0.053	0.8267	<0.01
Initiation of hormonal therapy: Concurrent vs. After RT	−0.0307	0.0551	0.5774	0.04

*bolded values indicate statistical significance.

Table 3
Multivariable models predicting ESAS fatigue scores.

Multivariable models predicting fatigue	Coefficient	Standard Error	p-value	R^2 (%)
Baseline ESAS fatigue before RT				
Locoregional RT (Yes vs. No)	0.1584	0.0465	**0.0007**	**3.33**
Stage (overall effect)			**0.0014**	
1 vs. 0	0.0609	0.0713	0.3932	
2 vs. 0	0.1916	0.0738	**0.0096**	
3 vs. 0	0.3035	0.0969	**0.0018**	
4d vs. 0	−0.1809	0.2459	0.4621	
1 vs. 2			**0.0089**	
1 vs. 3			**0.0026**	
1 vs. 4d			0.3141	
2 vs. 3			0.159	
2 vs. 4d			0.1196	
3 vs. 4d			0.0589	
Change in ESAS fatigue (after RT - before RT)				
Adjuvant chemotherapy (Yes vs. No)	−0.4561	0.1783	**0.0107**	**2.18**
Locoregional RT (Yes vs. No)	−0.4509	0.1679	**0.0073**	

*bolded values indicate statistical significance.

High baseline fatigue scores in patients with higher disease stage may be due to the added morbidity from advanced disease, including more aggressive treatments and greater psychological stressors from a worse prognosis [10]. Depression, pain and sleep disturbances have significant associations with fatigue levels in breast cancer patients [13]. This may also explain the results of locoregional RT being associated with higher baseline fatigue scores, as patients who received this treatment tend also to be those with higher risk disease [14]. Despite this, patients with locoregional radiation tended to also have significant reductions in fatigue scores. This suggests that the higher baseline fatigue score in these patients was transient in nature and tended to subside after completion of RT to levels similar to the overall patient population.

Patients who received adjuvant chemotherapy also had significant reductions in their fatigue scores. However, baseline fatigue was significantly higher in those with chemotherapy in the univariate analysis, suggesting that it did not persist after treatment completion. This is further supported by the finding that patients with more time between completion of chemotherapy and the completion of the baseline ESAS had lower fatigue scores. This trend is consistent with several studies that found increasing reports of fatigue from start of chemotherapy which stabilised during treatment and then declined after treatment completion [15,16].

Interestingly, we did not observe increased fatigue in patients who received hypofractionated regimens involving fewer fractionations. Nor did we find associations between greater fatigue and regimens with greater side effects and treatment times, such as boost and chest wall radiation [17]. These results may be explained by the timing of our post-RT ESAS, being taken on average 4.7 months after completion of RT. This may be too late to capture the early fatigue experienced by up to 80% women receiving RT which occurs during, and for a short period after treatment [1].

Our study is limited by the retrospective nature, the heterogeneity of the patients, lack of surgical data, and the lack of medication information. There was a large range of ESAS scores before and after RT, indicating considerable heterogeneity among patients; additionally, timing of ESAS assessments before, during and after RT was variable among patients. These issues could somewhat limit the application of our results. Polypharmacy is often responsible for fatigue in cancer patients, particularly those on opioids for management [18]. However, we conducted a detailed examination on whether the components of RT influence fatigue using a large study population. Future studies may aim to stratify the length of post-RT follow-up assessments into short-term and long-term to differentiate between factors associated with early fatigue and persistent fatigue. Moreover, trends between patients reaching high fatigue scores may be compared with those with low or moderate scores. These studies may enable us to better understand the nature of fatigue presenting in breast cancer patients and allow for more effective prediction and identification of those at a higher risk.

Table 4
Predictors of changes in ESAS fatigue scores.

Univariate Predictive factors for change in fatigue after RT	Coefficient	Standard Error	p-value	R^2 (%)
Age at start of RT (Years)	0.0088	0.006	0.1411	0.18
Stage (overall effect)			0.059	0.96
1 vs. 0	−0.0244	0.2412	0.9194	
2 vs. 0	−0.4647	0.2477	0.0608	
3 vs. 0	**−0.6676**	**0.3195**	**0.0369**	
4d vs. 0	−0.2869	0.8255	0.7283	
1 vs. 2	–	–	**0.0072**	
1 vs. 3	–	–	**0.0134**	
1 vs. 4d	–	–	0.7442	
2 vs. 3	–	–	0.4456	
2 vs. 4d	–	–	0.8255	
3 vs. 4d	–	–	0.647	
Radiation				
RT Site (Breast vs. Chest wall)	**0.4054**	**0.1614**	**0.0122**	**0.52**
Hypofractionation (≤16) vs. conventional fractionation (>16)	**0.452**	**0.1495**	**0.0025**	**0.74**
Boost radiation (Yes vs. No)	0.078	0.1507	0.6049	0.02
Simultaneous vs. Subsequent boost	−0.1839	0.2985	0.5382	0.09
Locoregional RT (Yes vs. No)	**−0.6632**	**0.1462**	**<.0001**	**1.66**
Duration of radiation course in days (log)	**−0.6714**	**0.3024**	**0.0266**	**0.4**
Chemotherapy				
Adjuvant Chemotherapy (Yes vs. No)	**−0.693**	**0.1554**	**<.0001**	**1.6**
Chemo completed prior to vs. Ongoing during baseline ESAS	0.1812	0.2093	0.3870	0.13
No. of days since chemotherapy completion before completing ESAS (log)	**0.3563**	**0.1122**	**0.0016**	**2.66**
Hormonal therapy (Yes vs. No)	0.0263	0.1767	0.8818	<0.01
Initiation of hormonal therapy: Concurrent vs. After RT	−0.2017	0.1774	0.256	0.15

*bolded values indicate statistical significance.

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Conflicts of interest

None to declare.

Ethics approval

This study was approved by the institutional Research Ethics Board prior to study initiation (REB # 151–2017).

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Appendix A. Fatigue comparison between bilateral synchronous and unilateral breast cancer patients

	Bilateral synchronous breast cancer (N = 33)	Unilateral breast cancer (N = 1190)	p-value
ESAS Fatigue score at baseline			0.7848
Median (Inter-quartiles)	2 (0, 4)	2 (0, 4)	
Min, Max	0, 8	0, 10	
ESAS Fatigue score after RT			0.7915
Median (Inter-quartiles)	2 (0, 5)	2 (1, 5)	
Min, Max	0, 9	0, 10	
Fatigue increase from baseline			0.5923
No (%)	57.58	61.93	
Yes (%)	42.42	38.07	

Appendix B. Predictors of ESAS fatigue scores after radiation therapy

Predictive factors	Coefficient	Standard Error	p-value	R^2 (%)
Age at start of RT (Years)	−0.0002	0.0018	0.9221	<0.01
Stage (overall effect)			0.1152	0.61
1 vs. 0	0.05	0.0724	0.49	
2 vs. 0	0.1073	0.0743	0.1489	
3 vs. 0	0.1925	0.0959	0.0448	
4d vs. 0	−0.2608	0.2477	0.2926	
1 vs. 2	–	–	0.243	
1 vs. 3	–	–	0.0677	
1 vs. 4d	–	–	0.1981	
2 vs. 3	–	–	0.2857	
2 vs. 4d	–	–	0.1284	
3 vs. 4d	–	–	0.0693	
Radiation				
RT Site (Breast vs. Chest wall)	−0.0602	0.0484	0.2137	0.13
Hypofractionation (≤16) vs. Conventional fractionation (>16)	−0.0232	0.0449	0.606	0.02
Boost radiation (Yes vs. No)	−0.0105	0.0452	0.8158	<0.01
Simultaneous vs. Subsequent boost	0.0293	0.0848	0.73	0.03
Locoregional RT (Yes vs. No)	0.0063	0.0442	0.887	<0.01
Duration of radiation course in days (log)	0.04	0.0908	0.6593	0.02
Chemotherapy				
Adjuvant Chemotherapy (Yes vs. No)	−0.0337	0.0469	0.4724	0.04
Chemo completed prior to vs. Ongoing during baseline ESAS	−0.0966	0.0624	0.1221	0.40
No. of days since chemotherapy completion before completing ESAS (log)	0.0211	0.0356	0.5533	0.10
Hormonal therapy (Yes vs. No)	−0.0256	0.0531	0.6295	0.02
Initiation of hormonal therapy: Concurrent vs. After RT	−0.0725	0.0558	0.1943	0.20

Appendix C. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2019.06.004.

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