Symptoms Predictive of Overall Quality of Life Using the Edmonton Symptom Assessment Scale in Breast Cancer Patients Receiving Radiotherapy

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Abstract

Different symptoms have varying impact on quality of life (QOL). We determined that the extent of 9 symptoms using the Edmonton Symptom Assessment Scale from 1224 breast cancer patients were significantly associated with overall QOL before, at the end of, and after adjuvant radiotherapy. Pain, tiredness, and anxiety correlated with overall QOL at all time points; these symptoms should be screened and managed early to improve overall well-being.

Background: Breast cancer patients often experience multiple symptoms that negatively affect quality of life (QOL). Patient-reported scores on symptom screening tools are used by health care professionals to manage QOL. We aimed to examine which symptoms from the Edmonton Symptom Assessment Scale (ESAS) were most predictive of overall well-being (QOL) in breast cancer patients over the course of radiotherapy (RT). **Patients and Methods:** ESAS results completed before, at the end of, and after RT were obtained from all nonmetastatic breast cancer patients. Univariate and multivariable (backward stepwise selection) linear regression analyses were applied to select the most significant ESAS symptoms or treatment variables related to overall QOL at all 3 time points. **Results:** A total of 1224 patients were included in the study. Before RT, multivariable analysis identified 5 symptoms that were significantly associated with overall QOL: pain, tiredness, anxiety, depression, and loss of appetite. At the end of RT, pain, tiredness, and anxiety were the most significant predictors of QOL. After RT, 6 symptoms were found to have the strongest correlation with QOL: pain, tiredness, anxiety, depression, loss of appetite, and drowsiness. At each time point, patients with higher scores for the identified significant symptoms were likely to have a worse overall QOL. **Conclusion:** Of the ESAS symptoms identified as significant predictors of QOL, pain, tiredness, and anxiety correlated with overall well-being at all time points. Special attention should be paid to manage symptoms that are most predictive of overall QOL in order to ensure optimal symptom management in breast cancer patients receiving RT.

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Introduction

As a result of advances in treatment methods, survival rates for breast cancer patients are increasing, and thus a greater emphasis in clinical practice is placed on managing symptoms of survivors and improving the quality of life (QOL).[1] Breast cancer patients often experience multiple symptoms, which may vary in severity and can negatively affect their QOL.[1] Fatigue, depression, and menopausal symptoms are the most common among individuals with breast cancer.[1,2] QOL is a multidimensional construct that comprises both

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physical and psychosocial aspects.[3,4] Standardized measurements of QOL are collected from the patient through self-reported questionnaires and symptom screening tools.[3] One such tool commonly used with cancer patients is the Edmonton Symptom Assessment Scale (ESAS).[5] Patient-reported scores on these questionnaires give health care professionals a better understanding of the impact of cancer and anticancer treatments on the patient's QOL, and may assist clinicians in prioritizing the focus of symptom management and care provided.[3,6]

The purpose of this study was to examine which symptoms from the ESAS are most predictive of overall well-being in breast cancer patients over the course of adjuvant radiotherapy (RT).

Patients and Methods

The study population comprised all nonmetastatic breast cancer patients receiving RT at the Odette Cancer Centre between 2011 and June 2017. Data were collected from patients who completed at least one ESAS before and after RT, with some patients also completing an ESAS within 1 week after RT completion. Pre- and post-RT ESAS were completed on average 28 and 142 days before and after RT, respectively. The ESAS is a validated self-administered questionnaire used to rate 9 symptoms—pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, shortness of breath, and overall sense of well-being—from 0 (no symptom) to 10 (most severe symptom).[5] For overall sense of well-being, a score of 0 represents best well-being and a score of 10 indicates worst well-being.[7] The ESAS has high internal consistency, test−retest reliability, and convergent and divergent validity for physical symptoms.[8]

Demographic information, treatment, and disease characteristics were collected from existing databases and chart review, including age, cancer stage, radiation site and dose, and chemotherapy and/or hormone therapy regimens, if applicable. This study was approved by the hospital research ethics board.

Patient demographic and clinical characteristics were summarized using median and interquartile ranges for age, and proportions for categorical variables. Mean, standard deviation, and proportions for ESAS score < 3 were calculated for each of the ESAS items. To compare ESAS scores (natural logarithm) or proportion of ESAS score < 3 between end of RT and before RT, or between after RT and before RT, the paired t test or the Fisher exact test were performed. $P < .05$ was considered statistically significant.

The univariate linear regression model was applied for detecting significant relationships between overall well-being and the other 8 ESAS symptoms or treatment variables at each time point. The outcome was the natural logarithm scale for overall well-being, and the independent variable was each of the remaining 8 ESAS natural logarithm scales and binary treatment variables such as chemotherapy, hormone treatment, radiation site of breast or chest wall, radiation boost, hypofractionation, regional RT, or disease stage of ductal carcinoma-in-situ only or non−ductal carcinoma-in-situ breast cancer. Analysis was conducted using PROC GLM in Statistical Analysis Software (SAS 9.4 for Windows; SAS Institute, Cary, NC). After conducting univariate linear regression analysis on the independent variables (8 ESAS items and 7 treatment/disease variables), a backward stepwise selection procedure was used to select the most significant ESAS symptoms or treatment/disease variables related to overall well-being at all 3 time points in a multivariable model. Variables that were significant from the univariate analysis ($P < .10$) were added in the backward selection procedure to allow potential significant variables to be considered. As a result of multiple comparisons, Bonferroni-adjusted $P < .003$ (0.05/15 variables) was used as the threshold for statistical significance. The coefficient, standard error of the coefficient, P value, and mean square error of the model were calculated. A positive coefficient denotes a positive relationship with the outcome, where the score for overall well-being increases (worse QOL) when a particular symptom increases in value (severity) or with certain treatments. Mean square error is used to refer to the estimate of error variance, where an mean square error close to zero indicates a smaller estimated error variance.

Results

There were 1224 patients in the study. At the start of RT, the median age was 58 years. Most patients had stage 1 (44%) and 2 (35%) breast cancer. Most patients (63%) received the conventional radiation dose of fractions (25 fractions), and 64% of patients did not receive boost radiation. Among the study population, 78% of patients whose hormonal therapy status was known received hormone therapy, and 49% of patients received chemotherapy. Of the patients who received chemotherapy, 62% finished treatment within 6 months before the first ESAS and 36% completed the first ESAS during chemotherapy (Table 1).

ESAS data were collected from patients before, at the end of, and within 1 week of the end of RT. Table 2 shows the mean scores for each ESAS item. The ESAS scores for all 9 items remained relatively constant between the 3 time points. Spearman correlations for all ESAS items were highly significant ($P < .0001$). In general, the low scores (< 3) reflected that patients reported low to moderate symptoms. Overall, 7 of 9 symptoms were lower at the end of RT compared to before RT (only drowsiness and nausea were higher). In comparing post-RT scores with pre-RT scores, 6 of 9 symptoms were lower after RT (only pain, tiredness, and drowsiness were higher).

Before RT

At baseline, all ESAS symptoms were highly positively associated with overall well-being ($P < .0001$) in the univariate analysis. Patients who received chemotherapy were more likely to have higher overall well-being scores ($P < .0001$). In multivariable analysis, 5 symptoms were significantly associated with overall well-being: pain, tiredness, depression, anxiety, and loss of appetite ($P < .0001$), with higher scores associated with worse overall well-being. Tiredness had the largest coefficient of 0.315, followed by anxiety (0.191) and depression (0.159) (Table 3).

End of RT

Within 1 week after the end of RT, all ESAS symptoms were positively associated with overall well-being ($P < .0001$) in the univariate analysis. Patients who received hypofractionation were more likely to have lower scores of overall well-being (negative coefficient, $P = .0006$). The multivariable analysis identified 3 symptoms—pain, tiredness, and anxiety—that were significantly associated with overall well-being ($P < .0001$). Individuals experiencing greater severity of these 3 symptoms were more likely to have

Table 1 Demographics of 1224 Subjects

Characteristic	Value
Age at start of treatment (y), median (interquartile range)	58 (50–68)
Age Group at Start of Treatment	
<30 y	5 (0.41)
30 to < 50 y	317 (25.90)
50 to < 70 y	666 (54.41)
≥70 y	235 (19.20)
Unknown	1 (0.08)
Stage	
0	137 (11.19)
1	538 (43.95)
2	425 (34.72)
3	114 (9.31)
4	10 (0.82)
Treatment Site	
Chest	341 (27.97)
Breast	878 (72.03)
Fractionation and Dose	
Hypofractionation (42.6 Gy in 16 fractions)	449 (36.68)
Conventional fractionation (50 Gy in 25 fractions)	775 (63.32)
Boost radiation	439 (35.87)
Subsequent boost	328 (74.72)
Concurrent (simultaneous) boost	111 (25.28)
Regional RT	494 (40.36)
Adjuvant chemotherapy	594 (48.53)
Finished > 6 months before first ESAS	13 (2.19)
Finished within 6 months before first ESAS	365 (61.55)
First ESAS during chemotherapy	215 (36.26)
Hormone therapy status (n = 1189)	930 (78.22)
Initiated after RT completion	273 (29.35)
Initiated concurrently with RT	571 (61.40)
Unknown	86 (9.25)
ESAS Collected Before RT (N = 1224)	
No. of days, mean (SD), range	28.3 (22.9), 0–420
≤7 days at end of RT	147 (12.01)
8–28 days at end of RT	698 (57.03)
>28 days at end of RT	379 (30.96)
ESAS Collected at End of RT (N = 310)	
No. of days, mean (SD), range	4.4 (2.5), 0–7
≤7 days at end of RT	310 (100)
ESAS Collected After RT (N = 1224)	
No. of days, mean (SD), range	142.3 (191.3), 0–1596
≤7 days at end of RT	60 (4.90)
8–28 days at end of RT	154 (12.58)
>28 days at end of RT	1010 (82.52)

Data are presented as n (%) unless otherwise indicated.
Abbreviations: ESAS = Edmonton Symptom Assessment Scale; RT = radiotherapy; SD = standard deviation.

poorer overall well-being. Among these 3 significant symptoms, tiredness had the highest coefficient (0.454), followed by anxiety (0.266) and pain (0.199) (Table 3).

After RT

From the data collected after RT, all ESAS symptoms had significant positive associations with overall well-being ($P < .0001$) in the univariate analysis. All treatment variables were not significantly related to overall well-being. After multivariable analysis, 6 symptoms remained significantly correlated to overall well-being: pain, tiredness, depression, anxiety, drowsiness, and loss of appetite ($P < .0001$). Patients experiencing greater symptom burden of these 6 items were more likely to have worse overall well-being. Tiredness had the highest coefficient (0.314), followed by anxiety (0.172) and pain (0.171).

Discussion

The findings of the current study suggest that overall well-being is influenced by several other symptoms on the ESAS. Most notably, pain, tiredness, and anxiety correlated with overall well-being at all time points (Table 4), of which tiredness, followed by anxiety, consistently had the highest coefficients, indicating that these 2 symptoms had the largest influence on overall well-being.

These results are consistent with the literature, where similar studies have reported that fatigue or anxiety are most predictive of QOL in breast cancer patients.[9-14] Abu-Saad Huijer and Abboud[9] assessed health-related QOL among breast cancer patients using the European Organization for Research and Treatment of Cancer—Quality of Life Questionnaire (EORTC QLQ C-30), Memorial Symptom Assessment Scale (MSAS), Barthel index, and the Needs at End of Life Screening Tool. Among all the items on the MSAS, emotional functioning and psychologic symptoms—including feeling nervous, sad, and worrying—had the highest correlation to QOL.[9] Higher symptom scores for emotional functioning and psychologic symptoms on the MSAS were most significantly associated with lower global health and functional scores on the EORTC QLQ C-30 subscales.[9]

In the present study, tiredness was identified as the most predictive symptom of QOL before, at the end of, and after RT. A number of other studies have also reported fatigue as the most prominent symptom contributing to QOL in breast cancer patients.[10,11] In a study conducted in Kuwait by Alawadi and Ohaeri,[10] fatigue had the highest correlation to global QOL in the EORTC QLQ C-30. A similar study conducted in Lithuania by Ivanauskienė et al[11] found that fatigue and pain had the greatest influence on QOL in patients with breast cancer.

The significant influence of fatigue on QOL has also been reported in breast cancer patients after surgery but before adjuvant systemic therapy, 1 year after diagnosis, and in disease-free survivors at more than 1 year after diagnosis.[12-14] Kawaguchi et al[12] analyzed factors from the EORTC QLQ-C30 and BR23 affecting QOL in postoperative patients before receiving adjuvant systemic therapy. Statistical analysis identified 5 symptoms affecting QOL: fatigue, emotional functioning, systemic therapy side effects, future

Table 2 Scores and Low to Moderate Symptoms (Score < 3) for ESAS Items

ESAS Item	Before RT (N = 1224)	End of RT (N = 310)	After RT (N = 1224)	*P* Comparing End of RT to Before RT	*P* Comparing After RT to Before RT
Pain					
Mean ± SD	1.52 ± 2.09	1.37 ± 1.88	1.62 ± 2.21	.4293	.4115
Low to moderate symptom	922 (75.33%)	245 (79.03%)	927 (75.74%)	.1804	.8508
Tiredness					
Mean ± SD	2.71 ± 2.53	2.64 ± 2.18	2.86 ± 2.57	.2719	.1520
Low to moderate symptom	659 (53.84%)	174 (56.13%)	619 (50.57%)	.4832	.1145
Nausea					
Mean ± SD	0.41 ± 1.21	0.45 ± 1.34	0.42 ± 1.34	.9869	.5297
Low to moderate symptom	1156 (94.44%)	290 (93.55%)	1149 (93.87%)	.5841	.6052
Depression					
Mean ± SD	1.62 ± 2.29	1.42 ± 1.98	1.62 ± 2.34	.4525	.8027
Low to moderate symptom	904 (73.86%)	233 (75.16%)	900 (73.53%)	.6637	.8905
Anxiety					
Mean ± SD	2.36 ± 2.58	1.71 ± 2.09	2.05 ± 2.45	.0002[a]	.0006[a]
Low to moderate symptom	768 (62.75%)	225 (72.58%)	820 (66.99%)	.0011[a]	.0308[a]
Drowsiness					
Mean ± SD	1.41 ± 2.17	1.43 ± 2.03	1.46 ± 2.20	.3562	.5282
Low to moderate symptom	931 (76.06%)	237 (76.45%)	927 (75.74%)	.9406	.8873
Appetite					
Mean ± SD	1.31 ± 2.13	0.97 ± 1.93	1.08 ± 2.07	.0033[a]	.0006[a]
Low to moderate symptom	957 (78.19%)	261 (84.19%)	1013 (82.76%)	.0185[a]	.0050[a]
Well-being					
Mean ± SD	2.66 ± 2.45	2.51 ± 2.22	2.66 ± 2.52	.8239	.8624
Low to moderate symptom	676 (55.23%)	176 (56.77%)	707 (57.76%)	.6544	.2213
Dyspnea					
Mean ± SD	1.05 ± 1.95	0.76 ± 1.45	1.04 ± 1.91	.0016[a]	.9350
Low to moderate symptom	1019 (83.25%)	271 (87.42%)	1024 (83.66%)	.0819	.8278

P value was obtained by either paired *t* test or Fisher exact test to compare ESAS scores or proportions of low to moderate symptoms between end of RT and before RT, or between after RT and before RT, respectively.
Abbreviations: ESAS = Edmonton Symptom Assessment Scale; RT = radiotherapy; SD = standard deviation.
[a]Statistically significant ($P < .05$).

perspectives, and loss of appetite. Of these, fatigue had the strongest effect on QOL. Indeed, Kawaguchi et al found that the influence of fatigue on QOL was 2 times greater than that of the other factors.

Arndt et al[13] also used the EORTC QLQ-C30 and BR23 and examined the impact of specific symptoms on QOL in women with breast cancer 1 year after diagnosis. Fatigue emerged as the strongest predictor by far of QOL, accounting for 30% to 50% of variability within function scores and overall QOL. For breast cancer survivors, Ahn et al[14] found that depression and fatigue were the strongest predictors of reduced health-related QOL.

Fatigue is one of the most prevalent symptoms in cancer patients and can negatively affect overall QOL.[13,15] Moreover, fatigue is also associated with psychosocial, physical, and medical conditions, including depression, anxiety, pain, weakness, nausea, and loss of appetite.[13,16-20] In the current study, fatigue was consistently the most significant predictor of QOL throughout the course of RT.

Our study has several limitations. This retrospective study uses data collected from the ESAS; however, the ESAS is limited in its assessment of symptomology. Of the 1224 patients who completed the ESAS before and after RT, only 310 patients completed the ESAS within 1 week of the end of RT. With this smaller sample size, the data collected from patients at the end of RT are limited. In addition, of the 1224 patients receiving RT, 594 patients had either received or were receiving chemotherapy, and 930 patients previously had received or were receiving hormone therapy at the time of the ESAS. Moreover, we interpreted radiation to the breast versus chest wall as a surrogate for surgical information on whether patients received lumpectomy or mastectomy. Thus, it is possible that some patient-reported scores for the ESAS may not be due to RT alone.

Our large sample size enabled the detection of small differences in ESAS scores to be statistically significant. However, most of the ESAS score changes are less than 1, which is lower than the minimal clinically important difference as determined by Hui et al.[21] This suggests that our results are detecting subclinical changes in symptoms that influence overall QOL.

Future research in this area should examine which symptoms are most predictive of QOL between patients on the basis of treatment types and demographic factors. Previous studies have showed that patients with breast cancer may experience different symptom profiles on the basis of age, breast cancer stage, or treatment regimen

Table 3 Univariate and Multivariable Linear Regression Analysis With Predictive Factors of Overall Well-being

Analysis	Before RT				End of RT				After RT			
	Coefficient	SE	*P*	MSE	Coefficient	SE	*P*	MSE	Coefficient	SE	*P*	MSE
Univariate Analysis												
Pain	0.480	0.026	<.0001[a]	0.42	0.507	0.050	<.0001[a]	0.36	0.540	0.024	<.0001[a]	0.39
Tiredness	0.591	0.022	<.0001[a]	0.34	0.681	0.046	<.0001[a]	0.28	0.648	0.021	<.0001[a]	0.31
Nausea	0.454	0.044	<.0001[a]	0.50	0.336	0.079	<.0001[a]	0.46	0.519	0.042	<.0001[a]	0.49
Depression	0.543	0.023	<.0001[a]	0.37	0.520	0.047	<.0001[a]	0.35	0.558	0.023	<.0001[a]	0.37
Anxiety	0.514	0.023	<.0001[a]	0.38	0.536	0.046	<.0001[a]	0.33	0.564	0.022	<.0001[a]	0.36
Drowsiness	0.477	0.025	<.0001[a]	0.42	0.443	0.050	<.0001[a]	0.38	0.530	0.024	<.0001[a]	0.40
Loss of appetite	0.473	0.025	<.0001[a]	0.42	0.427	0.055	<.0001[a]	0.40	0.503	0.027	<.0001[a]	0.43
Dyspnea	0.401	0.029	<.0001[a]	0.47	0.367	0.064	<.0001[a]	0.44	0.441	0.029	<.0001[a]	0.46
Chemotherapy (yes vs. no)	0.188	0.042	<.0001[a]	0.53	0.114	0.079	.1494	0.48	0.040	0.042	.3426	0.55
Hormone treatment (yes vs. no)	0.025	0.052	.6246	0.54	0.129	0.101	.2001	0.47	−0.022	0.052	.6704	0.54
Radiation site (breast vs. chest wall)	−0.120	0.047	.0105	0.54	−0.139	0.094	.1416	0.48	−0.069	0.047	.1429	0.55
Radiation boost (yes vs. no)	−0.031	0.044	.4762	0.54	0.013	0.079	.8648	0.48	−0.006	0.044	.8914	0.55
Hypofractionation (yes vs. no)	−0.100	0.044	.0218	0.54	−0.271	0.078	.0006[a]	0.46	−0.039	0.044	.3807	0.55
Locoregional RT (yes vs. no)	0.085	0.043	.0490	0.54	0.205	0.080	.0114	0.47	0.049	0.043	.2550	0.55
Disease stage (DCIS vs. non-DCIS)	−0.120	0.067	.0743	0.54	−0.124	0.139	.3748	0.49	−0.108	0.068	.1126	0.56
Multivariate Analysis												
Intercept	0.290	0.027	<.0001[a]	0.27	0.222	0.054	<.0001[a]	0.23	0.288	0.026	<.0001[a]	0.25
Pain	0.138	0.024	<.0001[a]		0.199	0.046	<.0001[a]		0.171	0.024	<.0001[a]	
Tiredness	0.315	0.025	<.0001[a]		0.454	0.049	<.0001[a]		0.314	0.028	<.0001[a]	
Anxiety	0.191	0.027	<.0001[a]		0.266	0.044	<.0001[a]		0.172	0.028	<.0001[a]	
Depression	0.159	0.029	<.0001[a]		NS				0.106	0.028	<.0001[a]	
Loss of appetite	0.113	0.024	<.0001[a]		NS				0.110	0.024	<.0001[a]	
Drowsiness	NS				NS				0.073	0.026	<.0001[a]	

Bonferroni adjusted $P < .003$ was considered statistically significant. Final multivariable model only included variables with significant *P* after conducting backward selection procedure.
Abbreviations: DCIS = ductal carcinoma-in-situ; MSE = mean square error; NS = nonsignificant in multivariable analysis; RT = radiotherapy; SE = standard error.
[a]Statistically significant.

Table 4 Predictors of Overall Well-Being Over RT Course

ESAS Symptom at:		
Before RT	**End of RT**	**After RT**
• Pain • Tiredness • Anxiety • Depression • Loss of appetite	• Pain • Tiredness • Anxiety	• Pain • Tiredness • Anxiety • Depression • Loss of appetite • Drowsiness

Abbreviations: ESAS = Edmonton Symptom Assessment Scale; RT = radiotherapy.

if receiving a combination of chemotherapy, surgery, and radiation compared to chemotherapy alone or a combination of chemotherapy and surgery.[9-11,13,22,23] Symptom management should be approached in a multidisciplinary setting and continuously assessed at each visit. Symptoms with available pharmacologic therapies such as pain or nausea should be targeted early, and for symptoms such as fatigue, in which pharmacologic solutions are unavailable, self-management may be recommended, including moderate exercise or psychologic interventions.[24]

Conclusion

Among the ESAS symptoms identified as significant predictors of QOL, tiredness had the largest influence, followed by anxiety, at all 3 time points before, at the end of, and after RT. These findings are consistent with similar studies in the literature examining symptoms predictive of QOL in patients with breast cancer. Special attention should be paid to manage symptoms that are most predictive of overall QOL in order to ensure optimal symptom management in breast cancer patients receiving RT.

Clinical Practice Points

- Previous studies have showed that patients with breast cancer may experience different symptom profiles based on age, breast cancer stage, or treatment regimen if receiving a combination of chemotherapy, surgery, and radiation compared to chemotherapy alone or a combination of chemotherapy and surgery.
- Overall, fatigue and anxiety have been identified as predictive of overall QOL. However, few studies have investigated the time course of the impact of cancer-associated symptoms in patients receiving RT.
- Using the ESAS, our study identified tiredness as having the largest influence on QOL, followed by anxiety. This was found across all 3 time points: before the start of RT, at the end of RT, and after RT completion.
- Special attention should be paid to manage symptoms that are most predictive of overall QOL in order to ensure optimal symptom management in breast cancer patients receiving RT.
- In the case of breast cancer, tiredness and anxiety should be targeted early and should be considered even before initiation of RT in order to maximize patients' overall well-being throughout the trajectory of their cancer journey.

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Disclosure

The authors have stated that they have no conflict of interest.

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