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Symptom clusters in patients with breast cancer receiving radiation therapy

Selina Chow[a], Bo Angela Wan[a], William Pidduck[a], Liying Zhang[a], Carlo DeAngelis[a], Stephanie Chan[a], Caitlin Yee[a], Leah Drost[a], Eric Leung[a], Philomena Sousa[a], Donna Lewis[a], Henry Lam[a], Ronald Chow[b], Michael Lock[b], Edward Chow[a,*]

[a] Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada
[b] London Regional Cancer Program, London Health Sciences Centre, University of Western Ontario, London, Ontario, Canada

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ABSTRACT

Purpose: Symptoms experienced by breast cancer patients often cluster together in groups known as "symptom clusters". The aim was to determine the symptom clusters in women with non-metastatic breast cancer treated by radiation therapy (RT).

Methods: Edmonton Symptom Assessment Scale (ESAS) scores were taken from breast cancer patients receiving RT before, at completion of RT, and after RT. Exploratory factor analysis (EFA), principal component analysis (PCA), and hierarchical cluster analysis (HCA) were used to identify symptom clusters among the nine ESAS items at all three time points.

Results: This study included 1224 patients. The PCA and EFA identified the same two symptom clusters before the start of RT: 1) pain, tiredness, nausea, drowsiness, appetite, and dyspnea; 2) depression, anxiety, and wellbeing. The HCA further split the symptoms into three clusters. Wellbeing, depression, and anxiety consistently clustered together. Among the ESAS scores collected at the end of and after RT, each statistical method identified different symptom clusters. For the symptom clusters experienced at the end of RT, the following symptoms were always in the same cluster: wellbeing, depression, and anxiety; nausea and appetite; drowsiness and dyspnea. Following RT, depression and anxiety consistently clustered together, with nausea and appetite in a second cluster.

Conclusion: Among the symptom clusters derived before, at the end of RT, and after RT, the following symptoms consistently presented together: depression and anxiety, nausea and appetite, pain and tiredness, and drowsiness, dyspnea, and tiredness. Understanding symptom clusters in this population can improve management of symptoms.

1. Introduction

Breast cancer patients typically receive systemic treatments, radiation therapy (RT), and/or surgery (Nguyen et al., 2011). While the disease in itself does not typically lead to specific symptoms in the absence of metastases, symptoms may be a result treatment-related or psychosocial aspects of the illness (Kim et al., 2008; Matthews et al., 2012). With increased survival rates for individuals with breast cancer, improving the quality of life and symptom management of survivors have become increasingly important priorities in clinical care (Nguyen et al., 2011).

Breast cancer patients usually experience fatigue, depression, menopausal symptoms and others (Dodd et al., 2010; Nguyen et al., 2011). Most of the time, symptoms do not occur in isolation, but rather, several symptoms occur simultaneously. Due to this concurrence of symptoms, earlier studies aimed at treating individual symptoms did not always improve quality of life (Miaskowski, 2006). Systematic attention to the presence of symptoms in cancer patients led to the concept of symptom clusters (Chow et al., n.d.). In 2001, Dodd et al. were one of the first to define a "symptom cluster" consisting of three or more concurrent and related symptoms, which do not necessarily share the same etiology (Dodd et al., 2001). According to Kim et al., a symptom cluster is a stable group of two or more related symptoms that occur together, which is relatively independent of other clusters (Kim et al., 2005; Kirkova and Walsh, 2007).

There are relatively few breast symptom cluster studies conducted to date; some existing studies have evaluated how the symptom clusters experienced by patients with breast cancer change across different time

* Corresponding author. Department of Radiation Oncology Odette Cancer Centre, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue Toronto, Ontario, M4N 3M5, Canada.
E-mail address: edward.chow@sunnybrook.ca (E. Chow).

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points in their disease course with some conflicting results (Bender et al., 2005; Kim et al., 2009, 2008; Matthews et al., 2012). Some of these studies identified symptom clusters that remained consistent throughout the duration of treatment, while others found that particular symptom clusters were dynamic.

Through studying symptom clusters, there will likely be an increased understanding about the relationship between a particular set of symptoms of cancer and its treatment, as well as how they influence one another and outcomes of interest (Barsevick et al., 2006). Given that symptom clusters may have an unfavourable effect on patient outcomes including quality of life, research in this field has the potential to aid in symptom screening, identification, and management and clinical practice (Walsh and Rybicki, 2006).

The purpose of this study was to determine the clustering of symptoms before RT, at the end of RT, and after RT in women with non-metastatic breast cancer using three common analytical methods for symptom cluster identification. The secondary objective was to compare the results of the three analytical symptom cluster methods and place them in context of existing literature, as there is currently no consensus on the optimal method.

2. Methods

Non-metastatic breast cancer and pre-cancer (ductal carcinoma in-situ) patients treated at a cancer centre between January 2011 and June 2017 were eligible for study enrollment. English-speaking patients completed the Edmonton Symptom Assessment Scale (ESAS) before and after RT (n = 1224), and a subset of patients (n = 310) also completed it within one week following the end of RT. The ESAS is used to quantify symptom burden with respect to the domains of pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, shortness of breath, and overall sense of well-being; higher scores on the 11-point Likert scale denoted greater symptom severity (Bruera et al., 1991; Ecclestone et al., 2016). This tool has been validated in the cancer population (Richardson and Jones, 2009).

Patient demographics, treatment and disease characteristics were obtained from existing databases and chart review, and included information such as: age, cancer stage, radiation dose, radiation site, as well as chemotherapy and/or hormone therapy regimes if applicable. This study was approved by the institutional research ethics board.

2.1. Statistical analyses

Patient demographic, clinical characteristics and ESAS scores were summarized in total patients using mean, standard deviation (SD), median, interquartile, and ranges for age and 9 ESAS items, and proportions for categorical variables. Three statistical procedures were used: the principal component analysis (PCA), exploratory factor analysis (EFA), and hierarchical cluster analysis (HCA).

PCA with Varimax rotation was also used on the ESAS items, in order to analyze the interrelationships between symptoms before, at the end of (within 1 week following RT completion), and after RT. PCA groups a number of observed variables (symptoms) into a smaller number of variables, called principal components (clusters), by determining which variables correlate together in a distinct pattern (Chen et al., 2012; Skerman et al., 2009). The first principal component accounts for as much of the variability in the data as possible. The highest loading factor score determines which symptoms are assigned to certain clusters (Chen et al., 2012). To identify significant clusters, a pre-determined Eigenvalue greater than 0.8 and a component accounting for more than 10% of the total variance was required. Cronbach's alpha was also used to assess the consistency and reliability of the clusters (Chen et al., 2012). Among the components produced by the PCA method, a Varimax rotation was performed to make the solution easier to interpret. A Varimax rotation is an orthogonal rotation that results in uncorrelated components and maximizes the variance of a column of the factor pattern matrix. FACTOR procedure was also used for PCA method, and biplots were generated for the first two principal components before RT, end of RT, and after RT, respectively.

EFA is the most commonly used method of symptom cluster identification in cancer research (Barsevick et al., 2006; Kim et al., 2005). It assumes that symptoms in a cluster share a common or latent factor that binds two or more symptoms together (Kim and Abraham, 2008; Kim and Muller, 1978). For symptoms to be grouped together and associated with a specific latent factor, they must have a stronger covariance with that latent factor compared with symptoms due to other latent factors (Barsevick et al., 2006). In our study, EFA was used and the maximum likelihood method was applied for approximately multivariate normal data. The number of factors was also selected based on predetermined Eigenvalues greater than 0.8, which means that nearly 10% of variance in the symptom is shared with the latent factor after accounting for the correlation between factors. FACTOR procedure in Statistical Analysis Software (SAS version 9.4, Cary, NC) was conducted for this analysis. For each cluster, Cronbach's alpha was calculated to determine internal consistency (Chen et al., 2012).

The third method, HCA, is a statistical method that uses cluster analysis, where individuals with a similar symptom experience or profile are grouped together (Walsh and Rybicki, 2006). The objective of HCA is to classify and group similar entities into a cluster, while separating this cluster from other clusters. The VARCLUS procedure runs clusters on the basis of centroid components, and Tree plots were generated before RT, end of RT, and after RT, respectively.

Identified clusters are independent of each other.

3. Results

The median age of the 1224 accrued patients was 58 years (interquartile range: 50–68). The largest proportion of patients had stage 1 cancer (44%); only 37% of patients received hypofractionated radiation of 42.6 Gy in 16 fractions; 49% were administered adjuvant chemotherapy, of which 62% completed treatment within 6 months of first ESAS scoring. Other demographics are reported in Table 1.

All patients completed the ESAS before and after RT (average: 142 days post-treatment), with a subset of 310 patients who also completed an ESAS within one week after the end of RT. The mean scores for all nine ESAS items are shown in Table 2. The most prevalent symptom is tiredness at the end of RT, and overall wellbeing at the beginning of RT and following RT. The scores for ESAS items range from 0 to 10. Spearman correlations for all ESAS items are statistically significant ($p < 0.0001$) and the ESAS scores remained relatively constant among the three data collection periods.

3.1. Symptom clusters among ESAS items before RT

The PCA method identified two symptom clusters. Cluster 1 includes pain, tiredness, nausea, drowsiness, appetite, and dyspnea. Cluster 2 consists of depression, anxiety, and well-being. Final community values range from 0.42 for pain to 0.80 for depression and anxiety (Appendix 2). The two symptom clusters derived had high internal consistency and reliability, with Cronbach's alpha values of 0.83 and 0.84. Fig. 1a shows a biplot of the first two components, where a higher correlation between symptoms is represented by arrows that are longer and closer together.

The EFA method identified two symptom clusters, which have a cumulative variance of 89.4% (Appendix 1). The first cluster includes tiredness, drowsiness, pain, nausea, loss of appetite, and dyspnea. The second cluster comprises of well-being, depression, and anxiety. The Cronbach's alpha is 0.82 for the first cluster and 0.84 for the second cluster, demonstrating high internal consistency.

The HCA method identified three final clusters (Appendix 3). Cluster 1 consists of pain, tiredness, drowsiness, and dyspnea. Cluster 2 encompasses depression, anxiety, and wellbeing. Lastly, Cluster 3

Table 1
Patient demographics.

Variable	Total (N = 1224)
Age at RT start (years)	
Mean ± SD	58.6 ± 12.1
Median (Inter-quartiles)	58 (50, 68)
Min, Max	25, 94
Stage	
0	137 (11.19%)
1	538 (43.95%)
2	425 (34.72%)
3	114 (9.31%)
4d	10 (0.82%)
RT Site	
Chest	341 (27.97%)
Breast	878 (72.03%)
Any dose with fractions ≤16 or > 16	
> 16 (conventional fractionation)	775 (63.32%)
≤16 (hypofractionation)	449 (36.68%)
Boost radiation	
No	785 (64.13%)
Yes	439 (35.87%)
Subsequent boost (Sub)	328 (74.72%)
Concurrent (simultaneous) boost (Sim)	111 (25.28%)
Regional RT	
No	730 (59.64%)
Yes	494 (40.36%)
Adjuvant chemotherapy in all patients	
No	630 (51.47%)
Yes	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	
No	259 (21.78%)
Yes	930 (78.22%)
Initiated after RT completion	273 (29.35%)
Initiated concurrently with RT	571 (6.14%)
Unknown	86 (9.25%)

includes nausea and loss of appetite. The three clusters identified by the HCA method are visually displayed in Fig. 2a. All three clusters account for 69% of the total variation among all ESAS items.

From the three statistical analyses (PCA, EFA, and HCA), the same two clusters were identified from PCA and EFA. The HCA method further splits the symptoms into three clusters. The following symptoms are always present in the same cluster: wellbeing, depression, and anxiety.

3.2. Symptom clusters among ESAS items at the end of RT

The PCA method identified two symptom clusters with good internal consistency of 0.85 and 0.75 for the Cronbach's alpha. Cluster 1 contains pain, tiredness, depression, anxiety and wellbeing. Cluster 2 consists of nausea, drowsiness, appetite loss, and dyspnea. All variables are well accounted for by these two components, with final communality values ranging from 0.40 for dyspnea to 0.79 for anxiety (Appendix 2). The first two components are represented on a biplot graph in Fig. 1b.

EFA identified two symptom clusters. The first cluster contains tiredness, drowsiness, nausea, loss of appetite, and dyspnea. The second cluster encompasses pain, wellbeing, depression, and anxiety (Appendix 2). The Cronbach's alpha is 0.82 for the first cluster and 0.80 for the second cluster, indicating good internal consistency.

HCA method identified three clusters, which account for 68% of the variability among the nine symptoms (Appendix 3). Cluster 1 consists of pain, depression, anxiety, and wellbeing. Cluster 2 contains tiredness, drowsiness, and dyspnea, and Cluster 3 includes nausea and appetite. The cluster hierarchy is displayed in Fig. 2b.

From these three analyses, each statistical method identified different symptom clusters. The following items are always in the same cluster: wellbeing, depression, and anxiety in one cluster; nausea and appetite in one cluster; and drowsiness and dyspnea in a second cluster.

3.3. Symptom clusters among ESAS items after RT

The PCA method derived two symptom clusters with high internal reliabilities of 0.88 and 0.63. Cluster 1 contains pain, tiredness, depression, anxiety, wellbeing, drowsiness, and dyspnea. Cluster 2 includes nausea and appetite. The final communality values range from 0.46 for dyspnea to 0.82 for nausea, demonstrating that all the variables are well accounted for by the two components (Appendix 2). The first two components are visually displayed on a biplot graph in Fig. 1c.

From the Eigenvalues and proportions of variance listed in Appendix 1, the EFA method only yielded one symptom cluster including all nine ESAS items (Appendix 2). The Cronbach's alpha is 0.89 for the cluster.

The HCA method identified three final clusters, which collectively account for 70% of the variability in the nine items (Appendix 3). Cluster 1 consists of pain, tiredness, drowsiness, wellbeing, and dyspnea. Cluster 2 includes nausea and appetite, and Cluster 3 consists of depression and anxiety. These three clusters are displayed in Fig. 2c.

From these three analyses, different clusters were identified with each statistical analysis. Among all the symptom clusters identified, the following items are always in the same cluster: depression and anxiety in one cluster, and nausea and appetite in a second cluster.

4. Discussion

Three statistical methods (PCA, EFA, and HCA) were used to derive symptom clusters experienced before, at the end of, and after RT in women with breast cancer. When comparing the clustering of symptoms throughout RT (Table 3), there are several pairs of symptoms that

Table 2
Mean (± SD) scores for ESAS items.

	Before RT (N = 1224)		End of RT (N = 310)		After RT (N = 1224)	
ESAS Item	% Prevalence	Mean ± SD	% Prevalence	Mean ± SD	% Prevalence	Mean ± SD
Pain	51.2%	1.52 ± 2.09	50.3%	1.37 ± 1.88	52.5%	1.62 ± 2.21
Tiredness	73.8%	2.71 ± 2.53	82.6%	2.64 ± 2.18	75.3%	2.86 ± 2.57
Nausea	16.7%	0.41 ± 1.21	15.2%	0.45 ± 1.34	14.3%	0.42 ± 1.34
Depression	47.7%	1.62 ± 2.29	48.1%	1.42 ± 1.98	46.8%	1.62 ± 2.34
Anxiety	66.4%	2.36 ± 2.58	58.7%	1.71 ± 2.09	59.6%	2.05 ± 2.45
Drowsiness	42.0%	1.41 ± 2.17	49.0%	1.43 ± 2.03	43.8%	1.46 ± 2.20
Appetite	38.3%	1.31 ± 2.13	31.0%	0.97 ± 1.93	31.7%	1.08 ± 2.07
Wellbeing	75.5%	2.66 ± 2.45	77.7%	2.51 ± 2.22	75.8%	2.66 ± 2.52
Dyspnea	32.8%	1.05 ± 1.95	29.7%	0.76 ± 1.45	33.5%	1.04 ± 1.91

SD: Standard deviation; Prevalence was calculated by 100 × (number of patients with ESAS symptom score 1 or higher/total number of patients before RT, end of RT, or after RT).

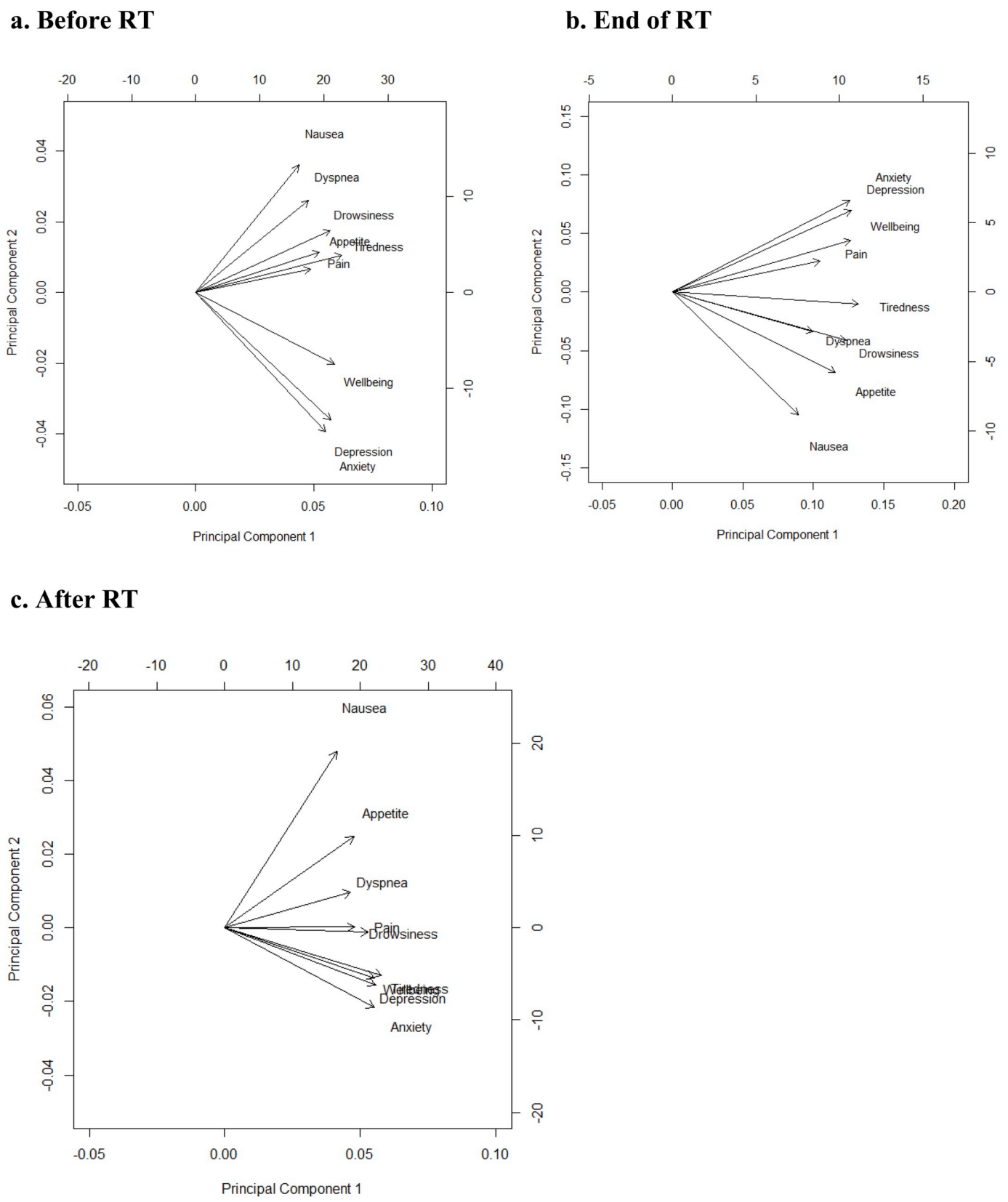

Fig. 1. Biplot for the ESAS symptom clusters from the PCA method.

are always experienced together: depression and anxiety, and nausea and appetite. The symptoms of pain and tiredness also consistently cluster together, with the exception of the symptom clusters derived from EFA and HCA for the ESAS data collected at the end of RT. Likewise, drowsiness, dyspnea, and tiredness always co-occur together, except for the clusters identified by PCA at the end of RT.

The symptoms present within each cluster at the three time points are also shown to change using PCA, EFA, and HCA methods (Table 3).

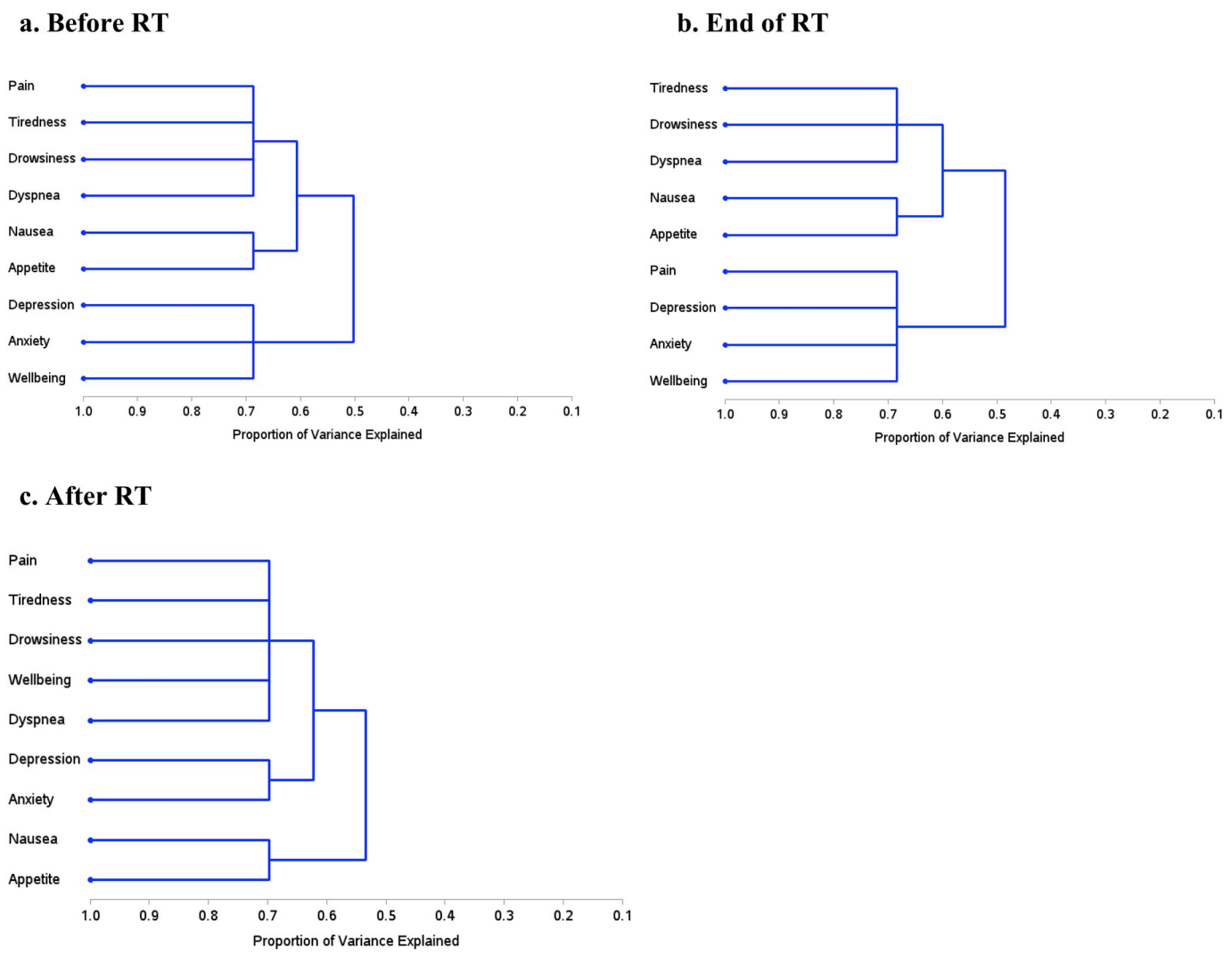

Fig. 2. Tree plots for the ESAS Symptom Clusters from the HCA Method.

Using the PCA method, the symptom profile changes at the end of and after RT, where nausea and appetite become more distinct and are thus separated into a different cluster. On the contrary, with EFA, the symptomology changes throughout the course of RT such that the symptom profiles become less distinctive. Compared to the symptom clusters identified before RT through EFA, the cluster with depression, anxiety, and wellbeing expands to also include pain for the data collected at the end of RT. For the symptoms experienced after RT, the symptom profiles continue to become less distinctive, as EFA categorizes all nine symptoms into one cluster. Lastly, according to HCA, the symptom clusters are relatively consistent before, at the end of, and after RT, and the following symptoms are always in the same cluster – nausea and appetite, depression and anxiety, and tiredness and drowsiness.

Of the various symptoms experienced by patients with breast cancer, the most prevalent are fatigue, pain, anxiety, and depression (de Jong et al., 2002; Miaskowski and Dibble, 1995). In the present study, depression and anxiety consistently present together in the same symptom cluster before, at the end of, and after RT. The concurrence of depression and anxiety has been well reported in the literature in breast cancer patients (Bender et al., 2005; Kim et al., 2009; Matthews et al., 2012). Bender et al. investigated the clustering of symptoms at all four stages of breast cancer and found that feeling depressed or blue and feeling anxious and nervous consistently clustered together (Bender et al., 2005).

More specifically, the results of the current study are consistent with the findings of Kim et al. (2009). They used EFA to examine the changes in symptom clusters in breast and prostate cancer patients at the middle, end, and 1 month after the completion of RT (Kim et al., 2009). At all-time points, feeling sad and worrying always presented together in the same symptom cluster – labelled as the mood-cognitive cluster (Kim et al., 2009). Matthews et al. also identified three distinct clusters during RT in women with breast cancer: pain-insomnia-fatigue, cognitive disturbance-outlook, and gastrointestinal symptoms (Matthews et al., 2012). The cognitive disturbance-outlook cluster includes both depression and anxiety (Matthews et al., 2012). However, Matthews et al. separated mood-related symptoms from pain and fatigue, which is not consistent with our findings (Matthews et al., 2012).

Pain and tiredness also cluster together in the present study in all statistical analyses, with the exception of the symptom clusters identified at the end of RT by EFA and HCA. The concurrence of pain and fatigue in breast cancer patients has been documented in other studies (Bender et al., 2005; Kim et al., 2009, 2008; Matthews et al., 2012). Matthews et al. reported that breast cancer patients receiving RT experience pain and tiredness together in the pain-insomnia-fatigue cluster (Matthews et al., 2012). Kim et al. found that pain and lack of energy clustered together in the sickness-behaviour symptom cluster at both the middle and end of RT (Kim et al., 2009). Moreover, clustering of pain and fatigue has also been reported by Bender et al. in early-stage breast cancer patients following primary surgery (Bender et al., 2005).

Table 3
Comparison of Symptom Clusters Before, at the End of, and After RT.

	Before RT (N = 1224)	End of RT (N = 371)	After RT (N = 1224)
Principal Component Analysis (PCA)	**Cluster 1**	**Cluster 1**	**Cluster 1**
	Pain	Pain	Pain
	Tiredness	Tiredness	Tiredness
	Nausea	Depression	Drowsiness
	Drowsiness	Anxiety	Dyspnea
	Appetite	Wellbeing	Depression
	Dyspnea		Anxiety
		Cluster 2	Wellbeing
	Cluster 2	Drowsiness	
	Depression	Dyspnea	**Cluster 2**
	Anxiety	Nausea	Nausea
	Wellbeing	Appetite	Appetite
Exploratory Factor Analysis (EFA)	**Cluster 1**	**Cluster 1**	**Cluster 1**
	Pain	Tiredness	Pain
	Tiredness	Nausea	Tiredness
	Nausea	Drowsiness	Drowsiness
	Drowsiness	Appetite	Dyspnea
	Appetite	Dyspnea	Depression
	Dyspnea		Anxiety
		Cluster 2	Wellbeing
	Cluster 2	Pain	Nausea
	Depression	Depression	Appetite
	Anxiety	Anxiety	
	Wellbeing	Wellbeing	
Hierarchical Cluster Analysis (HCA)	**Cluster 1**	**Cluster 1**	**Cluster 1**
	Pain	Pain	Pain
	Tiredness	Depression	Tiredness
	Drowsiness	Anxiety	Drowsiness
	Dyspnea	Wellbeing	Dyspnea
			Wellbeing
	Cluster 2	**Cluster 2**	**Cluster 2**
	Depression	Tiredness	Nausea
	Anxiety	Drowsiness	Appetite
	Wellbeing	Dyspnea	
	Cluster 3	**Cluster 3**	**Cluster 3**
	Nausea	Nausea	Depression
	Appetite	Appetite	Anxiety

In a factor analysis study on symptom clusters of breast cancer patients conducted by Kim HJ et al. Pain and fatigue consistently clustered together prior when assessed before treatment, 48 h after the second cycle of chemotherapy, during the last of six weeks of RT, and 48 h after the third cycle of chemotherapy, or one month after completing RT (Kim et al., 2008).

Lastly, another pair of concurrent symptoms in the present study is nausea and loss of appetite, which has also been documented in various studies (Bender et al., 2005; Fu et al., 2009; Kim et al., 2008). Kim HJ et al. found that nausea, loss of appetite, and other upper gastrointestinal symptoms clustered together in patients undergoing radiation and/or chemotherapy (Kim et al., 2008). However, the concurrence of nausea and loss of appetite was only present after treatment commenced (Kim et al., 2008). In the current study, nausea and appetite clustered together at all time points, including at baseline before RT. Thus, even in symptom cluster research focusing solely on breast cancer patients, there are discrepancies in the symptom clusters identified due to differences in the symptom assessment tools used, the stage of disease of the patient population, and the type of treatment received by the patients in the study (Nguyen et al., 2011).

Some possible explanations for the discrepancies in the results from use of different analytical methods may be from low communality, or a small number of variables. In addition, PCA, EFA, and HCA utilise different principals to arrive at symptom clusters. For example, while EFA and HCA take into account cooccurrence and relatedness of symptoms, PCA does not. Therefore, these underlying differences may contribute to disagreements on the final clusters.

There are several limitations to the current retrospective study. First, symptom clusters in this study were based on longitudinal data collected from the ESAS, which is limited in its assessment of symptomatology. The data were collected from 1224 patients receiving RT; 594 received chemotherapy and 930 received hormone therapy at the time of the ESAS. It is possible that some of the reported ESAS symptoms experienced by patients were due to chemotherapy and/or hormone therapy, rather than RT. Although 1224 patients were included in the study that completed the ESAS before and after RT, only 310 patients completed the ESAS within one week of the end RT. The smaller sample size is a limitation for the data collected from patients at the end of RT. Further research in this area is warranted to explore and identify well-defined symptom clusters for breast cancer patients receiving RT. In particular, future analyses should investigate whether the symptom clusters experienced by this population change with the dosage of radiation (hypofractionated versus conventional dose fractionations) or when patients have previously or are concurrently receiving chemotherapy, hormone therapy, and/or boost radiation.

5. Conclusion

Among the symptom clusters identified before, at the end of, and after RT, the following symptoms consistently clustered together: depression and anxiety, nausea and appetite, pain and tiredness, and drowsiness, dyspnea, and tiredness. Similar patterns are reported in the literature in both the patient population of breast cancer patients, as well as the subpopulation of those receiving RT. Well-defined symptom clusters in breast cancer patients receiving radiation can lead to improved management of symptoms.

Conflicts of interest

None to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejon.2019.07.004.

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