Symptom Clusters in Patients With Brain Tumors Undergoing Proton Beam Therapy

Ulrica Langegård, MSc, RN, Birgitta Johansson, PhD, RN, Thomas Bjork-Eriksson, PhD, MD, Per Fransson, PhD, RN, Emma Ohlsson-Nevo, PhD, RN, Katarina Sjövall, PhD, RN, and Karin Ahlberg, PhD, RN

OBJECTIVES: To explore symptom clusters during proton beam therapy in patients with primary brain tumors and investigate associations among symptom clusters, demographic variables, and comorbidity in this patient population.

SAMPLE & SETTING: Data were collected from 187 adult patients with primary brain tumors during their treatment periods in the Skandion Clinic in Uppsala, Sweden. Symptoms were assessed with the Radiotherapy-Related Symptoms Assessment Scale, and comorbidity was evaluated with the Self-Administered Comorbidity Questionnaire.

METHODS & VARIABLES: The study used a quantitative and longitudinal design. Exploratory factor analysis was used to determine the underlying structure of symptom clusters.

RESULTS: Three clusters were identified: mood, reduced appetite, and reduced energy. The mood cluster had the highest factor loadings (0.71–0.86). In addition, demographic and comorbidity characteristics were associated with symptom clusters in this group of patients.

IMPLICATIONS FOR NURSING: Building knowledge about how these symptoms interact and are clustered will support healthcare professionals to more efficiently relieve symptom clusters during proton beam therapy.

KEYWORDS brain tumor; radiation therapy; proton beam therapy; symptom clusters

***ONF, 46*(3), 349–363.**

DOI 10.1188/19.ONF.349-363

Clinical experiences and studies have shown that patients with tumors often experience multiple concurrent symptoms during their disease trajectories. However, the majority of symptom research focuses on single symptoms. Dodd, Miaskowski, and Paul (2001) studied symptom clusters and suggested that research should focus on evaluating associations among multiple symptoms and the possible synergistic adverse effects on patients' future morbidity. The concept has continued to be discussed in scientific contexts (Dodd, Miaskowski, & Lee, 2004; Dong et al., 2016; Fox, Lyon, & Farace, 2007; Kim, McGuire, Tulman, & Barsevick, 2005; Miaskowski, Dodd, & Lee, 2004; Xiao, 2010). Symptom clusters refer to stable groups of symptoms that are relatively independent of other symptom clusters (Kim et al., 2005). Fatigue, insomnia, pain, and depression constitute the most prevalent symptom cluster in cancer (Barsevick, 2007). There are several nursing theories and models of symptom experience and management (Brant, Beck, & Miaskowski, 2010). Most symptom management models assume that the healthcare provider will only focus on one symptom at a time. However, an exception is the theory of unpleasant symptoms (TUS) developed by Lenz, Pugh, Milligan, Gift, and Suppe (1997). This theory postulates that symptoms co-occur and do not exist in isolation. Therefore, the TUS provides a good basis for research regarding symptom clusters.

Proton beam therapy (PBT) is a radiation therapy modality in which proton particles penetrate deep into the target and stop at a certain depth, depending on their energy (Durante & Loeffler, 2010). With PBT, the risk of damage to healthy tissues is potentially reduced. In addition, the dose targeted at the tumor may be increased in some cases, meaning control over the tumor is potentially increased (Schulz-Ertner & Tsujii, 2007). PBT may also have fewer medical side effects than

observed in conventional radiation therapy (Glimelius et al., 2005; Maquilan, Grover, Alonso-Basanta, & Lustig, 2014; Schulz-Ertner & Tsujii, 2007; Yuh et al., 2004). However, studies of the side effects of PBT using patient-reported outcomes are lacking.

In Sweden, about 1,400 patients are diagnosed with a primary brain tumor each year, and about 50% of these tumors are malignant (National Board of Health and Welfare, 2017). Benign and malignant brain tumors affect people of all ages but commonly occur in individuals aged older than 60 years. The distinction between a cancer diagnosis and a benign tumor in the central nervous system when it comes to patient-related outcomes prior to treatment, during treatment, and post-treatment may not be two distinct separate categories divided by whether the tumor is malignant or benign. Initial symptoms in patients with brain tumors are dependent on the location of the tumor and may include headache, anorexia, nausea, vomiting, seizures, sleeping longer at night, and drowsiness with napping during the day (Levin, Leibel, & Gutin, 2001). Most patients also experience clinical symptoms, such as fatigue, double vision, neurologic deficits, and cognitive impairment (Combs et al., 2013; Wen & Kesari, 2008). Other symptoms (e.g., personality changes, mood disturbances, decreased mental capacity, decreased concentration) can occur later in the course of the disease (Levin et al., 2001). Previous research shows that these symptoms are commonly amplified during conventional radiation therapy and negatively influence patients' daily life (Durand et al., 2015; Li, Bentzen, Li, Renschler, & Mehta, 2008; Scoccianti et al., 2012; Tallet et al., 2012). A key symptom cluster previously described in patients with brain tumors is a cognitive cluster (Armstrong, Cohen, Eriksen, & Hickey, 2004), which includes difficulties in reading, writing, and finding the right words. A mood cluster has also been reported, including feelings of sadness, anxiety, and depression (Fox et al., 2007; Gleason et al., 2007).

Previous studies have shown that patient characteristics (e.g., age, comorbidity) affect an individual's treatment and outcomes (Søgaard, Thomsen, Bossen, Sørensen, & Nørgaard, 2013). For example, some comorbidities may influence the patient's treatment compliance or survival (Daskivich et al., 2011) or affect treatment decisions (Berglund et al., 2012). To the current authors' knowledge, no previous study has investigated demographic variables and comorbidity in relation to symptom clusters during PBT. Therefore, this study aimed to explore symptom clusters that occurred during PBT in patients with primary brain tumors and investigate associations between demographic variables and comorbidity and symptom clusters in this patient group.

Methods

The current study used a quantitative longitudinal design to investigate symptom clusters during PBT in patients with primary brain tumors. In Sweden, PBT is centralized to the Skandion Clinic, located in Uppsala. The Skandion Clinic is organized in a model of distributed competence and shared governance between the seven Swedish regions with university hospital radiation therapy departments (Karlsson et al., 2006). All patients who receive PBT are identified and prepared for treatment at their home clinic and then treated at the Skandion Clinic. Patients receive PBT via a dedicated pencil-beam scanning system from Ion Beam Applications. The treatment is delivered as five weekly fractions over 35 days. After completion of PBT, patients are referred back to their home clinic for long-term follow-up. Because a need exists for clinical trials to establish scientific evidence regarding the advantages of PBT compared to conventional radiation therapy, at least 80% of patients treated at the Skandion Clinic are expected to be included in a prospective clinical treatment protocol (Glimelius et al., 2005). In addition, all patients are asked to provide patient-reported outcomes as part of a prospective longitudinal research project, conducted in close collaboration with the physicians responsible for the treatment protocols.

Patients and Procedures

A consecutive sample of 217 patients treated at the Skandion Clinic from August 2015 to January 2018 were invited to participate in the study. These patients were part of a multicenter prospective PBT protocol that included adult patients with primary central nervous system tumors (Uppsala University, 2015). Inclusion criteria were adult patients aged 18 years or older who were diagnosed with primary brain tumor, receiving PBT, and able to communicate in Swedish. Further inclusion criteria according to PRO-CNS are available in the published protocol (Uppsala University, 2015). Patients with benign tumors were included in the PRO-CNS protocol and the current study because they were nonresectable tumors with substantial tumor volumes and continuous tumor growth. Therefore, patients with benign tumors constituted a subgroup of patients with life-threatening tumors requiring the same treatment as malignant brain tumors. Target volumes (including margins) and target doses for these patients were

comparable with those used for malignant primary brain tumors.

Coordinators at the university hospitals were responsible for identifying eligible patients. Information about the study was provided to potential participants orally by the first author via telephone. Written information, including the voluntary nature of participation, confidentiality, and freedom to withdraw from the study at any time without providing a reason for withdrawal, was then sent to interested patients by mail. All participants provided informed consent before data collection started. During treatment, participants were asked to complete the Radiotherapy-Related Symptom Assessment Scale (RSAS) questionnaire each day. The RSAS could be completed online or as a paper-based questionnaire, according to patients' condition and choice. Online questionnaires were sent to participants' email addresses every day during the treatment period. An email reminder was sent on each day that the questionnaire was not completed. Patients who chose a paper-based format were handed one questionnaire for each treatment day at the start of treatment by an oncology nurse at the Skandion Clinic. Those who used paper-based questionnaires were provided with a prepaid envelope and asked to return the questionnaires at the end of treatment via regular mail. A reminder was sent by mail if the questionnaires were not returned within one week after the end of treatment.

Data Collection

Medical data regarding the participants' tumor and treatment were collected from their medical records. Demographic data (e.g., age, sex, occupational status, education) were collected from participants using a project-specific questionnaire. Comorbidity was reported via a project-specific questionnaire based on the Self-Administered Comorbidity Questionnaire (SCQ) originally developed by Sangha, Stucki, Liang, Fossel, and Katz (2003). The SCQ asks if patients have comorbidities using a list of 15 defined medical problems. The problems covered are diseases related to the heart, lung, ulcer, stomach, liver, kidney, blood (e.g., anemia), connective tissue/muscle, skin, other cancer, high blood pressure, diabetes, depression, arthritis, or rheumatoid arthritis. Participants also had the option of adding additional conditions in an open-ended format. For each problem, participants were asked if they received treatment as a proxy for disease severity. To capture participants' burden for reported conditions, the current authors asked if the condition limited daily activities. Participants were scored a maximum of 3 points for each medical

TABLE 1. Sample Characteristics (N = 187)

Characteristic	n	%
Sex		
Female	95	51
Male	92	49
Diagnosis		
Malignant brain tumor	101	54
Benign brain tumor	86	46
Comorbidity		
Hypertension	30	16
Skin disease	22	12
Depression	20	11
Bowel disease	14	8
Gastric ulcer	14	8
Arthritis	13	7
Other cancer disease	10	5
Diabetes	9	5
Muscle disease	6	3
Pulmonary disease	6	3
Heart disease	4	2
Anemia	3	2
Arthritis urica	3	2
Liver disease	2	1
Kidney disease	1	< 1
No response	8	4
SCQ		
0	99	53
1–3	56	30
4–10	28	15
Greater than 10	2	1
No response	2	1
Marital status		
Married	129	69
Single	58	31
Education		
Elementary	15	8
Secondary	86	46
University	76	41
No response	10	5
Questionnaire format		
Paper	143	76
Digital	44	24

SCQ—Self-Administered Comorbidity Questionnaire
Note. Participants could choose as many or as few comorbidities as applicable; therefore, n values do not total the N value.
Note. Because of rounding, percentages may not total 100.

condition: 1 point for the presence of the problem, 1 point if they received treatment for it, and 1 point if the problem caused a limitation in functioning (maximum score of 45 points).

The newly developed RSAS was used to assess patients' daily experiences of 12 symptoms: fatigue, insomnia, pain, appetite loss, dyspnea, cognitive impairment, anxiety, worry, nausea, sadness, constipation, and diarrhea. These are regarded as a core set of clinically relevant symptoms most commonly reported in patients with cancer and recommended to be included in clinical trials (Reeve et al., 2014). The authors' previous interview-based study suggested that patients commonly experienced these symptoms during the treatment period (Langegård et al., 2018). Preliminary analysis of the RSAS indicated moderate to strong correlations (r = 0.4–0.71) among the symptoms covered by the RSAS and those assessed with the EORTC QLQ-C30, indicating the RSAS had sufficient criterion-related validity. The RSAS was created based on the Quality From the Patient's Viewpoint tool developed by Wilde, Starrin, Larsson, and Larsson (1993). The RSAS assesses symptom frequency and intensity (1 = not at all to 4 = very much) and symptom distress (1 = of no concern to 4 = of greatest concern). Each item is transformed into scores ranging from 0–100, with higher scores indicating more severe symptoms.

Data Analysis

Missing values were imputed using the last-value-carried-forward method (Twisk & de Vente, 2002). Four percent of the values for the analyzed items were imputed at day 15, 8% at day 25, and 29% at day 35.

Descriptive statistics were used to analyze frequencies and intensity of participants' daily symptoms

TABLE 2. Patterns of 12 Individual Symptoms During Proton Beam Therapy Among Patients With Primary Brain Tumors Using RSAS (N = 187)

	Day 1				Day 35						
	Frequency of Symptom				Frequency of Symptom				Change From Day 1 to 35		
Variable	Not at All	Very Much	$\bar{X}$	SD	Not at All	Very Much	$\bar{X}$	SD	$\bar{X}$	SD	p
Anxiety	144	2	10.2	20.7	156	4	8.4	21.2	−1.8	19.8	0.27
Cognitive impairment	130	1	11.6	19	118	1	15	21.6	3.4	18.5	0.01
Constipation[a]	170	1	3.74	13.1	164	3	6.1	18.3	2.3	19.3	0.12
Diarrhea[a]	165	2	4.99	15.4	171	1	3.4	12.3	−1.6	17	0.14
Dyspnea[a]	180	–	1.43	7.6	164	1	4.8	14.1	3.4	15.7	0.01
Fatigue	85	7	26.9	29	62	12	33.3	29.7	6.4	31.8	0.01
Insomnia	100	11	22.5	29	104	5	21.2	27.4	−1.3	30.6	0.57
Loss of appetite	163	–	4.81	13.2	129	4	13.9	23.6	9.1	24.8	< 0.0001
Nausea	170	1	3.57	12.4	146	5	10.2	22.1	6.6	21.5	< 0.0001
Pain	141	2	10.9	21.2	127	3	15.2	24.7	4.3	24.8	0.02
Sadness	122	2	14.3	21.8	136	4	12.3	22.9	−1.9	23.5	0.29
Worry	82	5	23.5	24.8	131	4	13.2	23	−10.3	26.8	< 0.0001

[a] Excluded from the factor analysis because of low frequencies and low intensity. The Wilcoxon signed rank test was used for comparisons within groups.
RSAS—Radiotherapy-Related Symptoms Assessment Scale
Note. The RSAS assesses symptom frequency and intensity (0 = not at all, 33.3 = a little, 66.6 = quite a bit, and 100 = very much). In the presentation of frequency, not at all and very much are shown; in the mean and SD values, all scores are summarized.

TABLE 3. Symptom Clustering in Patients With Primary Brain Tumors Receiving Proton Beam Therapy Using RSAS (N = 187)

	Mood			Reduced Appetite			Reduced Energy		
	Day 15	Day 25	Day 35	Day 15	Day 25	Day 35	Day 15	Day 25	Day 35
Item in RSAS	Factor Loading	Factor Loading	Factor Loading	Factor Loading	Factor Loading	Factor Loading	Factor Loading	Factor Loading	Factor Loading
Anxiety	0.86	0.84	0.86	–	–	–	–	–	–
Cognitive impairment	–	–	–	–	–	–	0.72	0.72	0.61
Constipation[a]	–	–	–	–	–	–	–	–	–
Diarrhea[a]	–	–	–	–	–	–	–	–	–
Dyspnea[a]	–	–	–	–	–	–	–	–	–
Fatigue[b]	–	–	0.41[b]	–	–	–	0.8	0.65	0.63
Insomnia[b]	–	–	0.69[b]	–	–	–	0.74	0.74	0.7
Loss of appetite	–	–	–	0.66	0.67	0.84	–	–	–
Nausea[b]	–	0.47[b]	0.4[b]	0.74	0.56	0.62	–	–	–
Pain	–	–	–	–	–	–	0.66	0.81	0.7
Sadness	0.8	0.7	0.71	–	–	–	–	–	–
Worry	0.83	0.85	0.84	–	–	–	–	–	–

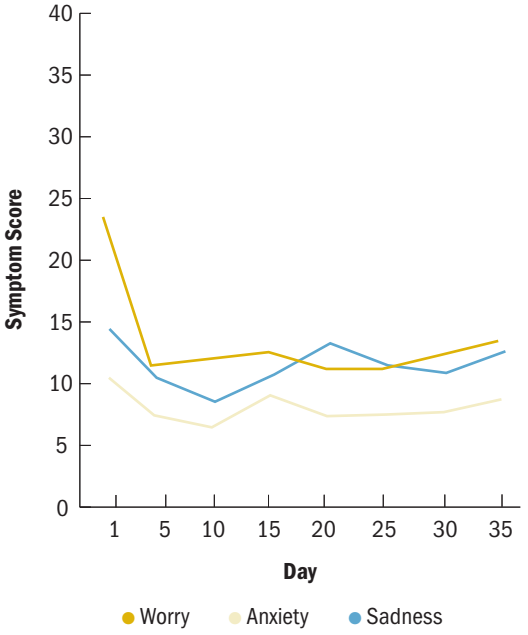
[a] Removed because of low variance over time and irrelevant clustering
[b] Symptoms loaded onto different clusters.
RSAS—Radiotherapy-Related Symptoms Assessment Scale
Note. Factor loadings lower than 0.4 are not presented. Eigenvalues were 4.29, 4.36, and 4.5 for the mood cluster on days 15, 25, and 35, respectively; 1.05, 1, and 0.92 for the reduced appetite cluster on days 15, 25, and 35, respectively; and 1.21, 1.2, and 1.21 for the reduced energy cluster on days 15, 25, and 35, respectively.

during the entire treatment period. Numbers and percentages are presented for categorical variables and mean and standard deviation (SD) for continues variables, except for age, where range is also presented. For symptom patterns, the mean score and frequency of the lowest and highest scores are presented. The Wilcoxon signed rank test was used to compare changes in symptoms from day 1 to day 35.

A sample size of 187 patients is regarded sufficient for an exploratory factor analysis including 12 variables (McNeish, 2017). Symptom clusters based on symptom intensity ratings were analyzed using exploratory factor analysis, which is widely used to identify symptom clusters (Thompson, 2004). The factorability of the remaining nine symptoms (excluding dyspnea, constipation, and diarrhea) were examined for the 35 days. All symptoms correlated (minimum of 0.3) with at least one other symptom, suggesting reasonable factorability. The Kaiser-Meyer-Olkin measure and Bartlett's test were performed before proceeding with the factor analysis. Given these indicators, factor analysis with varimax rotation including the nine symptoms was considered appropriate. Only factor loadings (rotated factors) greater than 0.4 were calculated. Factor loadings quantify how much each variable fits into a given factor; variables that load heavily onto the same factor are correlated. The authors chose to present the results for days 15, 25, and 35 because the expected perceived symptoms occur two to three weeks after the start of treatment, tend to peak at the end of the treatment, and are commonly used in research during conventional radiation therapy (Jakobsson, Ekman, & Ahlberg, 2015; Wengstrom, Haggmark, Strander, & Forsberg, 2000). The number of factors selected was based on those with an eigenvalue equal or higher than 1. However, day 35 was an exception, when a factor was chosen independently of the eigenvalue if a previous pattern was identified.

Linear regression analyses were used to analyze how medical and demographic data were associated

FIGURE 1. Longitudinal Profile of Mood Symptom Cluster in Patients Undergoing Proton Beam Therapy (N = 187)



Note. Symptom scores range from 0 (best) to 100 (worst).

with symptom clusters. Variables that were significant in the univariate analysis ($p < 0.1$) were entered into a backward stepwise multivariate regression model. Beta estimates with 95% confidence intervals, p values, and r^2 were calculated. There were no linear associations between the SCQ and the symptom clusters. Therefore, to include this variable, patients were dichotomized based on SCQ cutoff points of 0–3 or greater than 4 points.

Ethical Considerations

The current multicenter study was approved by the research ethics committee in Gothenburg, Sweden. All participants provided written informed consent before the study started.

Results

Demographics

In total, 187 of 217 (86%) patients diagnosed with primary brain tumor agreed to participate in this study; 4 declined to participate and 26 were nonresponders. Participants' mean age was 48 years (SD = 14, range = 18–79). Participant demographic and comorbidity information was collected at baseline (see Table 1).

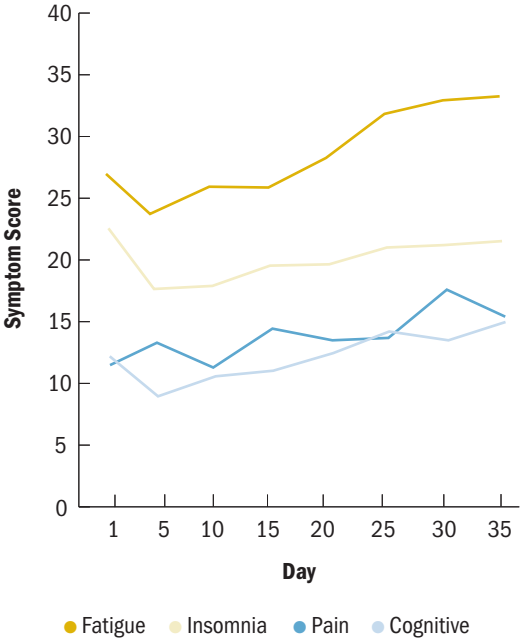
Patterns of Single Symptoms

No statistically significant differences were found between the malignant and benign groups during the treatment period regarding symptom experience (data not shown); therefore, the authors combined both patient groups in the subsequent analyses. Participants' symptom levels were generally low, with the highest level for fatigue. Fatigue, pain, loss of appetite, cognitive impairment, and nausea increased from day 1 to day 35 ($p = 0.02$ to $p < 0.001$), but worry decreased ($p < 0.0001$) (see Table 2). Three symptoms (dyspnea, constipation, and diarrhea) were excluded from the factor and regression analyses because of low frequencies. In addition, it was not expected that PBT targeted to the brain would cause such symptoms.

Symptom Clusters

The remaining nine symptoms in the RSAS are presented in symptom clusters (see Table 3 and Figures 1–3). The Kaiser-Meyer-Olkin measure of sampling adequacy was between 0.76 and 0.88 for the 35 days, which was above the commonly recommended value of 0.6. Bartlett's test of sphericity was significant ($p < 0.0001$) for all days. A three-factor solution was

FIGURE 2. Longitudinal Profile of Reduced Energy Symptom Cluster in Patients Undergoing Proton Beam Therapy (N = 187)



Note. Symptom scores range from 0 (best) to 100 (worst).

obtained from the principal component analysis, which explained 66% of the variance in day 15, 65% in day 25, and 66% in day 35. This solution was preferred because the eigenvalues were higher than 1. The three clusters were as follows:

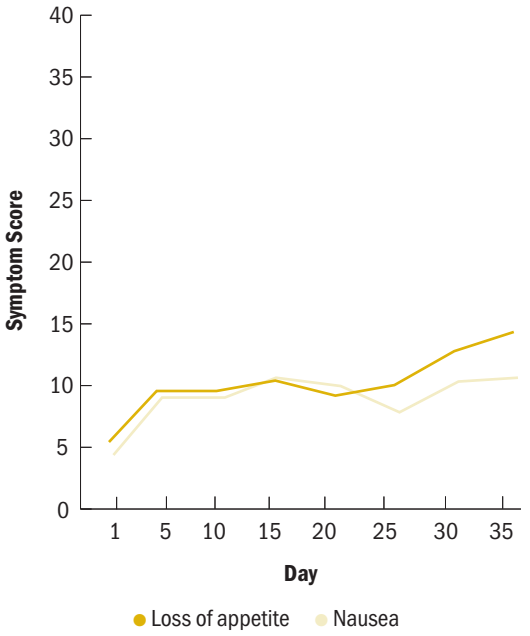
- Mood (worry, anxiety, and sadness)
- Reduced appetite (loss of appetite and nausea)
- Reduced energy (fatigue, insomnia, pain, and cognitive impairment)

The mood cluster had the highest factor loading on day 35 (0.71–0.86), followed by the reduced appetite cluster (0.6–0.84), and then the reduced energy cluster (0.61–0.7). The clusters were evaluated for the entire treatment period and found to be similar from baseline to end of treatment and relatively stable over time. The symptoms were categorized into the clusters for which they showed the highest factor loading. Fatigue, insomnia, and nausea revealed factor loadings greater than 0.4 in the mood cluster, but these were not as high as their factor loadings in the reduced energy cluster (fatigue and insomnia) and the reduced appetite cluster (nausea). The reduced energy and reduced appetite clusters were significantly increased ($p = 0.01$ and $p \leq 0.0001$, respectively), and the mood cluster was significantly decreased ($p = 0.001$) from day 1 to day 35.

Risk Factors for Symptom Clusters

In the mood cluster, the univariate analysis showed that sex, comorbidity, gastric ulcer, bowel disease, depression, and muscle disease were significantly associated with experiencing more anxiety, worry, and sadness (see Table 4). However, the multivariate analysis indicated that only female sex ($p = 0.04$) and more comorbidity ($p < 0.001$) were associated with worse mood cluster symptoms. In the reduced appetite cluster, the univariate analysis showed that sex, education, and muscle disease were significantly associated with loss of appetite and nausea, whereas low education ($p = 0.04$) was the only significant variable in the multivariate analysis and was associated with worse reduced appetite cluster symptoms. In the reduced energy cluster, the univariate analysis showed that sex, comorbidity, hypertension, gastric ulcer, depression, and muscle disease were significantly associated with fatigue, insomnia, pain, and cognitive impairment. The multivariate analysis identified female sex ($p = 0.01$) and gastric ulcer ($p = 0.01$) as significant variables. However, sex and comorbidity contributed to the increased insensitivity of symptom clusters during the treatment period and were significant risk factors during PBT.

FIGURE 3. Longitudinal Profile of Reduced Appetite Symptom Cluster in Patients Undergoing Proton Beam Therapy (N = 187)



Note. Symptom scores range from 0 (best) to 100 (worst).

Discussion

Symptom intensity during PBT for patients with brain tumors was generally low, with the highest levels found for fatigue. Participants' symptoms formed mood, reduced appetite, and reduced energy clusters. These clusters were consistent over time and relatively stable during the treatment period. The reduced energy and reduced appetite clusters worsened during the treatment period, whereas the mood cluster improved. Female sex and comorbidity were associated with more mood and reduced energy symptoms, gastric ulcer with more reduced energy symptoms, and higher education with fewer reduced appetite symptoms.

The mood cluster had the highest factor loadings and did not change, except that fatigue and insomnia also showed high loading (less than 0.4) onto this cluster at the end of treatment. This may indicate that fatigue and insomnia are associated with worry, anxiety, and sadness. It is known that patients with cancer (including brain cancer) experience emotional symptoms, such as feeling sad and worrying, at the time of early diagnosis or during cancer-related therapy (Kim & Byun, 2018). Emotional symptoms

TABLE 4. Results of Linear Regression Analyses for Demographic and Comorbidity Characteristics Related to Risk Factors Affecting Symptom Clusters During Proton Beam Therapy Among Patients With Primary Brain Tumors

				Univariate Analysis				Multivariate Analysis		
Variable	$\bar{X}$	SD	n	β	95% CI	p	R	β	95% CI	p
Mood cluster										
Age (years)										
18–41	11.11	20.22	62	–	–	–	–	–	–	–
42–53	13.08	20.96	62	–	–	–	–	–	–	–
54–79	9.7	2.4	63	−0.06	[−0.27, 0.15]	0.56	0.00	–	–	–
Sex										
Male	8.16	14.68	94	–	–	–	–	–	–	–
Female	14.46	24.67	93	6.3	[0.45, 12.2]	0.04	0.02	6.03	[0.32, 11.75]	0.04
Marital status										
Married or living with partner	10.34	18.05	130	–	–	–	–	–	–	–
Living alone	13.45	25.17	57	3.11	[−3.31, 9.52]	0.34	0.00	–	–	–
Occupational status										
Retired or unemployed	12.61	22.4	37	–	–	–	–	–	–	–
Employed or student	10.88	20.22	142	−1.74	[−9.27, 5.8]	0.65	0.00	–	–	–
Education										
Elementary[a]	8.73	13.2	14	–	–	–	–	–	–	–
Secondary	11.11	22.29	82	–	–	–	–	–	–	–
University	11.24	19.97	83	0.75	[−4.1, 5.6]	0.76	0.00	–	–	–
Comorbidity (SCQ)										
0–3	9.03	17.12	155	–	–	–	–	–	–	–
4 or greater	23.7	30.57	30	14.67	[6.85, 22.5]	< 0.001	0.07	14.41	[6.66, 22.16]	< 0.001
Hypertension										
Yes	14.07	24.05	30	–	–	–	–	–	–	–
No	10.9	19.84	155	−3.18	[−11.3, 4.91]	0.44	0.00	–	–	–
Gastric ulcer										
Yes	23.02	30.96	14	–	–	–	–	–	–	–
No	10.46	19.27	171	−12.55	[−23.7, −1.41]	0.03	0.03	–	–	–
Bowel disease										
Yes	28.57	31.04	14	–	–	–	–	–	–	–
No	10.01	18.89	171	−18.56	[−29.5, −7.6]	0.001	0.06	–	–	–
Depression										
Yes	23.89	35.92	20	–	–	–	–	–	–	–
No	9.9	17.4	165	−13.99	[−23.4, −4.59]	< 0.001	0.04	–	–	–
Muscle disease										
Yes	27.78	31.23	6	–	–	–	–	–	–	–
No	10.86	19.99	179	−16.91	[−33.6, −0.23]	0.05	0.02	–	–	–

Continued on the next page

TABLE 4. Results of Linear Regression Analyses for Demographic and Comorbidity Characteristics Related to Risk Factors Affecting Symptom Clusters During Proton Beam Therapy Among Patients With Primary Brain Tumors *(Continued)*

				Univariate Analysis				Multivariate Analysis		
Variable	**$\bar{X}$**	**SD**	**n**	**β**	**95% CI**	**p**	**R**	**β**	**95% CI**	**p**
Reduced appetite cluster										
Age (years)										
18–41	10.48	16.87	62	–	–	–	–	–	–	–
42–53	13.71	21.24	62	–	–	–	–	–	–	–
54–79	11.9	20.83	63	0.07	[−0.12, 0.27]	0.46	0.00	–	–	–
Sex										
Male	8.69	16.71	94	–	–	–	–	–	–	–
Female	15.41	21.87	93	6.72	[1.11, 12.3]	0.01	0.03	–	–	–
Marital status										
Married or living with partner	10.9	18.99	130	–	–	–	–	–	–	–
Living alone	14.62	21.15	57	3.72	[−2.44, 9.89]	0.23	0.01	–	–	–
Occupational status										
Retired or unemployed	11.71	23.53	37	–	–	–	–	–	–	–
Employed or student	11.97	18.45	142	0.26	[−6.87, 7.39]	0.94	0.00	–	–	–
Education										
Elementary[a]	20.24	22.81	14	–	–	–	–	–	–	–
Secondary	13.21	23.24	82	–	–	–	–	–	–	–
University	9.24	14.55	83	−4.82	[−9.42, −0.21]	0.04	0.02	−4.82	[−9.42, −0.21]	0.04
Comorbidity (SCQ)										
0–3	11.18	18.52	155	–	–	–	–	–	–	–
4 or greater	17.22	24.95	30	6.04	[−1.71, 13.8]	0.13	0.01	–	–	–
Hypertension										
Yes	13.89	22.35	30	–	–	–	–	–	–	–
No	11.83	19.27	155	−2.06	[−9.85, 5.73]	0.6	0.00	–	–	–
Gastric ulcer										
Yes	15.48	21.15	14	–	–	–	–	–	–	–
No	11.89	19.68	171	−3.59	[−14.4, 7.27]	0.52	0.00	–	–	–
Bowel disease										
Yes	15.48	21.15	13	–	–	–	–	–	–	–
No	11.89	19.68	171	−3.59	[−14.4, 7.27]	0.52	0.00	–	–	–
Depression										
Yes	20	29.91	20	–	–	–	–	–	–	–
No	11.21	18.05	165	-8.79	[−18, 0.38]	0.06	0.02	–	–	–
Muscle disease										
Yes	27.78	32.77	6	–	–	–	–	–	–	–
No	11.64	19.1	179	−16.14	[−32.2, −0.09]	0.04	0.02	–	–	–

Continued on the next page

TABLE 4. Results of Linear Regression Analyses for Demographic and Comorbidity Characteristics Related to Risk Factors Affecting Symptom Clusters During Proton Beam Therapy Among Patients With Primary Brain Tumors *(Continued)*

				Univariate Analysis				Multivariate Analysis		
Variable	**$\bar{X}$**	**SD**	**n**	**β**	**95% CI**	**p**	**R**	**β**	**95% CI**	**p**
Reduced energy cluster										
Age (years)										
18–41	21.64	17.76	62	–	–	–	–	–	–	–
42–53	25.13	21.68	62	–	–	–	–	–	–	–
54–79	16.8	16.36	63	−0.12	[−0.31, 0.07]	0.21	0.01	–	–	–
Sex										
Male	17.82	14.95	94	–	–	–	–	–	–	–
Female	24.55	21.82	93	6.73	[1.34, 12.1]	0.01	0.03	6.63	[1.42, 11.9]	0.01
Marital status										
Married or living with partner	20.19	18.09	130	–	–	–	–	–	–	–
Living alone	23.39	20.74	57	3.2	[−2.73, 9.13]	0.29	0.01	–	–	–
Occupational status										
Retired or unemployed	18.92	21.4	37	–	–	–	–	–	–	–
Employed or student	21.6	18.28	142	2.68	[−4.23, 9.58]	0.45	0.00	–	–	–
Education										
Elementary[a]	20.24	16.25	14	–	–	–	–	–	–	–
Secondary	22.76	21.28	82	–	–	–	–	–	–	–
University	18.78	15.98	83	−2.19	[−6.57, 2.19]	0.32	0.01	–	–	–
Comorbidity (SCQ)										
0–3	19.52	16.81	155	–	–	–	–	–	–	–
4 or greater	31.11	25.52	30	11.59	[4.33, 18.9]	0.001	0.05	7.06	[−0.77, 14.9]	0.07
Hypertension										
Yes	28.06	22.37	30	–	–	–	–	–	–	–
No	20.11	17.96	155	−7.95	[−15.3, −0.58]	0.03	0.02	–	–	–
Gastric ulcer										
Yes	38.1	26.7	14	–	–	–	–	–	–	–
No	20.03	17.54	171	−18.07	[−28.1, −8.01]	< 0.001	0.06	−13.83	[−24.7, −2.92]	0.01
Bowel disease										
Yes	29.17	23.96	14	–	–	–	–	–	–	–
No	20.76	18.38	171	−8.41	[−18.7, 1.92]	0.11	0.01	–	–	–
Depression										
Yes	30.42	27.34	20	–	–	–	–	–	–	–
No	20.3	17.42	165	−10.11	[−18.9, −1.38]	0.02	0.03	–	–	–
Muscle disease										
Yes	36.11	32.77	6	–	–	–	–	–	–	–
No	20.9	18.22	179	−15.21	[−30.6, 0.16]	0.05	0.02	–	–	–

[a] Reference group
CI—confidence interval; SCQ—Self-Administered Comorbidity Questionnaire
Note. Univariate significant variables ($p < 0.1$) were entered into a backward stepwise multivariate regression model.

are also known to be highly correlated (Pelletier, Verhoef, Khatri, & Hagen, 2002). Beck, Dudley, and Barsevick (2005) argued that, because these symptoms were seen as normal responses in patients with cancer facing the stress of a cancer diagnosis, patients with cancer may have a high degree of negative emotions. In the current study, the mood cluster and emotional symptoms, such as worry and anxiety (as single symptoms), decreased significantly over time. The authors' previous study (Langegård et al., 2019) showed a decreased need for support concerning symptoms, such as worry and anxiety, during the treatment period, even if there was still a discrepancy between patients' experiences of care received and how important they perceived access to care with regard to these symptoms. Pelletier et al. (2002) found that emotional well-being was difficult to interpret and needed further research, particularly in this population. However, there were differences with regard to depression between the current study and previous research. Pelletier et al. (2002) found that a high level of patients experienced depression, which was similar to the prevalence of depression found in patients with brain tumors by other investigators. In the current study, the authors found that depression was significant in the univariate analysis but not in the multivariate analysis. In the multivariate analysis, a higher total comorbidity burden (including depression and female sex) were associated with more mood cluster symptoms. This indicates that patients who are referred to the Skandion Clinic may need support to manage mood symptoms during their five-week stay at the hotel where out-of-town patients stay during PBT treatment.

Fatigue, pain, loss of appetite, cognitive impairment, and nausea increased during PBT, which was consistent with previous findings. Armstrong et al. (2004) identified neurologic symptoms in patients with brain tumor and noted that treatment with radiation therapy increased intracranial pressure, which resulted in increased symptoms experienced during the treatment. This was supported by Khan et al. (2013), who showed that cognitive symptoms (e.g., memory loss, confusion, trouble concentrating) always loaded onto the same cluster. Similar patterns were found in the current study. Cognitive impairment increased significantly over time and loaded onto the reduced energy cluster at day 15, which was expected if fatigue, insomnia, and pain affect cognitive capability. In addition, cognitive impairment (e.g., behavioral, emotional, and intellectual difficulties) is the most common neurologic issue associated with brain tumors (Combs et al., 2013; Durand et al., 2015; Osoba, Brada, Prados, & Yung, 2000; Tucha, Smely, Preier, & Lange, 2000). Such impairment also compromises patients' ability to live independently and perform their usual work and other activities, which places additional strain on patients and caregivers (Meyers, Weitzner, Valentine, & Levin, 1998; Tucha et al., 2000). The authors' previous study regarding quality of care (Langegård et al., 2019) revealed that care was perceived as inadequate in several aspects according to patient ratings, particularly regarding support for symptom management. In addition, the previous study showed that symptom intensity had a major effect on the daily life of patients with brain tumors receiving PBT, and the patient was an important asset to the symptom management process (Langegård et al., 2019). If healthcare professionals can counteract symptoms, including in the reduced energy cluster, at an early stage, it is possible that cognitive impairment may be prevented or relieved.

Substantial research has been done on symptom clusters of cognitive impairment and emotional symptoms among patients with primary brain tumor receiving conventional radiation therapy. However, to the authors' knowledge, no previous research reported a cluster comprising reduced appetite and nausea in patients with primary brain tumors. A study involving patients with brain metastasis showed that nausea and vomiting were present in the same cluster (Chow et al., 2008; Khan et al., 2013). In the current study, the reduced appetite cluster was relatively stable over time, but nausea also loaded in the mood cluster (greater than 0.4) on days 25 and 35. A reasonable explanation for this is that nausea, which is a common side effect of brain radiation, increased at the end of the treatment, which may increase mood symptoms. This is consistent with Giovagnoli et al. (2014), who also found that nausea was associated with emotional symptoms.

This analysis was guided, in part, by the TUS, which presents symptoms as occurring in clusters rather than in isolation. The model reflects the importance of influencing factors, which in this study were the interactions between comorbidity, demographic factors, and symptom clusters. Comorbidity, female sex, and low education increased patients' symptom burden. The mood cluster was significantly worsened by more comorbidity and female sex, and the reduced energy cluster was worsened by female sex. The same pattern was shown in previous studies (Berglund et al., 2012; Gijsen et al., 2001; Lemanska et al., 2017; Mao et al., 2007). It is known that women

report higher symptom scores (Cheung, Le, Gagliese, & Zimmermann, 2011; Valeberg & Grov, 2013). Lower education resulted in increased loss of appetite in the current study, with gastric ulcers also affecting the reduced energy cluster. This result was not surprising because patients with brain tumors undergoing treatment with radiation therapy often receive cortisone treatment, and gastric ulcer is a well-known side effect of cortisone (Hirschl, 1988). The symptoms of gastric ulcer may cause pain and loss of appetite, which may affect other symptoms in the reduced energy cluster.

Strengths and Limitations

A clear strength of the present study was the high response rate. The instrument (RSAS) was validated and had psychometric characteristics within the expected range. Another strength was that the authors performed daily measurement of symptoms, which resulted in a thorough analysis. Symptom clusters in patients receiving PBT have not previously been investigated, so the current findings offer important implications. A limitation that should be acknowledged is that the data collection instrument was designed for patients receiving radiation therapy and not specifically for patients with a brain tumor. This may mean that there were some symptoms in the current population that were omitted from the instrument.

Implications for Nursing

The current results clarify the pattern of symptoms and symptom clusters in patients with brain tumors during PBT. In addition, the authors identified risk factors that may worsen these symptom clusters. This knowledge may facilitate healthcare professionals' identification of patients who experience symptoms with greater or lesser intensity and, therefore, prevent or reduce symptoms experienced by these subgroups. Further research is needed on whether conventional treatments are effective for specific symptoms and what effect (if any) the alleviation of one symptom has on other symptoms in a cluster. Further study is also warranted to better understand symptoms and their inter-relationships with other subjective symptoms in the natural illness trajectory.

This study may help clinicians to better understand the symptomatology among patients with brain tumors undergoing PBT. It may also help them to identify patient subgroups and provide a basis for development of supportive care during PBT. Symptom clusters may also provide a target for specific interventions. It would be particularly useful to know which interventions are most efficient for patients suffering particular symptom clusters. To help patients participate more in their self-care, the clinic could implement interventions, such as developing collaborations with relevant professionals (e.g., dietitians and physiotherapists) and arranging common group activities to support patients in managing their symptoms.

KNOWLEDGE TRANSLATION

- Symptom intensity during proton beam therapy was generally low.
- Three symptom clusters related to proton beam therapy were identified: mood, reduced appetite, and reduced energy.
- Demographic and comorbidity characteristics were associated with the symptom clusters.

Conclusion

Symptoms reported by patients with primary brain tumors receiving PBT were generally low. The findings show that the reported symptoms formed three clusters: mood, reduced appetite, and reduced energy. More comorbidity, female sex, and low education levels may worsen symptom clusters. This study contributes to the limited body of research on symptom clusters; however, further studies on symptom clusters are warranted, including investigating their patterns across the illness trajectory and comparing symptom clusters in PBT with patients receiving conventional radiation therapy.

Ulrica Langegård, MSc, RN, is a PhD student in the Institute of Health and Care Sciences of Sahlgrenska Academy at the University of Gothenburg; **Birgitta Johansson, PhD, RN,** is a senior lecturer in the Department of Immunology, Genetics, and Pathology at Uppsala University; **Thomas Bjork-Eriksson, PhD, MD,** is a manager at the Regional Cancer Center West in Gothenburg; **Per Fransson, PhD, RN,** is an associate professor and senior lecturer in the Department of Nursing at Umeå University; **Emma Ohlsson-Nevo, PhD, RN,** is a research leader in the University Healthcare Research Centre and Faculty of Medicine and Health at Örebro University; **Katarina Sjövall, PhD, RN,** is a research and development leader in the Department of Oncology at Skane University Hospital; and **Karin Ahlberg, PhD, RN,** is a senior lecturer in the Institute of Health and Care Sciences of Sahlgrenska Academy at the University of Gothenburg, all in Sweden. Langegård can be reached at ulrica.langegard@gu.se, with copy to ONFEditor@ons.org. (Submitted October 2018. Accepted December 10, 2018.)

The authors gratefully acknowledge all employees at the Skandion Clinic for their support with the data collection, particularly Caroline Wenngren, RN.

This research was funded by grants (CAN2015/428 and CAN 2016/809) from the Swedish Cancer Foundation.

Langegård, Johansson, Bjork-Eriksson, Fransson, Ohlsson-Nevo, and Ahlberg contributed to the conceptualization and design and provided the analysis. Langegård, Johansson, Bjork-Eriksson, and Fransson completed the data collection. Langegård, Bjork-Eriksson, Fransson, and Ahlberg provided statistical support. All authors contributed to the manuscript preparation.

REFERENCES

Armstrong, T.S., Cohen, M.Z., Eriksen, L.R., & Hickey, J.V. (2004). Symptom clusters in oncology patients and implications for symptom research in people with primary brain tumors. *Journal of Nursing Scholarship, 36*, 197–206.

Barsevick, A.M. (2007). The elusive concept of the symptom cluster. *Oncology Nursing Forum, 34*, 971–980. https://doi.org/10.1188/07.ONF.971-980

Beck, S.L., Dudley, W.N., & Barsevick, A. (2005). Pain, sleep disturbance, and fatigue in patients with cancer: Using a mediation model to test a symptom cluster [Online exclusive]. *Oncology Nursing Forum, 32*, 542. doi:10.1188/04.ONF.E48-E55

Berglund, A., Wigertz, A., Adolfsson, J., Ahlgren, J., Fornander, T., Wärnberg, F., & Lambe, M. (2012). Impact of comorbidity on management and mortality in women diagnosed with breast cancer. *Breast Cancer Research and Treatment, 135*, 281–289. https://doi.org/10.1007/s10549-012-2176-4

Brant, J.M., Beck, S., & Miaskowski, C. (2010). Building dynamic models and theories to advance the science of symptom management research. *Journal of Advanced Nursing, 66*, 228–240. https://doi.org/10.1111/j.1365-2648.2009.05179.x

Cheung, W.Y., Le, L.W., Gagliese, L., & Zimmermann, C. (2011). Age and gender differences in symptom intensity and symptom clusters among patients with metastatic cancer. *Supportive Care in Cancer, 19*, 417–423. https://doi.org/10.1007/s00520-010-0865-2

Chow, E., Fan, G., Hadi, S., Wong, J., Kirou-Mauro, A., & Filipczak, L. (2008). Symptom clusters in cancer patients with brain metastases. *Clinical Oncology, 20*, 76–82. https://doi.org/10.1016/j.clon.2007.09.007

Combs, S.E., Adeberg, S., Dittmar, J.O., Welzel, T., Rieken, S., Habermehl, D., . . . Debus, J. (2013). Skull base meningiomas: Long-term results and patient self-reported outcome in 507 patients treated with fractionated stereotactic radiotherapy (FSRT) or intensity modulated radiotherapy (IMRT). *Radiotherapy and Oncology, 106*, 186–191. https://doi.org/10.1016/j.radonc.2012.07.008

Daskivich, T.J., Chamie, K., Kwan, L., Labo, J., Palvolgyi, R., Dash, A., . . . Litwin, M.S. (2011). Overtreatment of men with low-risk prostate cancer and significant comorbidity. *Cancer, 117*, 2058–2066. https://doi.org/10.1002/cncr.25751

Dodd, M.J., Miaskowski, C., & Lee, K.A. (2004). Occurrence of symptom clusters. *Journal of the National Cancer Institute. Monographs, 32*, 76–78. https://doi.org/10.1093/jncimonographs/lgh008

Dodd, M.J., Miaskowski, C., & Paul, S.M. (2001). Symptom clusters and their effect on the functional status of patients with cancer. *Oncology Nursing Forum, 28*, 465–470.

Dong, S.T., Costa, D.S., Butow, P.N., Lovell, M.R., Agar, M., Velikova, G., . . . Fayers, P.M. (2016). Symptom clusters in advanced cancer patients: An empirical comparison of statistical methods and the impact on quality of life. *Journal of Pain and Symptom Management, 51*, 88–98. https://doi.org/10.1016/j.jpainsymman.2015.07.013

Durand, T., Bernier, M.O., Léger, I., Taillia, H., Noël, G., Psimaras, D., & Ricard, D. (2015). Cognitive outcome after radiotherapy in brain tumor. *Current Opinion in Oncology, 27*, 510–515. https://doi.org/10.1097/cco.0000000000000227

Durante, M., & Loeffler, J.S. (2010). Charged particles in radiation oncology. *Nature Reviews. Clinical Oncology, 7*, 37–43. https://doi.org/10.1038/nrclinonc.2009.183

Fox, S.W., Lyon, D., & Farace, E. (2007). Symptom clusters in patients with high-grade glioma. *Journal of Nursing Scholarship, 39*, 61–67.

Gijsen, R., Hoeymans, N., Schellevis, F.G., Ruwaard, D., Satariano, W.A., & van den Bos, G.A.M. (2001). Causes and consequences of comorbidity: A review. *Journal of Clinical Epidemiology, 54*, 661–674. https://doi.org/10.1016/S0895-4356(00)00363-2

Giovagnoli, A.R., Meneses, R.F., Silvani, A., Milanesi, I., Fariselli, L., Salmaggi, A., & Boiardi, A. (2014). Quality of life and brain tumors: What beyond the clinical burden? *Journal of Neurology, 261*, 894–904. https://doi.org/10.1007/s00415-014-7273-3

Gleason, J.F., Jr., Case, D., Rapp, S.R., Ip, E., Naughton, M., Butler, J.M., Jr., . . . Shaw, E.G. (2007). Symptom clusters in patients with newly-diagnosed brain tumors. *Journal of Supportive Oncology, 5*, 427–433, 436.

Glimelius, B., Ask, A., Bjelkengren, G., Björk-Eriksson, T., Blomquist, E., Johansson, B., . . . Zackrisson, B. (2005). Number of patients potentially eligible for proton therapy. *Acta Oncologica, 44*, 836–849. https://doi.org/10.1080/02841860500361049

Hirschl, M. (1988). Report of experience with stomach-protective therapy in high-dosage corticosteroid treatment of patients with brain tumors [Article in German]. *Wiener Medizinische Wochenschrift, 138*(5), 97-101.

Jakobsson, S., Ekman, T., & Ahlberg, K. (2015). Living through pelvic radiotherapy: A mixed method study of self-care activities and distressful symptoms. *European Journal of Oncology Nursing, 19*, 301–309. https://doi.org/10.1016/j.ejon.2014.10.014

Karlsson, M., Björk-Eriksson, T., Mattsson, O., Mattsson, S., Montelius, A., Nilsson, P., & Zackrisson, B. (2006). "Distributed proton radiation therapy"—A new concept for advanced competence support. *Acta Oncologica, 45*, 1094–1101. https://doi.org/10.1080/02841860600897876

Khan, L., Cramarossa, G., Lemke, M., Nguyen, J., Zhang, L., Chen, E., & Chow, E. (2013). Symptom clusters using the Spitzer

quality of life index in patients with brain metastases—A reanalysis comparing different statistical methods. *Supportive Care in Cancer, 21*, 467–473. https://doi.org/10.1007/s00520-012-1540-6

Kim, H.-J., McGuire, D.B., Tulman, L., & Barsevick, A.M. (2005). Symptom clusters: Concept analysis and clinical implications for cancer nursing. *Cancer Nursing, 28*, 270–282.

Kim, S.H., & Byun, Y. (2018). Trajectories of symptom clusters, performance status, and quality of life during concurrent chemoradiotherapy in patients with high-grade brain cancers. *Cancer Nursing, 41*, E38–E47. https://doi.org/10.1097/NCC.0000000000000435

Langegård, U., Ahlberg, K., Björk-Eriksson, T., Fransson, P., Johansson, B., Ohlsson-Nevo, E., . . . Sjövall, K. (2019). The art of living with symptoms: A qualitative study in patients with primary brain tumors receiving proton beam therapy. *Cancer Nursing*. Advance online publication. https://doi.org/10.1097/NCC.0000000000000692

Langegård, U., Ahlberg, K., Fransson, P., Johansson, B., Sjövall, K., Björk-Eriksson, T., & Ohlsson-Nevo, E. (2018). Evaluation of quality of care in relation to health-related quality of life of patients diagnosed with brain tumor: A novel clinic for proton beam therapy. *Supportive Care in Cancer*. Advance online publication. https://doi.org/10.1007/s00520-018-4557-7

Lemanska, A., Chen, T., Dearnaley, D.P., Jena, R., Sydes, M.R., & Faithfull, S. (2017). Symptom clusters for revising scale membership in the analysis of prostate cancer patient reported outcome measures: A secondary data analysis of the Medical Research Council RT01 trial (ISCRTN47772397). *Quality of Life Research, 26*, 2103–2116. https://doi.org/10.1007/s11136-017-1548-y

Lenz, E.R., Pugh, L.C., Milligan, R.A., Gift, A., & Suppe, F. (1997). The middle-range theory of unpleasant symptoms: An update. *Advances in Nursing Science, 19*(3), 14–27.

Levin, V.A., Leibel, S.A., & Gutin, P.H. (2001). Neoplasms of the central nervous system. In V.T. DeVita Jr., & S. Hellman (Eds.), *Cancer: Principles and practice of oncology* (6th ed., pp. 2100–2160). Philadelphia, PA: Lippincott Williams and Wilkins.

Li, J., Bentzen, S.M., Li, J., Renschler, M., & Mehta, M.P. (2008). Relationship between neurocognitive function and quality of life after whole-brain radiotherapy in patients with brain metastasis. *International Journal of Radiation Oncology, Biology, Physics, 71*, 64–70. https://doi.org/10.1016/j.ijrobp.2007.09.059

Mao, J.J., Armstrong, K., Bowman, M.A., Xie, S.X., Kadakia, R., & Farrar, J.T. (2007). Symptom burden among cancer survivors: Impact of age and comorbidity. *Journal of the American Board of Family Medicine, 20*, 434–443. https://doi.org/10.3122/jabfm.2007.05.060225

Maquilan, G., Grover, S., Alonso-Basanta, M., & Lustig, R.A. (2014). Acute toxicity profile of patients with low-grade gliomas and meningiomas receiving proton therapy. *American Journal of Clinical Oncology, 37*, 438–443. https://doi.org/10.1097/COC.0b013e31827de86b

McNeish, D. (2017). Exploratory factor analysis with small samples and missing data. *Journal of Personality Assessment, 99*, 637–652. https://doi.org/10.1080/00223891.2016.1252382

Meyers, C.A., Weitzner, M.A., Valentine, A.D., & Levin, V.A. (1998). Methylphenidate therapy improves cognition, mood, and function of brain tumor patients. *Journal of Clinical Oncology, 16*, 2522–2527. https://doi.org/10.1200/jco.1998.16.7.2522

Miaskowski, C., Dodd, M., & Lee, K. (2004). Symptom clusters: The new frontier in symptom management research. *Journal of the National Cancer Institute. Monographs, 32*, 17–21. https://doi.org/10.1093/jncimonographs/lgh023

National Board of Health and Welfare. (2017). Statistical database: Cancer. Retrieved from https://www.socialstyrelsen.se/statistics/statisticaldatabase/cancer

Osoba, D., Brada, M., Prados, M.D., & Yung, W.K. (2000). Effect of disease burden on health-related quality of life in patients with malignant gliomas. *Neuro-Oncology, 2*, 221–228. https://doi.org/10.1093/neuonc/2.4.221

Pelletier, G., Verhoef, M.J., Khatri, N., & Hagen, N. (2002). Quality of life in brain tumor patients: The relative contributions of depression, fatigue, emotional distress, and existential issues. *Journal of Neuro-Oncology, 57*, 41–49.

Reeve, B.B., Mitchell, S.A., Dueck, A.C., Basch, E., Cella, D., Reilly, C.M., . . . Bruner, D.W. (2014). Recommended patient-reported core set of symptoms to measure in adult cancer treatment trials. *Journal of the National Cancer Institute, 106*(7), dju129. https://doi.org/10.1093/jnci/dju129

Sangha, O., Stucki, G., Liang, M.H., Fossel, A.H., & Katz, J.N. (2003). The self-administered comorbidity questionnaire: A new method to assess comorbidity for clinical and health services research. *Arthritis and Rheumatism, 49*, 156–163. https://doi.org/10.1002/art.10993

Schulz-Ertner, D., & Tsujii, H. (2007). Particle radiation therapy using proton and heavier ion beams. *Journal of Clinical Oncology, 25*, 953–964. https://doi.org/10.1200/jco.2006.09.7816

Scoccianti, S., Detti, B., Cipressi, S., Iannalfi, A., Franzese, C., & Biti, G. (2012). Changes in neurocognitive functioning and quality of life in adult patients with brain tumors treated with radiotherapy. *Journal of Neuro-Oncology, 108*, 291–308. https://doi.org/10.1007/s11060-012-0821-8

Søgaard, M., Thomsen, R.W., Bossen, K.S., Sørensen, H.T., & Nørgaard, M. (2013). The impact of comorbidity on cancer survival: A review. *Clinical Epidemiology, 5*(Suppl. 1), 3–29. https://doi.org/10.2147/CLEP.S47150

Tallet, A.V., Azria, D., Barlesi, F., Spano, J.P., Carpentier, A.F., Gonçalves, A., & Metellus, P. (2012). Neurocognitive function impairment after whole brain radiotherapy for brain metastases: Actual assessment. *Radiation Oncology, 7*, 77. https://doi.org/10.1186/1748-717x-7-77

Thompson, B. (2004). *Exploratory and confirmatory factor analysis:*

Understanding concepts and applications. Washington, DC: American Psychological Association.

Tucha, O., Smely, C., Preier, M., & Lange, K.W. (2000). Cognitive deficits before treatment among patients with brain tumors. *Neurosurgery, 47*, 324–334. https://doi.org/10.1097/00006123-200008000-00011

Twisk, J., & de Vente, W. (2002). Attrition in longitudinal studies: How to deal with missing data. *Journal of Clinical Epidemiology, 55*, 329–337.

Uppsala University. (2015). Proton radiotherapy for primary central nerous system tumours in adults (PRO-CNS). Retrieved from https://clinicaltrials.gov/ct2/show/NCT02797366

Valeberg, B.T., & Grov, E.K. (2013). Symptoms in the cancer patient: Of importance for their caregivers' quality of life and mental health? *European Journal of Oncology Nursing, 17*, 46–51. https://doi.org/10.1016/j.ejon.2012.01.009

Wen, P.Y., & Kesari, S. (2008). Malignant gliomas in adults. *New England Journal of Medicine, 359*, 492–507. https://doi.org/10.1056/NEJMra0708126

Wengstrom, Y., Haggmark, C., Strander, H., & Forsberg, C. (2000). Perceived symptoms and quality of life in women with breast cancer receiving radiation therapy. *European Journal of Oncology Nursing, 4*, 78–88. https://doi.org/10.1054/ejon.1999.0052

Wilde, B., Starrin, B., Larsson, G., & Larsson, M. (1993). Quality of care from a patient perspective—A grounded theory study. *Scandanavian Journal of Caring Sciences, 7*, 113–120.

Xiao, C. (2010). The state of science in the study of cancer symptom clusters. *European Journal of Oncology Nursing, 14*, 417–434. https://doi.org/10.1016/j.ejon.2010.05.011

Yuh, G.E., Loredo, L.N., Yonemoto, L.T., Bush, D.A., Shahnazi, K., Preston, W., . . . Slater, J.D. (2004). Reducing toxicity from craniospinal irradiation: Using proton beams to treat medulloblastoma in young children. *Cancer Journal, 10*, 386–390.