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# Symptom clusters in patients with head and neck cancer receiving concurrent chemoradiotherapy

**Canhua Xiao**[a,*], **Alexandra Hanlon**[b], **Qiang Zhang**[c], **Kian Ang**[d], **David I. Rosenthal**[d], **P. Felix Nguyen-Tan**[e], **Harold Kim**[f], **Benjamin Movsas**[g], and **Deborah Watkins Bruner**[a]

[a]Emory University School of Nursing, 1520 Clifton Road NE, Atlanta, GA 30322, USA

[b]University of Pennsylvania School of Nursing, Claire M. Fagin Hall, 418 Curie Boulevard, Philadelphia, PA 19104, USA

[c]RTOG Statistical Center, RTOG Headquarters, 1818 Market St., Suite 1600, Philadelphia, PA 19103, USA

[d]University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA

[e]Centre Hospitalier de l'Université de Montréal (CHUM), 3840 St. Urbain St., Montréal, QC, Canada H2W 1T8

[f]Wayne State University Karmanos Cancer Institute, 4100 John R, Detroit, MI 48201, USA

[g]Department of Radiation Oncology, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI 48202, USA

## SUMMARY

**Objectives—**This study is to identify symptom clusters for head and neck (HNC) patients treated with con-current chemoradiotherapy.

**Patients and methods—**A secondary data analysis of 684 HNC patients treated on the Radiation Therapy Oncology Group (RTOG) 0129 trial comparing different RT fractionation schedules with concurrent chemotherapy was used to examine clusters. Treatment-related symptoms were measured by clinicians at three time-points during and after chemoradiotherapy using the National Cancer Institute Common Toxicity Criteria v2.0. Exploratory factor analysis was applied to identify symptom clusters, which was further verified by confirmatory factor analysis. Coefficients of congruence and alpha coefficients were employed to examine generalizability of cluster structures over different time-points and in different subgroups.

**Results—**Two clusters were identified. The HNC specific cluster is composed of radiodermatitis, dysphagia, radiomucositis, dry mouth, pain, taste disturbance, and fatigue. The gastrointestinal (GI) cluster involves nausea, vomiting, and dehydration. With the exception of patients 65 years old or older, diagnosed with larynx cancer, or with stage III cancer, the two clusters were generalizable to different subgroups defined by age, gender, race, education, marital status, history of tobacco use, treatments, primary sites, disease stages, and tube feedings, as well as to the three symptom assessment time-points.

**Conclusions—**The data provides preliminary support for two stable clusters in patients with HNC. These findings may serve to inform the symptom management in clinical practice.

[*]Corresponding author. Tel.: +1 404 712 9823; fax: +1 404 727 9382. Canhua.xiao@emory.edu (C. Xiao).

Conflict of interest statement
None declared.

Moreover, the findings necessitate future research to examine the generalizability of identified clusters in the late symptom phase or other treatment modalities, and to understand the underlying biological mechanism.

### Keywords

Head and neck neoplasms; Chemoradiotherapy; Symptom clusters; Symptoms

## Introduction

Radiotherapy (RT) is the major effective treatment for patients with head and neck cancer (HNC); however, these patients often experience multiple symptoms induced by radiation.[1] The wide use of concurrent chemotherapy worsen these symptoms by interfering with the DNA, RNA, or protein synthesis in related areas.[2] These treatment-related symptoms, such as mucositis, dry mouth, and swallowing problem, have detrimental influence on patients' quality of life.[3] In addition, side effect-induced treatment breaks and dose reductions decrease rates of locoregional tumor control and survival.[4] Substantial increases in cost of care have also been associated with radiation-related symptoms.[5] While symptoms experienced by HNC patients who undergo RT have been a major concern for research over the past decades, the focus has primarily been on listing symptom prevalence or on single symptoms, rather than on symptom clusters.

The concept of symptom clusters has been proposed as a new direction for future research to understand better the complexity of the multiple symptoms experienced by cancer patients. Symptom clusters are defined as groups of at least two or three concurrent symptoms that are related to each other.[6,7] Symptom clusters have a more negative impact on patient's quality of life than single symptoms because of the synergistic effect of multiple symptoms.[8] Additionally, if symptom clusters are identified, it is possible that by treating the first presenting or the most influential symptom the cascade of symptoms may be prevented. Although the number of studies focusing on cancer symptom clusters has been significantly increased since the first paper was published in 2001,[9] there are no studies investigating symptom clusters in patients with HNC.

The purpose of this study is to identify symptom clusters and to examine the generalizability of the identified symptom clusters over different time-points and in different subgroups for patients with HNC receiving concurrent chemoRT. A longitudinal database from the Radiation Therapy Oncology Group (RTOG) 0129 clinical trial was used to investigate clusters. RTOG is a multi-institutional, international clinical cooperative group funded primarily by the National Cancer Institute (NCI). The current study used a clinician-observed toxicity data for symptom cluster identification, and is the first part of our study; in the future, a further comparison between clinician-observed symptom clusters and patient-reported symptom clusters will be presented.

## Patients and methods

### Study design

The current study is an institutional review board approved secondary data analysis of the RTOG 0129, a phase III randomized trial comparing the efficacy of the combination of accelerated fractionation radiotherapy (AFRT) with cisplatin to that of standard fractionation radiotherapy (SFRT) with cisplatin in the management of patients with HNC. Patients in the AFRT arm received 72 Gy in 42 fractions for 6 weeks, plus cisplatin: 100 mg/m$^2$ on days 1 and 22. Patients in the SFRT arm received 70 Gy in 35 fractions for 7 weeks, plus concurrent cisplatin: 100 mg/m$^2$ on days 1, 22, and 43.

## Sample and setting

The subjects in RTOG 0129 were patients ($N$ = 721) with HNC from 95 institutes at both US and Canadian. The major eligibility criteria included: histological proof of squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx; selected stage III–IV disease (T2N2-3M0, T3-4 any N M0); Zubrod Performance Status of 0–1; ≥ 8 years of age; having adequate bone marrow, kidney, and heart function; patients with previous invasive malignancies but remaining disease free for >3 years. The main exclusion criteria were: evidence of metastases; prior chemotherapy, RT, or initial surgical treatment to the head and neck region; patients with simultaneous primaries; and pregnant women. Further inclusion criteria for this proposed study were: patients having symptom assessment within at least one of the three time points (99% patients had at least two time points), and receiving at least 90% of protocol radiation dose of 71 Gy (the average of 72 Gy in AFRT and 70 Gy in SFRT). Patients who did not receive any cycle of chemotherapy were excluded from this study.

## Measurements

RT-related symptoms were assessed at Time 1 (the end of the first cycle of chemotherapy), Time 2 (the end of second cycle of chemotherapy), and Time 3 (three months after the start of RT) by clinicians using NCI Common Toxicity Criteria (CTC) 2.0. The severity of toxicities in the CTC 2.0 was graded from 1 through 4 or 5, with 1 meaning minimal AEs, 4 representing maximum AEs, and grade 5 representing death when appropriate. The focus of this study was on symptoms, and symptoms are defined as subjective phenomena that reflect changes in normal functioning as experienced by patients (Hegyvary, 1993). Therefore, adverse events without a subjective component, including blood creatinine, hemoglobin, hyponatremia, leukopenia, neutropenia, and along with others, were excluded from data analysis. Once the CTC items that fit the designated definition of symptoms were identified, only symptoms with more than 10% average prevalence across the three time points were chosen for examination. Rationale for the prevalence cut-off is that symptoms with lower prevalence are most likely not the key symptoms, and they are not stable for symptom cluster identification. Twelve symptoms met the criteria for inclusion in data analysis: dehydration, dry mouth, dysphagia, esophagitis, fatigue, nausea, pain, radiodermatitis, radiomucositis, taste disturbance, vomiting, and weight loss.

## Data analysis

**Statistical methods for research question one—**Common factor analysis with principal axis factoring was applied for 50% randomly selected sample (342 out of a total of 684 patients). In order to construct a set of symptom clusters that may be uniformly applicable during treatment and that may be generalizable across relevant demographic and clinical groups, a pooled data set combining data across three time points was created. The symptom score in the pooled data set was the average CTC score for each symptom across three time points. The average scores for all symptoms were then submitted to common factor analysis to determine a latent factor (cluster) structure.

The methods of determining the number of factors (clusters) involved included: Bartlett's chi-square criteria,[10] parallel analysis,[11] and Minimum Average Partial test (MAP test).[12] Because Bartlett's chi-square criteria and parallel analysis might overestimate the number of factors,[13] both methods were applied to suggest the potential upper bound limit of the number of factors. As the MAP test has a tendency of underestimating the number of factors,[13] this method was used to decide the possible lower bound limit of the number of clusters. The final number of clusters was confirmed by the simple structure of factor models and clinical meaningfulness.

Each model was evaluated for its ability to produce a simple structure that: (a) retained three or more symptoms that had eigenvalues equal to or greater than 0.40[14,15]; (b) produced internal consistency with alpha coefficients equal to or more than 0.7; (c) had the highest hyperplane count;[16] (d) obtained a parsimonious coverage (mutually exclusive assignment of symptoms to clusters, and maximum number of symptoms retained); and (e) made clinical and theoretical sense as determined by expert review.[17]

To confirm the most robust symptom cluster structure, the structural model from the final exploratory solution was submitted to confirmatory factor analysis (CFA) via Mplus 6.1 for the remaining 50% of the sample that was not used in exploratory factor analysis (EFA). The Comparative Fit Index (CFI), Root-Mean-Square Error of Approximation (RMSEA), and Standardized Root Mean Square Residual (SRMR) were applied to assess the extent to which the model fit the data.[15] Furthermore, the model invariance was tested by conducting the same common factor analysis for each of 12 subsamples randomly selected from the complete data set (i.e., subsample $N = 342$, representing six pairs of mutually exclusive halves of the complete sample). Congruence of coefficients was used to assess the matching symptom cluster structures across the random subsamples and the complete sample.

Relationships between or among clusters were assessed through intercorrelations and variance partitioning of cluster scores. Cluster variance was partitioned by submitting the correlation matrix for the identified clusters to a higher-order common factor analysis to extract stable communality estimates, and there-after separate specific and error variance in each cluster. Because the higher-order common factor analysis uses symptom cluster scores instead of individual symptom scores, symptom cluster scores for each subject were computed. The derived cluster scores were based on standardized unit weighting[18] of symptom scores within each cluster. Raw cluster scores were transformed by area conversion[19] to T scores (*Mean* = 50, *SD* = 10).

**Statistical methods for research question two—**As a method to ensure that the cluster structures are generalizable to important subgroups, the common factor analysis was repeated for pertinent subsamples. Generalizability was examined by repeating the analysis at each symptom assessment time point, and for subsamples defined by: age (<65 years and ≥ 65 years), gender (males and females), race (White and non-White), education (≤12 years and >12 years), marital status (married and unmarried), a history of tobacco use (no and yes), treatment arm (SFRT and AFRT), cancer site (non-larynx and larynx), cancer stage (stage III and stage IV), and tube feeding (no and yes). Coefficients of congruence based on correlations among unit-weighted cluster scores across pooled data and pertinent subsamples were used to compare the solution derived for each analysis to that for the pooled data.[20] Additionally, the coefficient alpha (Cronbach's alpha) was calculated for each subsample mentioned above to examine the internal consistency.

## Results

### Demographic and clinical characteristics

The sample size available for the proposed study included 684 patients, which was ample for reliable estimates in EFA,[21] the major statistical method used in this study. The demographic and clinical characteristics of the participants in the original sample (RTOG 0129) and the final sample (in this study) are shown in Table 1. With the exception of radiation dose, the differences between the two datasets' demographic and clinical characteristics were not significant.

### Research question 1: symptom clusters identified in the targeted population

A two-cluster promax ($k = 2$) model satisfied all of the stated criteria and, thus, was retained. The two clusters were defined based on their component symptoms: the HNC specific cluster (Cluster 1) and the gastrointestinal (GI) cluster (Cluster 2). The HNC specific cluster was composed of radiodermatitis, dysphagia, pain, taste disturbance, fatigue, radiomucositis, and dry mouth. The GI cluster involved nausea, vomiting, and dehydration (see Table 2). The Cronbach's alphas were 0.70 for the HNC specific cluster and 0.74 for the GI cluster. Moreover, model invariance, with an average value of 99.57 and 99.29 for the two clusters respectively, clearly showed that the two-cluster structure remained stable over random replications. Additionally, the results from CFA confirmed the final two-cluster structure, with CFI = 0.90, RMSEA = 0.07, and SRMR = 0.06.[22]

Further support for the interpretability of the two cluster solution was produced through variance components analysis (see Table 3). The correlation coefficient between the two clusters was low (0.28), demonstrating the unique interpretation of each cluster. The results from variance components analysis further demonstrated this distinctive attribution: about half of the variance (44% for the HNC specific cluster, and 49% for the GI cluster), which was also greater than that attributable to error variance, remained both unique and reliable for interpretation.

### Research question 2: generalizability of identified symptom clusters

Both congruence of coefficients and alpha coefficients verify that the two-cluster structure is generalizable across most of the subgroups tested, with the exception of patients 65 years of age or older or those with larynx cancer or in cancer stage III. The average congruence coefficients ranged from 87.96 to 99.91, with the majority above 96 (see Tables 4.1 and 4.2), which means almost identical cluster structure matching.[23] The average alpha coefficients varied from 0.60 to 0.79, with most higher than 0.70 (see Tables 5.1 and 5.2), demonstrating adequate internal consistency.

The lowest congruence coefficients for similarity (89.98 for Cluster 1, and 88.38 for Cluster 2) were from patients 65 years or older. In comparison with the full sample, the symptoms of taste disturbance and fatigue were dropped from the HNC specific cluster in patients 65 years or older. In addition, the symptoms of fatigue and weight loss fit better within the GI cluster for this subgroup.

The two lowest alpha coefficients were 0.60 and 0.64, which were generated from the HNC specific cluster for patients diagnosed with larynx cancer and those with stage III disease. For patients diagnosed with larynx cancer, three symptoms, dysphagia, fatigue, and radiomucositis, dropped out of the HNC specific cluster, while symptoms in the GI cluster stayed the same. This changed cluster structure in the HNC specific cluster was mirrored in patients with stage III cancer, but weight loss joined the GI cluster for those with stage III disease.

## Discussion

This is the first study exploring symptom clusters in patients diagnosed with HNC. Two distinct and stable clusters, the HNC specific cluster and the GI cluster, were identified through factor modeling among 10 identified treatment-related symptoms. The cluster structure was verified by CFA in half of the randomly assigned sample and by the model invariance test in 12 random replications. Moreover, the amount of variation uniquely associated with each cluster was substantial, and thus, further supported the reliable nature of the two symptom clusters identified.

### The HNC specific cluster

The HNC specific cluster is composed of five very specific treatment- related symptoms: radiodermatitis, dysphagia, radiomucositis, dry mouth, and taste disturbance, and two relatively general symptoms: fatigue and pain. Because this is the first symptom cluster study on patients with HNC, no previous evidence could be compared with this HNC specific cluster. However, the interrelationship among symptoms in the HNC specific cluster could be partly supported by previous investigations. For instance, mucositis has been associated with symptoms of pain, dysphagia, and taste disturbance[24–26]; xerostomia has been related to dysphagia,[27] and taste disturbance.[28] Although a direct relationship between mucositis and xerostomia has not been identified, both are connected to dysphagia.[24,28] Results from these clinical studies might be further supported by research on pathophysiological pathways that may explain associations among symptoms. For example, the inflammatory reactions caused by RT lead to mucositis, pain, and xerostomia.[29] These acute side effects, along with long-term fibrotic changes, contribute to dysphagia.[4] In addition, as a general symptom, fatigue is correlated with pain,[30] taste disturbance,[31] and dry mouth[32] in a variety of cancer populations. While evidence appears to support the clinical identification of a HNC specific cluster, the underlying bio-mechanisms that link symptoms in this cluster require further research.

It is also interesting to notice that the HNC specific cluster includes both acute (radiomucositis) and chronic (xerostomia) symptoms induced from the treatment. This finding supports the merging of treatment related acute and late symptoms, the determination of which previously used arbitrary “90-day rule”, into a single uniform system as proposed by NCI. This uniform symptom assessment system has been used for all new versions of CTC, renamed as Common Terminology Criteria for Adverse Events (CTCAE), including 3.0 and 4.0.[33] The concept under this merging is that the current usage of complex multimodality produces augmented and inherent long-term treatment related symptoms,[33] and this concept has been further supported by a biological paradigm viewing acute and late tissue injure as a continuum of response.[34] In our study, dysphagia, which can be both acute (from pain during treatment) and chronic (from fibrosis of the swallowing musculature), is grouped together with other acute or late symptoms, such as radiomucositis and xerostomia. This cluster observation appears more accurate to reflect patients’ true symptom experience than classical (“90-day rule”) acute and late symptom phases. As suggested by the new CTCAE, a more individual and comprehensive symptom assessment system would be necessary for the current multimodality and intensive treatment plans.

### The GI cluster

A stable GI cluster identified in the current study includes nausea, vomiting, and dehydration. Although there is no previously published data in patients with HNC documenting the GI cluster, research on other cancer populations has provided strong support for this cluster. Nausea and vomiting have been consistently grouped together, regardless of cancer population, symptom measurement tools, or statistical methods in different studies.[35–37] As the effects of nausea and vomiting may result in dehydration,[38] the establishment of the GI cluster appears clinically plausible.

### Generalizability of identified symptom clusters

The results from both the congruence coefficients and the alpha coefficients supported the validity and reliability of the identified two cluster structures. The findings also demonstrate that the two clusters were generalizable over subgroups of patients including those: less than 65 years old, male, female, White, Non-white, receiving education less than or equal to 12 years, receiving education more than 12 years, married, unmarried, and with a history of tobacco use. Moreover, the two cluster structures were also generalizable to the three

symptom measurement time points and subgroups of patients defined by clinical characteristics: receiving SFRT, receiving AFRT, non-larynx cancer, stage IV, and use of tube feedings. However, the two clusters may not be as stable in patients 65 years old or older, diagnosed with larynx cancer, or those with stage III disease.

### Patients 65 years old or greater

Taste disturbance and fatigue dropped from the HNC specific cluster, while weight loss and fatigue joined into the GI cluster. The reasons for this variation may be different for all involved symptoms. For instance, it is well documented that elderly patients tend to have elevated taste thresholds (hypogeusia).[39] Accordingly, elderly patients might notice treatment- induced changes in taste later or less intensely, and taste disturbance is therefore not involved in the clusters for elderly patients. The reason for fatigue dropping out of the HNC specific cluster, but loading on the GI cluster for patients age 65 or older, is still uncertain.[40] The fact that weight loss was grouped into the GI cluster for the elderly patients has been supported in part by previous evidence: the elderly is more likely to have a loss in muscle and bone mass.[35,41] Meanwhile, a high correlation between weight loss and dehydration, one of the symptoms in GI cluster, among elderly patients in this study may further contribute to the involvement of weight loss in the GI cluster for the elderly. In summary, the elderly may be at higher risk for weight loss when they are experiencing treatment-related nausea, vomiting, and dehydration.

### Patients with larynx cancer

Cluster structures for patients with larynx cancer showed that mucositis, dysphagia, and fatigue were dropped from this cluster. The dropping of mucositis may be controversial. While at least one study found that patients with larynx cancer have lower severity of mucositis, compared to patients with non-larynx cancer,[24] other researchers have found no differences in risk, severity, or course of mucositis between patients with larynx cancers and those with non-larynx cancer.[25,42] One potential explanation for discrepancies in the effects of tumor/treatment site on mucositis may be the different symptom assessment measures used in these studies. In the current study and previous studies that showed differences in mucositis by tumor site, mucositis was assessed using clinician-reported measures. In contrast, the studies showing no difference by tumor sites used patient self-reported symptom assessment tools. Elting and colleagues[42] pointed out that it might be harder for clinicians to observe mucosa of the hypopharynx and/or larynx in a standard clinical examination, which may lead to the underestimation. As the true reason under this discrepancy is unknown, further research is still necessary.

The reason for dysphagia dropping from the HNC specific cluster among patients with larynx cancer is also uncertain. Further data analysis did not show significant difference on the average dysphagia severity score across three time points between patients with larynx cancer and those with non-larynx cancer. However, a statistically significant difference was found at Time 3: patients with larynx cancer had lower severity scores for dysphagia than patients with non-larynx cancer. Past studies also showed that patients with larynx cancer had better eating scores compared to patients with cancers of other head and neck sites.[43] It is possible that the relative lower dysphagia severity score at Time 3 contributes to the dropping of dysphagia from the HNC specific cluster.

As previous data have shown that mucositis and dysphagia are related to each other[24–26] and have lower severity levels in patients with larynx cancer,[24,43] thus, their dropping off together from the HNC specific cluster for this population does not surprising. This consistent multiple symptom experience pattern may indicate different symptom assessment strategies for clinicians. When evaluating patients without larynx cancer, clinicians could

expect more of these two symptoms than they evaluating those with larynx cancer. Nonetheless, this is only from clinician's symptom assessment viewpoints. Given the potential that patients' evaluation may differ from clinicians',[44] clinician should interpret the results with caution.

### Patients with stage III cancer

The symptom cluster structures from the full sample are not well generalizable to patients with stage III cancer. Cluster structures in patients with stage III cancer displayed very similar structure changes to those from patients with larynx cancer. Further analysis showed that patients with stage III cancer were significantly more likely to have larynx cancer than patients in cancer stage IV: 53% patients with stage III disease were diagnosed as larynx cancer, while only 18% patients in cancer stage IV had larynx caner ($\chi^2 = 74.23$, $p < 0.0001$). This high proportion of patients with larynx cancer having stage III disease might lead to the similarity of the cluster structures between the two subsamples, which further explains why the structures from patients with stage III cancer were different from the full sample.

### Limitations

Several limitations are imposed by using existing data in this study. One limitation is that there is no information about the management of the involved symptoms. Symptom management may change the natural course of these symptoms, which may lead to different symptom cluster structures. In addition, patients without records of certain symptoms were assumed as not having these symptoms in this study. It is not clear if these patients were those who truly did not have treatment-related symptoms, or those who were missing symptom measurements. The current study followed a standard RTOG reporting toxicity protocol using the CTC, and assumed that these patients did not have treatment-related symptoms if none were reported. Furthermore, symptom profiles at pretreatment are not available, which may produce biases. However, the symptoms analyzed are mainly treatment-related symptoms, which may not exist at pretreatment. Thus, the pretreatment symptom information may not have significant influence on the findings of this study.

### Conclusion

The study sought to identify symptom clusters for patients with HNC receiving concurrent chemoRT. The results from data analyses provide evidence of two stable clusters: the HNC specific cluster and the GI cluster. With the exception of patients 65 years old and older, those diagnosed with larynx cancer, and those with stage III cancer, the two clusters are generalizable to all different subgroups of patients, as well as to three symptom assessment time points. These findings will contribute to the assessment, prevention, and management of multiple symptoms. Furthermore, the findings warrant future exploration on the generalizability of the identified cluster structure to the late symptom phase, other treatment modalities, or other cancer populations, the underlying biological mechanism for identified clusters, and the comparison of clinician-observed clusters to patients-reported clusters.

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## Table 1

Demographic and clinical characteristics of the original and final samples.

| Variables | Original sample (*N* = 721) mean ± SD or *N* (%) | Final sample (*N* = 684) mean ± SD or *N* (%) |
|---|---|---|
| *Demographic characteristics* | | |
| Age (years) | 55.78 ± 8.84 | 55.70 ± 8.84 |
| *Gender* | | |
| Male | 597 (83) | 564 (83) |
| Female | 124 (17) | 120 (17) |
| *Race*[a] | | |
| White | 589 (82) | 558 (82) |
| Non-White | 130 (18) | 124 (18) |
| *Education*[a] | | |
| ≤12 years | 400 (63) | 379 (63) |
| >12 years | 231 (37) | 222 (37) |
| *Marital status*[a,b] | | |
| Married | 380 (56) | 361 (56) |
| Unmarried | 296 (44) | 283 (44) |
| *History of tobacco use*[a] | | |
| No | 113 (18) | 110 (18) |
| Yes | 525 (82) | 500 (82) |
| *Clinical characteristics* | | |
| Radiation dose (Gy) | **69.88 ± 8.43** | **71.24 ± 1.43** |
| *Treatment* | | |
| SFRT + cisplatin | 361 (50) | 349 (51) |
| AFRT + cisplatin | 360 (50) | 335 (49) |
| *Primary cancer site* | | |
| Non-larynx | 533 (74) | 508 (74) |
| Larynx | 188 (26) | 176 (26) |
| *Stage* | | |
| III | 158 (22) | 149 (22) |
| IV | 563 (78) | 535 (78) |
| *Tube feeding* | | |
| No | 553 (77) | 531 (77) |
| Yes | 168 (23) | 153 (23) |

SD = standard deviation, SFRT = standard fractionation radiotherapy, AFRT = Accelerated fractionation radiotherapy. Statistically significant differences are high-lighted in bold text.

[a]Having missing cases: Race (original sample: 2; final sample: 2); Education (original sample: 90; final sample: 83); Marital status (original sample: 45; final sample: 40); History of tobacco use (original sample: 83; final sample: 74).

[b]Married includes patients married or living as married; Unmarried includes patients single, separated, divorced, or widowed.

## Table 2

Exploratory and confirmatory structures of symptom clusters ($N$ = 684).

| Symptoms | Exploratory analysis N = 342 | | Confirmatory analysis $N$ = 342 | |
|---|---|---|---|---|
| | Cluster 1 loading | Cluster 2 loading | Cluster 1 loading | Cluster 2 loading |
| Radiodermatitis | 0.65 | | 0.62 | |
| Dysphagia | 0.51 | | 0.55 | |
| Pain | 0.50 | | 0.51 | |
| Taste disturbance | 0.47 | | 0.43 | |
| Fatigue | 0.47 | | 0.57 | |
| Radiomucositis | 0.46 | | 0.46 | |
| Dry mouth | 0.43 | | 0.51 | |
| Nausea | | 0.85 | | 0.92 |
| Vomiting | | 0.78 | | 0.78 |
| Dehydration | | 0.50 | | 0.50 |
| Esophagitis | | | | |
| Weight loss | | | | |

Entries are based on the descending order of the loading values.

## Table 3

Intercorrelations and variance components for identified symptom clusters ($N$ = 684).

| Cluster | Correlation[a] | Proportion of variance[b] | | |
|---|---|---|---|---|
| | Cluster 1 | Common | Specific | Error |
| Cluster 1 | | 0.27 | 0.44 | 0.29 |
| Cluster 2 | 0.28 | 0.27 | 0.49 | 0.24 |
| Average | | 0.27 | 0.47 | 0.26 |

[a] Intercorrelations are based on unit-weighted scores as derived through exploratory common factor analysis.

[b] Common variance for a cluster is expressed by final communality estimates derived in second-order common factoring. Specific variance indicates the proportion of variance that is both reliable and unique to a cluster, and is calculated by subtracting communality of a cluster from its reliability coefficient (alpha = 0.71 for cluster 1, and alpha = 0.76 for cluster 2). When the value of specific variance is larger than the value of variance explained by error (error variance = 1 − reliability coefficient), variance explained by a particular cluster is greater than that attributable to error. The sum of the proportion of variance for a cluster is equal to one.

**Table 4.1**

Generality of symptom cluster structures across demographic characteristics.

| **Cluster** | **Age < 65 (*N* = 586)** | **Age ≥ 65 (*N* = 98)** | **Male (*N* = 564)** | **Female (*N* = 120)** | **Whites (*N* = 558)** | **Non-White[a] (*N* = 124)** |
|---|---|---|---|---|---|---|
| Cluster 1 | 99.88 (17.06) | 89.98 (32.84) | 99.83 (21.02) | 97.21 (19.77) | 99.90 (19.64) | 96.83 (13.14) |
| Cluster 2 | 99.91 (17.02) | 88.38 (9.27) | 99.72 (17.05) | 98.29 (14.82) | 99.87 (16.14) | 98.25 (17.35) |
| Cluster | Education ≤ 12 years (*N* = 379) | Education > 12 years (*N* = 222) | Married[b] (*N* = 361) | Unmarried[b] (*N* = 283) | History of tobacco use: no (*N* = 110) | History of tobacco use: yes (*N* = 500) |
| Cluster 1 | 98.40 (20.54) | 97.63 (17.29) | 99.41 (22.19) | 99.65 (20.28) | 97.09 (26.26) | 99.55 (19.45) |
| Cluster 2 | 99.54 (16.03) | 97.87 (16.71) | 99.13 (14.60) | 99.58 (17.62) | 95.16 (19.61) | 99.86 (15.20) |

Entries are Wrigley–Neuhaus coefficients multiplied by 100 for convenient presentation. Nonparenthetical values represent similarity of the factors structures extracted from subsamples to complete samples. Parenthetical values indicate average similarity of the specific factor to all other factors extracted from subsamples.

[a]The subsample includes 109 Africa-American, and 15 other minority patients.

[b]Married is composed of patients married or living as married; Unmarried is patients single, separated, divorced, or widowed.

**Table 4.2**

Generality of symptom cluster structures for clinical characteristics.

| Cluster | Time 1 (*N* = 684) | Time 2 (*N* = 684) | Time 3 (*N* = 684) | SFRT (*N* = 349) | AFRT (*N* = 335) |
|---|---|---|---|---|---|
| Cluster 1 | 98.03 (18.83) | 99.41 (15.05) | 96.53 (21.37) | 99.88 (14.44) | 99.74 (21.65) |
| Cluster 2 | 99.48 (15.04) | 99.61 (17.38) | 98.51 (21.13) | 99.59 (18.10) | 99.49 (14.28) |

| Cluster | Non-larynx (*N* = 508) | Larynx (*N* = 176) | Stage III (*N* = 149) | Stage IV (*N* = 535) | Tube feeding: no (*N* = 531) | Tube feeding: yes (*N* = 153) |
|---|---|---|---|---|---|---|
| Cluster 1 | 99.78 (18.31) | 91.97 (41.86) | 90.37 (52.23) | 99.88 (13.24) | 99.70 (19.54) | 97.15 (13.17) |
| Cluster 2 | 99.63 (17.72) | 93.30 (7.91) | 87.96 (8.44) | 99.73 (17.06) | 99.43 (17.17) | 96.39 (21.67) |

Entries are Wrigley–Neuhaus coefficients multiplied by 100 for convenient presentation. Nonparenthetical values represent similarity of the factors structures extracted from subsamples to complete samples. Parenthetical values indicate average similarity of the specific factor to all other factors extracted from subsamples.

**Table 5.1**

Internal consistency of symptom cluster structures across demographic characteristics.

| **Cluster** | **Age < 65 (*N* = 586)** | **Age ≥ 65 (*N* = 98)** | **Male (*N* = 564)** | **Female (*N* = 120)** | **Whites (*N* = 558)** | **Non-white[a] (*N* = 124)** |
|---|---|---|---|---|---|---|
| Cluster 1 | 0.72 | 0.67 | 0.72 | 0.67 | 0.71 | 0.73 |
| Cluster 2 | 0.77 | 0.72 | 0.74 | 0.78 | 0.75 | 0.78 |
| Cluster | Education ≤ 12 years (*N* = 379) | Education > 12 years (*N* = 222) | Married[b] (*N* = 361) | Unmarried[b] (*N* = 283) | History of tobacco use: no (*N* = 110) | History of tobacco use: yes (*N* = 500) |
| Cluster 1 | 0.67 | 0.74 | 0.71 | 0.71 | 0.77 | 0.68 |
| Cluster 2 | 0.79 | 0.68 | 0.73 | 0.77 | 0.72 | 0.75 |

[a]The subsample includes 111 Africa-American, and 15 other minority patients.

[b]Married is composed of patients married or living as married; Unmarried is patients single, separated, divorced, or widowed.

**Table 5.2**

Internal consistency of symptom cluster structures for clinical characteristics.

| Cluster | Time 1 (*N* = 702) | Time 2 (*N* = 702) | Time 3 (*N* = 702) | SFRT (*N* = 349) | AFRT (*N* = 335) | Non-larynx (*N* = 508) | Larynx (*N* = 176) | Stage III (*N* = 149) | Stage IV (*N* = 535) | Tube feeding: no (*N* = 531) | Tube feeding: yes (*N* = 153) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cluster 1 | 0.68 | 0.70 | 0.66 | 0.75 | 0.67 | 0.74 | 0.60 | 0.64 | 0.73 | 0.70 | 0.75 |
| Cluster 2 | 0.73 | 0.71 | 0.75 | 0.76 | 0.75 | 0.76 | 0.73 | 0.69 | 0.77 | 0.75 | 0.76 |