



Change in symptom clusters in head and neck cancer patients undergoing postoperative radiotherapy: A longitudinal study

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ARTICLE INFO

Keywords:

Head and neck cancer
Radiotherapy
Symptom clusters
Longitudinal study

ABSTRACT

Purpose: Research on symptom clusters is a newly emerging field in oncology; however, little evidence regarding symptom clusters in head and neck cancer (HNC) is currently available. To clarify this under-researched area, we investigated symptom clusters among patients with HNC treated with surgery and postoperative radiotherapy. We also examined the pattern of symptom clusters throughout the treatment course.

Method: A convenience sample of 100 patients with HNC was recruited in the Ear, Nose, and Throat unit of a medical center in Taiwan. Before undergoing postoperative radiotherapy, patients were asked to complete the MD Anderson Symptom Inventory and a demographic sheet. Patients completed the same inventory questionnaire at week 1, 2, 3, 4, 5, and 6 of radiotherapy.

Result: Two symptom clusters were observed, and they were stable throughout the course of radiotherapy. Cluster 1, the HNC-specific cluster, comprised the symptoms of pain, dry mouth, lack of appetite, sleep disturbance, fatigue, drowsiness, distress, and sadness. Cluster 2, the gastrointestinal cluster, included nausea, vomiting, numbness, shortness of breath, and difficulty remembering.

Conclusion: This study advanced our knowledge of symptom clusters in patients with HNC. The results are expected to contribute to the development of appropriate assessment and nursing interventions targeting multiple symptoms that may coexist in postoperative radiotherapy.

This study is registered at [ClinicalTrials.gov](https://clinicaltrials.gov); ID: NCT03356093.

1. Introduction

Head and neck cancer (HNC) is the sixth most common malignancy worldwide (Heroiu Cataloiu et al., 2013) and caused more than 379,000 deaths in 2015 despite breakthroughs in cancer screening and treatment (Global Burden of Disease Study 2015 Mortality and Causes of Death Collaborators, 2016). Compared with other malignant tumors, HNC exerts a more profound impact on patients because of additional symptoms throughout and after treatment that warrant special attention from healthcare professionals (Taneja, 2013).

The primary treatment for HNC is a combination of surgery and radiotherapy, delivered either preoperatively or postoperatively (Marur and Forastiere, 2008). The purpose of preoperative radiotherapy is to decrease the tumor size to allow resection, while that of postoperative radiotherapy is to kill any remaining tumor cells that cannot be removed surgically to minimize the possibility of locoregional recurrence

(Shah et al., 2012). Although these treatments, especially postoperative radiotherapy, can greatly improve patient survival, patients experience numerous radiation-induced symptoms (Loorents et al., 2016; Mul et al., 2012; Siddiqui and Movsas, 2017; Srikantia et al., 2011; Żmijewska-Tomczak et al., 2014). Therapy-induced symptoms depend largely on the site and extent of HNC and the dose and type of radiation (Rose, 2013). Symptoms usually develop a few weeks after beginning radiotherapy (Mortensen et al., 2012) and include fatigue, nausea, vomiting, stomatitis, hoarseness, xerostomia, osteoradionecrosis, trismus, impaired thyroid function, and myelopathy (Loorents et al., 2016; Mul et al., 2012; Siddiqui and Movsas, 2017; Srikantia et al., 2011; Żmijewska-Tomczak et al., 2014).

Research on symptom clusters is an emerging field in oncology that aims to understand the complexity of multiple symptoms experienced by patients with cancer (Xiao et al., 2013). A symptom cluster is defined as a group of three or more concurrent symptoms that may or may not have a common etiology or underlying mechanism (Dodd et al., 2001). Compared with single symptoms, symptom clusters are more

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devastating to patients' physical and psychological functions and their quality of life because of the synergistic effect of multiple symptoms in the cluster (Xiao et al., 2013). A thorough understanding of symptom clusters helps physicians to devise comprehensive care plans targeting a likely group of symptoms, easing the total symptom burden in patients with cancer (Aktas et al., 2010; Özalp et al., 2017). Such understanding can also lead to early management of the most common symptom in a cluster to prevent a cascade of associated symptoms (Xiao et al., 2013).

Little evidence regarding symptom clusters in HNC is currently available. A literature review indicated that only two studies have evaluated symptom clusters in patients with HNC (Rosenthal et al., 2015; Xiao et al., 2013). Xiao et al. (2013) identified two symptom clusters, the HNC-specific cluster and the gastrointestinal (GI) cluster. The former cluster comprised seven symptoms (dry mouth, dysphagia, fatigue, pain, radiodermatitis, radiomucositis, and taste disturbance), while the latter comprised three symptoms (dehydration, nausea, and vomiting) (Xiao et al., 2013). However, their study involved patients who had received concurrent chemoradiotherapy; this compromised the generalizability of the findings to patients undergoing a combination of surgery and postoperative radiotherapy, which is the primary and most common treatment for HNC (Marur and Forastiere, 2008). Rosenthal et al. (2015) similarly identified two symptom clusters in patients with HNC who underwent either radiotherapy or concurrent chemoradiotherapy. The first cluster focused on local symptoms, while the second mainly included systemic and global symptoms. However, in addition to the shortcoming of the heterogeneous patient sample, their study also adopted a cross-sectional design. Such a design may not reveal trajectory of symptom clusters, especially when the clusters are highly dependent on disease progression during the course of treatment (Moroz et al., 2016). To address the knowledge gap in the existing literature, we evaluated symptom clusters among patients with HNC who were treated with surgery and postoperative radiotherapy. Additionally, a longitudinal approach was used to examine the pattern of symptom clusters over time.

2. Methods

2.1. Participants and settings

We performed a longitudinal study to identify symptom clusters and examine their pattern throughout postoperative radiotherapy. A convenience sample of 100 patients was recruited in the ear, nose, and throat unit of a medical center in Taiwan. Patients were eligible if they had been newly diagnosed with HNC, were aged > 18 years, were not receiving preoperative radiotherapy, had no cognitive impairment, and were able to communicate in Mandarin or Taiwanese. Patients who met the inclusion criteria were referred by their physicians to join this study. We excluded patients undergoing any other concurrent treatment for cancer (e.g., chemotherapy).

2.2. Measures

2.2.1. Taiwanese version of the MD Anderson Symptom Inventory (MDASI-T)

The MDASI-T was used in this study. This scale is designed to assess the severity of 13 symptoms that are most commonly reported by patients undergoing cancer treatment: dry mouth, fatigue, sleep disturbance, pain, drowsiness, lack of appetite, nausea, vomiting, shortness of breath, numbness, difficulty remembering, distress, and sadness. We asked patients to rate the severity of these symptoms on a 0- to 10-point scale, with 0 representing "not present" and 10 representing "as bad as you can imagine." Scores of 1–4, 5–6, and 7–10 are considered mild, moderate, and severe, respectively. The composite score is the average of the 13 scores for each of the 13 items (Cleeland et al., 2000). The psychometric properties of the Taiwanese version have been empirically examined (Lin et al., 2007), and the results indicated that the

Taiwanese version has good test–retest reliability, excellent internal consistency, and appropriate content and construct validity.

2.3. Demographic and clinical characteristics

The patients completed a demographic sheet regarding their age, sex, marital status, educational level, religious beliefs, and employment status. A research assistant also collected the following clinical data from the patients' medical records: diagnosis, cancer stage, performance status, treatment start date, dosage, and total amount of radiation received. The tumor and lymph node classifications were based on the 7th edition (2009) of the American Joint Committee on Cancer staging manual. The performance status was graded according to the Karnofsky scale, with a score ranging from 0 to 100; the higher the Karnofsky score, the better the performance status.

2.4. Data collection

This study was approved by the Institutional Review Board of Taipei Veterans General Hospital. Prior to data collection, a research assistant fully explained the study details to all referred patients, who were told that participation was totally voluntary and that refusal to answer any question or withdrawal from the study at any time would not prejudice their care. Those willing to participate were asked to provide written consent.

Before undergoing radiotherapy, patients were asked to respond to the MDASI-T, which can be completed within 15 min. Throughout the process, the research assistant was available on-site to answer patients' questions and clarify any ambiguity. The patients were invited to respond to the MDASI-T again at 1, 2, 3, 4, 5, and 6 weeks after starting radiotherapy.

2.5. Data analysis

We used the SPSS 23.0 standard version for Windows (IBM Inc., Armonk, NY) to analyze the data. Descriptive statistics were used to summarize patients' demographic and clinical characteristics and the occurrence and severity of symptoms during postoperative radiotherapy. Agglomerative hierarchical clustering with Wald's method was used to identify symptom clusters at each time point (week 1, 2, 3, 4, 5, and 6). Analysis began with each symptom as an individual cluster. To form larger clusters, symptoms were then merged according to their similarities, which were defined as the absolute value of the correlation between the symptoms. The hierarchical structure of symptoms at each time point was presented as a dendrogram.

3. Results

3.1. Patients' demographic and clinical characteristics

Table 1 shows the patients' demographic and clinical characteristics. Their mean \pm standard deviation age was 54.8 ± 12.5 years; 90% were male, 84% were married, 53% had religious beliefs, and 84% lived with their family. Approximately 32% were diagnosed with tongue cancer, 27% with buccal cancer, and 24% with hypopharyngeal cancer; 54% had stage III carcinoma, while 46% had stage IV. The mean Karnofsky score was 84.1 ± 7.4 at baseline. Throughout the study period, the participants received an average of 6241.4 ± 116.9 Gy of radiation.

3.2. Occurrence and severity of symptoms throughout the treatment period

Table 2 shows the occurrence and severity of symptoms during postoperative radiotherapy. We observed an increase in the number of participants reporting symptoms toward the end of treatment. The six most common symptoms were dry mouth, pain, lack of appetite,

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