

## Treatment Modalities, Analgesic Use, Cancer Stage, and Cancer Location on Symptom Clusters in Head and Neck Cancer Patients

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### ABSTRACT

**Introduction:** Head and neck cancer patients generally have the same symptoms, but the prevalence and severity can vary. The prevalence and severity of symptoms in a cluster are related to the overall symptom experience. The prevalence and severity of symptoms in a cluster can be related to the patient's health and illness state. **Objectives:** This research aims to determine the relationship between treatment modalities, analgesic use, cancer stage, and cancer location on symptom clusters in head and neck cancer patients. **Methods:** The method used is analytical observational with a cross-sectional approach. The sample inclusion criteria were as follows: head and neck cancer without metastatic disease to the brain, cooperative and good at communicating, and age 18-70 years. Meanwhile, the exclusion criteria are not completing the questionnaire due to critical condition, mental disorders, death, and patient going home. The sampling technique used was consecutive sampling, consisting of 111 patients at Dr. Kariadi Central General Hospital of Semarang. Data analysis using Spearman Rho. **Results:** The relationship between the significance values of the treatment modality variables for sickness and gastrointestinal symptom clusters, the use of analgesics for gastrointestinal symptom clusters, the location of cancer for emotional symptom clusters, and the stage with symptom clusters is  $<0.05$ . The research results also show that several variables also have a significance value of  $>0.05$ . **Conclusions:** Good identification of treatment modalities, use of analgesics, cancer stage, and cancer location is expected to be able to overcome symptom clusters in head and neck cancer.

## Introduction

Head and neck cancer is a disease that can cause death and pain in the world (Sung et al., 2021). Four hundred fifty thousand deaths in the world every year are attributed to this disease (Bray et al., 2018). This can be experienced by head and neck cancer patients due to physical and psychological changes and adjustments related to the disease and the management of the therapy undertaken. So that over time, unpleasant symptoms and even death are experienced by many patients related to this condition.

Treatment of cancer patients is still difficult and the results are less than satisfactory, which will affect the patient's quality of life. Treatment still focuses on identifying individual symptoms, not yet targeting symptom clusters. Previous studies only focused on treating individual symptoms, namely pain. The research results showed that although the pain management program reduced pain in 66.67% of respondents, 22.22% experienced no change; in fact, 111% experienced an increase in pain. Quality-of-life symptom scales were also low, as most patients reported untreated fatigue in the study (Mu'jizah et al., 2014).



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Research outcomes above illustrate that treatment using an individual symptom approach needs to be better validated. What is thought to be the cause is the form of symptom recognition, which is still a single (individual) complaint. In contrast to the results of other studies show that symptom clusters (depression, fatigue, and sleep disorders) are found in breast cancer patients. This is important for assessing, preventing, or providing psychological intervention strategies for symptoms that will appear so that they can help cancer patients overcome the severity of the symptom cluster (Ho et al., 2015).

A symptom cluster is a combination of two or more symptoms that occur simultaneously, are related to each other, and are independent of other symptoms or groups of symptoms (Dodd & Faan, 2001; Stapleton et al., 2016). Symptoms in a cluster may originate from the same etiology, but sometimes not. Symptom clusters in cancer patients generally include pain, fatigue, and other symptoms of the effects of therapeutic management (Barsevick, 2016; Franceschini et al., 2013; Kenne Sarenmalm et al., 2014; Kirkova et al., 2011), mood disorders (Barsevick, 2016; Kenne Sarenmalm et al., 2014; Kirkova et al., 2011), and sleep disorders or insomnia (Barsevick, 2016; Franceschini et al., 2013; Ho et al., 2015; Kirkova et al., 2011). The general symptoms that form a symptom cluster will experience differences in the prevalence and severity of each symptom (Barsevick, 2016).

Based on several studies above, cancer patients experience the same general symptoms, but the prevalence and severity can vary. The prevalence and severity of symptoms in a cluster will influence whether the overall symptom experience is better or worse. The prevalence and severity of symptoms in clusters are related to health-illness states (Dodd & Faan, 2001). These differences in treatment modalities will have an impact on patients, namely variations in the symptoms they experience (Jordan et al., 2014). Likewise, regarding the use of analgesics, which cannot be separated from pain management in cancer patients. The use of analgesics can cause other side effects, so it is important to investigate symptom clusters associated with analgesic consumption. The cancer stage also likely to affect variations due to differences in prognosis and symptoms at each stage. At a more advanced stage, both of these things will feel worse (Jordan et al., 2014). In addition, the location of the cancer also influences the prevalence and severity of symptoms within the cluster. Head and neck cancer is classified according to anatomical region, not according to cell type. The differences in each area's anatomical location will, of course, affect the function related to the anatomical relationship (McKenzi et al., 2019; Otto, 2005).

The results of a preliminary study conducted by researchers at Dr. Kariadi Central General Hospital of Semarang, found that the treatment of head and neck cancer patients who undergo treatment modalities with various stages of cancer, analgesic consumption, and having different locations of head and neck cancer is still oriented towards an individual symptom approach. The results of interviews with nurses showed that nurses were not familiar with the symptom clusters approach.

Based on the above, currently the focus of nursing action is still aimed at approaching individual symptoms, yet to be at symptom clusters. In addition, there has been no specific research on variations in symptom clusters in head and neck cancer patients that are influenced by differences in treatment modalities, use of analgesics, cancer stage, and cancer location. Another urgency of this study, is the need to pay attention to the impact of variations in symptom clusters because head and neck cancer patients experience different treatment modalities, use of analgesics, cancer stages, and cancer locations. In accordance with the results of the study above, that treatment by paying attention to symptom clusters is associated with a better quality of life. This underlies researchers conducting research with the aim of



determining the relationship between treatment modalities, use of analgesics, cancer stage, and cancer location on symptom clusters in head and neck cancer patients.

## Methods

This research is an analytical observational study with a cross-sectional design. This research was conducted at Dr. Kariadi Central General Hospital of Semarang in 2018. The population taken in this study were all head and neck cancer patients at the Dr. Kariadi Central General Hospital of Semarang. Consecutive sampling is the sampling technique used. The sample size was calculated using the Isaac and Michael table with an error rate of 5% using the sample size from previous research, namely 140 patients, so the total sample was 111 respondents. Sample selection was based on inclusion and exclusion criteria. Sample specifications with inclusion criteria are head and neck cancer without metastatic disease to the brain, age 18-70 years, cooperative, and good at communicating. Meanwhile, the exclusion criteria were that they did not complete the questionnaire due to critical condition, death, mental disorders, and the patient went home. Questionnaires on treatment modalities, use of analgesics, cancer stage, and cancer location were each divided into categories. The symptom cluster data collection tool uses a questionnaire from Watanabe et al. (2011), namely the Edmonton Symptom Assessment System Revised (ESAS-R). This instrument evaluates the severity of nine physical and psychological symptoms, namely: pain, fatigue/lack of energy, nausea, anxiety/nervousness, depression/feeling sad, sleepy, decreased appetite, general well-being, shortness of breath, and there are additional points to assess other symptoms that are not present in the previous nine symptoms, which are located at point 10. The severity of each symptom experienced by the respondent is measured within the previous week on a scale of 0 to 10. A scale of 0 means that the symptom is completely absent, and 10 indicates that These symptoms are at the worst intensity/worst possible. Prevalence is indicated by the percentage of presence or absence of symptoms, while severity is expressed in the mean score for each symptom between the ranges. Pearson product-moment correlation is used to test the validity of the questionnaire. The results of the questionnaire validity test are valid. It can be shown from the corrected item-total correlation value, which is  $\geq r$  table (0.619), and the degree of freedom value = 8. The reliability test for the questionnaire in this study used Cronbach's alpha. The results of the reliability test in the research showed that the symptom cluster questionnaire was reliable, with a value of 0,78. The data in this study was not normally distributed (tested using skewness and kurtosis ratios), so the Spearman Rho statistical test was used.

## Results

### Characteristics of Respondents according to Demographic Characteristics, Treatment Modalities, Use of Analgesics, Cancer Stage, and Cancer Location

Tabel 1 Characteristics of Respondents according to Demographic Characteristics, Treatment Modalities, Use of Analgesics, Cancer Stage, and Cancer Location (N=111)

Characteristics	Frequency	Percentage (%)
<b>Age</b>		
Early adulthood: 18 - 40 years old	25	22,5
Middle adulthood: 41 - 60 years old	58	52,3
Elderly: age > 61 years old	28	25,2
<b>Gender</b>		
Male	53	47,7
Female	58	52,3
<b>Education</b>		
Not attending school	6	5,4



Basic education (elementary - junior high school/ MTs/ equivalent)	62	55,9
Secondary education (senior high school/ SMK/ equivalent)	36	32,4
Higher education (D1, D2, D3, S1, S2, S3)	7	6,3
<b>Treatment Modalities</b>		
Have not undergone handling modalities	27	24,3
Surgery	9	8,1
Chemotherapy	66	59,5
Radiotherapy	3	2,7
Combination (chemoradiation)	6	5,4
<b>Analgesics Use</b>		
Non opioids	21	18,9
Strong opioids	45	40,5
<b>Cancer Stage</b>		
Stage II	5	4,5
Stage III	42	37,8
Stage IV	64	57,7
<b>Cancer Location</b>		
Oral cavity	8	7,2
Nasal cavity	4	3,6
Nasopharynx	28	25,2
Paranasalis sinus	4	3,6
Larynx	4	3,6
Salivary glands	4	3,6
Thyroid gland	59	53,2

Most of the age of respondents in this study is middle adult between the ages of 41-60 years with female gender and the average level of education is at the basic education level (SD-SMP / MTs / equivalent). Most respondents underwent chemotherapy as a cancer treatment modality, and the highest number of analgesic uses were strong opioids. The average stage of the respondent's disease is stage IV, while the location of the most cancer experienced by respondents is cancer of the thyroid gland

### Distribution of Symptom Clusters

Table 2 Distribution of Symptom Clusters (N=111)

Symptom Cluster	Mean (SD)	(Minimum - Maximum)
Sickness	4,65 (1,86)	1 - 9
Gastrointestinal	2,82 (3,06)	0 - 9
Emotional	4,03 (1,78)	1 - 8,5

The results of this study showed that the highest average severity of symptom clusters was in sickness symptom clusters, with the lowest value being 1 and the highest value being 9.

### Correlation between Treatment Modalities, Analgesic Use, Cancer Stage, and Cancer Location with Symptom Clusters

Table 3 Spearman Rho Test. Correlation between Treatment Modalities, Analgesic Use, Cancer Stage, and Cancer Location with Symptom Cluster (N=111)

Characteristics of Respondents	Symptom Cluster					
	Sickness		Gastrointestinal		Emotional	
	R	p	R	p	r	p



Treatment Modalities	0,16	0,04	0,54	0,00	-0,08	0,19
Analgesic Use	0,10	0,16	0,44	0,00	-0,08	0,19
Cancer Stage	0,56	0,00	0,29	0,00	0,31	0,00
Cancer Location	-0,11	0,13	-0,08	0,22	-0,17	0,04

The correlation between respondent characteristics and symptom clusters shows different significance values. The correlation between the significance values of the treatment modality variables for sickness and gastrointestinal symptom clusters, the use of analgesics for gastrointestinal symptom clusters, the location of cancer for emotional symptom clusters, and the stage with symptom clusters is  $<0.05$ . The research results also show that several variables also have a significance value of  $> 0.05$ . It shows that the correlation between several respondent characteristic variables has meaningful results, although several variables do not have meaningful results.

## Discussion

### Correlation between Treatment Modalities and Symptom Clusters

The results of the study show that there is a correlation between treatment modalities and sickness and gastrointestinal symptom cluster ( $p=0.04$ ,  $p=0.00$ ), with a positive relationship direction (unidirectional) ( $r=0.16$ ,  $r=0.54$ ). In contrast, the emotional symptom cluster does not have a significant correlation. Chemotherapy, radiotherapy, and chemoradiation were the most common treatment modalities undergone by patients in this study (67.6%). It can be interpreted that the higher the use of chemotherapy and radiotherapy treatment modalities, the higher the severity of sickness and gastrointestinal symptom cluster than patients who do not receive these two modalities. These results are supported by several studies conducted on all cancer populations, where head and neck cancer is one type of cancer in this population. Treatment modalities, especially chemoradiotherapy, are associated with higher scores on the sickness and gastrointestinal symptom cluster than patients who do not receive either treatment (Chen & Lin, 2007; Dong et al., 2014a; Mathew et al., 2021) and do not affect the emotional symptom cluster (Chen & Lin, 2007; Mathew et al., 2021) and cancer patients with radiation have a symptom cluster of fatigue-drowsiness which is the main symptom cluster found (Johnstone et al., 2017), where the symptoms of fatigue and drowsiness are also part of the sickness symptom cluster.

Chemotherapy has adverse effects on head and neck cancer patients, including nausea, vomiting, and mucositis. It is related to the mechanism of action of the drug, namely toxicity. Chemotherapy not only affects cancer cells but also disrupts normal cell cycle function. The use of other therapeutic modalities, namely radiotherapy, also produces negative impacts; if the use of this modality is prolonged, it will cause damage to organs and tissues related to or adjacent to the location of the tumor/cancer. Side effects caused by radiotherapy include pain, xerostomia, mucositis, and dysgeusia (Castelli et al., 2015; Fitriatuzzakiyyah et al., 2017; Otto, 2005; Yunus & Praja, 2016). It is a clinical factor that can be associated with symptoms or symptom clusters.

### Correlation between Analgesic Use and Symptom Clusters

This research shows that there is no correlation between the use of analgesics and sickness and emotional symptom clusters ( $p=0.16$ ,  $p=0.19$ ). The results of data on the distribution of respondents' characteristics show that consumption of strong opioid analgesics (MST 10 mg) in this study was low (40.5%). The analgesics available to respondents reflected those commonly prescribed in hospitals. If the results of this study are compared with the results of other studies, the amount of analgesic consumption in this study is much lower than the results of



other studies (40.5%). The results of a study on 725 patients in a hospital reported that 640 patients (88.3%) received an equivalent dose of intravenous morphine ( $M = 65.7$ ,  $SD = 45.6$ ), while another study of 435 cancer patients showed that 396 (91%) received oral morphine doses of 5–299 mg. It is also supported by a study report of the median value of oral morphine use at a dose of 120 mg/day in cancer patients in hospitals (Stapleton et al., 2016). The low amount of analgesic consumption is due to the reluctance of doctors, patients, and nurses to use high doses of morphine. The low dose of morphine may be the main factor causing the non-relief pain reported by respondents.

This research also shows other results, namely the existence of a correlation in a positive direction between the use of analgesics and the gastrointestinal symptom cluster ( $p=0.00$ ). The results of research conducted by researchers showed that there were 45 respondents (40.5%) who used strong opioids (MST 10mg). It can be interpreted as meaning that the higher the use of strong opioid analgesics, the higher the severity of the gastrointestinal symptom cluster. The National Comprehensive Cancer Network reported similar facts that the use of analgesics, especially opioids, apart from being able to relieve pain, can cause side effects, namely nausea and vomiting (Swarm et al., 2016), especially the use of strong opioids (morphine) (*Palliative Care Prescribing Guidelines. LANCASHIRE AND SOUTH CUMBRIA SPECIALIST PALLIATIVE CARE SERVICES- 2012, 2014*), so this is what causes the consumption of analgesics to be associated with the gastrointestinal symptom cluster.

### **Correlation between Cancer Stage and Symptom Cluster**

The findings of this study there was a significant correlation between disease stage and symptom cluster ( $p=0.00$ ). Notably, the majority of respondents in this study were diagnosed with stage IV cancer (57.7%), suggesting a direct correlation between cancer stage and symptom severity. These results are consistent with previous research, which has also identified a significant difference in symptom severity between metastatic and localized cancer stages (Chen & Lin, 2007). Furthermore, our study found that symptoms such as swallowing difficulties, pain, sadness, fatigue, and nausea were more prevalent and severe in participants with higher cancer stages (Ji et al., 2023).

Local spread in head and neck cancer patients occurs in stages III and IV, while in stages I and II, patients have not experienced the spread of the disease. Patients who experience stages III and IV/advanced stages will experience worse symptoms and prognosis (Guo et al., 2019; Hanna et al., 2015; Otto, 2005). Advanced stages of the disease will also influence the appearance of physical symptoms psychologically/emotionally; the patient will also perceive the disease as a state of stress and depression. The results of this analysis show that the predictor that needs to be considered from the patient's symptom cluster is the stage of the disease, where at a higher stage of the disease, the patient will also experience symptoms and a worse prognosis due to the spread of the disease, thus affecting the patient's sickness, gastrointestinal and emotional state.

### **Correlation between Cancer Location and Symptom Cluster**

The results of this study indicate that there is no correlation between the location of the cancer and sickness and gastrointestinal symptom cluster ( $p=0.13$ ,  $p=0.22$ ). Respondents in this study experienced cancer that was still located in the same region, namely the head, and neck when compared to previous studies with more varied cancer locations. The results of this study also showed that there was no difference in prevalence due to different cancer locations (Jane Walker 2014). The results of this analysis show that the prevalence and severity of sickness and



gastrointestinal symptom clusters in cancer patients are more related to treatment modalities and cancer stage (Dong et al., 2014a; Ji et al., 2023; Mathew et al., 2021).

Other research shows different results, namely that there is a correlation between the location of the cancer and the emotional symptom cluster ( $p=0.04$ ). It is supported by several studies which show that psychological symptoms such as anxiety and depression remain a significant source of distress for cancer patients related to the location of the cancer (Dong et al., 2014b, 2016). Cancer patients will experience psychological symptoms because cancer is a chronic disease that causes death and suffering (Cheng & Lee, 2011). It can explain that the differences in the location of the cancer in each respondent who has been diagnosed with head and neck cancer will still have psychological symptoms that are related to the patient's emotional state.

## Conclusion

The results showed that the use of analgesics (strong opioids), treatment modalities, cancer stage, and cancer location were not all related to symptom clusters. It may be related to the presence of other factors that are more related to the symptom cluster. Other factors that influence the characteristics of the respondents include gender (female), age, and level of education. Suggestions for further research are to use a prospective cohort design to be able to predict the time of occurrence of each variable and conduct further research on the characteristics of respondents related to the formation of symptom clusters, including treatment modality, stage, and location of cancer so that specific symptom management can be developed. It is hoped that they can design appropriate symptom management strategies for each symptom cluster group experienced by the patient.

## Ethics approval and consent to participate

Because "this research involves humans directly," this research must pay attention to research ethics. The ethics implemented include respect for human dignity, anonymity, beneficence and nonmaleficence, confidentiality, veracity, justice, and informed consent. Before collecting data at the hospital, this research obtained ethical clearance with number 76/EC/FK-RSDK/II2018.

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