

Predictive Factors of Crucial Nutrition Impact Symptom Clusters in Patients With Head and Neck Cancer Undergoing Radiotherapy

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Abstract

Purpose: To identify crucial nutrition impact symptom (NIS) clusters related to both weight loss rate (WLR) and quality of life (QoL) in patients with head and neck cancer (HNC) receiving RT, and analyze their predictive factors.

Methods: This prospective study enrolled 334 patients. At baseline (T_1), we collected the demographics, clinical information, nutritional risk (Nutritional risk screening 2002, NRS 2002), nutritional status (Global Leadership Initiative on Malnutrition, GLIM), weight, and QoL before RT. At the third week (T_2) and the end of RT (T_3), we evaluated the severity and interference of NIS using the head and neck patient symptom checklist (HNSC), weight, and QoL. Exploratory factor analysis was used to extract the symptom clusters. Generalized estimating equations were used to analyze NIS clusters' relationship with WLR and QoL, and cluster's predictive factors.

Results: Four NIS clusters were identified: RT-specific symptom cluster, upper gastrointestinal symptom cluster, psychological status cluster, and eating experience cluster. The former two NIS clusters had a negative impact on both WLR and QoL, so they were defined as crucial NIS clusters. Patients who were female, with older age, oral cavity cancer, had nutritional risk or were malnutrition at baseline were more likely to get severe RT-specific symptom cluster. Patients who were female, accepted intensive therapy were more likely to get severe upper gastrointestinal symptom cluster.

Conclusions: Healthcare professionals should recognize patients at risk and intervene early, and give early nutritional management before RT to improve HNC patients' NIS severity, nutritional status and QoL during treatment.

Introduction

According to the estimation from the Globocan 2020, more than seven hundred thousand patients got head and neck cancer (including lip cancer, salivary glands cancer, oropharynx cancer nasopharynx, and hypopharynx), which contributed to 3.9% of the new cases of all cancer [1]. Radiotherapy (RT) is a dominating therapy for HNC and nutritional problems are prevalent in patients receiving RT because of acute symptoms. About 62.3–71.8% of patients with HNC lose more than 5% weight at the end of RT [2, 3], and 74.0–92.7% of them get moderate or severe malnutrition [4, 5]. Critical weight loss and malnutrition have predictive value for patients' prognosis [6, 7]. Studies have suggested that nutrition impact symptoms (NISs, e.g., dysphagia, mucositis, xerostomia) are key influential factors of weight loss and malnutrition [3, 8, 9]. In addition, NIS could directly impact patients' quality of life (QoL) negatively [8]. Based on this, the management of NIS needs a high priority for improving HNC patients' nutritional status and QoL during RT.

Previous studies indicated that patients always experience multiple NISs during RT [3, 10]. They may have similar occurrence mechanism and may be members of a symptom cluster which is defined as "consisting of two or more symptoms that are related to each other and occur together" [11]. For example, dysphagia is related to edema and odynophagia induced by mucosal radiation injury [12]. Analysis of NISs clusters could help understand the intercorrelation between them and integrate interventions to promote the effectiveness of symptom management in HNC patients with RT. Several studies have explored symptom clusters in patients

with HNC. They adopted the National Cancer Institute Common Toxicity Criteria or the M. D. Anderson Symptom Inventory, and identified clusters like HNC-specific cluster (radiodermatitis, dysphagia, etc.), gastrointestinal cluster (dehydration, nausea, etc.), general cluster (numbness or tingling, etc.) and so on [13–15]. Nevertheless, these studies did not give specific attention to NIS, which may have a more significant impact on patients' outcomes. We explored the NIS clusters in HNC patients undergoing concurrent chemoradiotherapy with the head and neck symptom checklist (HNSC)-a NIS specific evaluation tool [16] and explored relationships between clusters and weight loss. But patients with RT with or without other therapy may have different NIS profiles. Also, QoL is an important patient-reported outcome and needs evaluation. Hence, it is necessary to identify the symptom pattern and explore the crucial NIS cluster that could influence both patients' weight and QoL in HNC patients receiving RT, so that we can take holistic and targeted intervention and improve patients' outcomes with limited medical resources.

Exploring predictive factors of symptoms could help identify at-risk patients and perform an early intervention to alleviate the severity of NIS, improve patients' nutritional status, QoL and prognosis. However, few studies explore the predictive factors of symptom clusters in HNC patients. Xiao et al.[17] found that patients who were White and accepted a higher level of education were more likely to get severe severity of HNC-specific symptom cluster. In contrast, female and never smoked patients could get more severe gastrointestinal symptom cluster. However, they only focused on patients' sociodemographic and clinical variables. Studies suggested that nutritional risk and nutritional status before treatment may also be associated with the severity of symptoms during treatment[18, 19]. At present, there lacks evidence about predictive factors of NIS clusters in patients with HNC receiving RT.

Therefore, this study aimed to analyze the NIS clusters in HNC patients receiving RT using a prospective longitudinal design. Then, we identified crucial clusters correlated with weight loss and QoL. Also, we attempted to explore predictive factors of the crucial NIS clusters, including sociodemographic factors, disease-related characteristics, nutritional risk identified by the Nutritional Risk Screening 2002 (NRS2002), and nutritional status identified by the Global Leadership Initiative on Malnutrition (GLIM), to direct future management of HNC patients.

Materials And Methods

Study design and participants

This was a prospective longitudinal study. Subjects who were pathologically diagnosed with HNC and scheduled for RT from March 2017 to December 2019 were recruited from one cancer hospital in Beijing. The other recruitment criteria were: (1) age \geq 18 years; (2) entirely voluntary participation; (3) ability to communicate clearly. Considering factor analysis, the number of subjects should be five to ten times the number of items on the scale. A total of 17 symptoms were assessed in this study, so 85 to 170 subjects were necessary [20].

All subjects were informed about the study, including the purpose and content of this study prior to the RT. This study had got approval from the Ethics Committee of the author's University (No. IRB00001052-17002), and the procedure adhered to the principles in the Declaration of Helsinki.

Define the crucial NIS cluster

In this study, we defined a crucial NIS cluster as the cluster that had significantly correlation with both weight loss rate (WLR) and QoL.

Variables and instruments

General and clinical information

We used a questionnaire to record the demographic, sociology, and clinical information at T₁ (age, gender, marital status, tumor site, tumor stage, and RT type).

Nutritional risk and nutritional status before RT

Nutritional risk was assessed by the NRS 2002 [21]. This tool comprises of three parts: undernutrition, disease severity, and age. The undernutrition assesses three aspects: patients' body mass index (BMI), recent weight change, and food intake change. The disease severity is determined by the nutritional requirements. Each aspect will be classified as absent (Score = 0), mild (Score = 1), moderate (Score = 2), and severe (Score = 3). Patients with score ≥ 3 had nutritional risk.

Nutritional status was evaluated by the GLIM which is newly proposed for diagnosing malnutrition [22]. Based on identified nutritional risk, the diagnosis criteria include three phenotypic criteria (non-volitional weight loss, low body mass index, and reduced muscle mass) and two etiologic criteria (reduced food intake or assimilation, and inflammation or disease burden). The muscle mass was measured by the InBody 120 (Biospace Co., Ltd, Seoul, South Korea) based on the bioelectrical impedance analysis. Appendicular skeletal muscle index (ASMI) and fat free mass index (FFMI) were used to define the low body mass index (male, ASMI ≤ 7 kg/m² or FFMI ≤ 17 kg/m²; female, ASMI ≤ 5.7 kg/m² or FFMI ≤ 15 kg/m² for Asian) [22]. Patients with at least one phenotypic criterion and one etiologic criterion would be diagnosed with undernutrition.

Occurrence of nutrition impact symptoms

We adopted the Head and neck patient symptom checklist (HNSC) to evaluate 17 NIS (oral mucositis and dry mouth, etc.) [23]. This checklist assesses two dimensions: the severity and interference with dietary of symptoms using a five-point Likert scale (1 = not at all to 5 = a lot). Jin et al. [24] had validated it in Chinese patients with HNC receiving RT. It had good psychometric performance and could be used to assess the NIS of patients with HNC.

Weight loss rate

Patients' weight was measured by the InBody120 device (Biospace Co., Ltd, Seoul, South Korea) when they wore light clothes and removed shoes. WLR was calculated using the equation: $WLR = (\text{baseline weight} - \text{present weight}) / \text{baseline weight} \times 100\%$.

Global quality of life

The global QoL was evaluated with the global QoL subscales from the European Organization for Research and Treatment of Cancer (EORTC) Questionnaire-Core 30 (QLQ-C30) [25]. The global QoL dimension includes two items on global health and global life quality with a seven-point Likert scale. Higher scores indicated better global life quality.

Data collection

Trained research fellows collected data by face-to-face interviews with uniform instruction at three follow-up visits in the outpatient. Before RT (baseline, T_1), the general information was reported by subjects. Information on disease and treatment characteristics was determined from the medical records. The occurrence of NIS, weight, QoL, nutritional risk, and nutritional status were evaluated. At the third week (T_2) and the end of RT (T_3), occurrence of NIS, present weight and QoL were reassessed.

Data analysis

All data analysis was conducted using the IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, N.Y., USA). The NIS's interference had several missing values and was filled up by the mean of the nearby two points [26]. Counts and percentages were used to report categorical variables, while mean and standard deviation were used to report continuous variables. Exploratory factor analysis (EFA) with orthogonal rotation and principal component analysis was used to extract symptom clusters. The individual measure of sampling adequacy (MSA) for each symptom was calculated to evaluate correlations between symptoms. We deleted symptoms with low MSA (< 0.5) as they could result in too many factors [27]. The average score of severity of NIS at T_2 and T_3 was used to conduct EFA. The number of factors was determined by the principle of eigenvalue > 1 . Symptoms with weak factor loadings (< 0.40) were deleted. If symptoms had fair loadings on more than one factor, it was placed with the factor that it was mostly related to conceptually. [27] Symptom clusters were named and interpreted based on analysis results and theoretical considerations. Cronbach's α coefficient was adopted to assess clusters' internal consistency. The unweighted mean of symptoms was calculated to get the composite scores of clusters at T_2 and T_3 [27]. Generalized estimating equations (GEE) were adopted to explore the association between clusters and WLR or global QoL, and the predictive factors of symptom clusters. Variables with $P < 0.1$ in univariable models were entered into the multivariable models. As the nutritional risk and nutritional status before RT had a closed correlation with each other, so they would be placed in two multivariable GEE models separately (Model 1 and Model 2).

Results

General information

There were 600 subjects receiving RT in the day-care ward. At baseline, a total of 537 eligible patients accepted the assessment. Finally, 334 subjects completed three follow-up visits. During the follow-up, 172 (32.0%) patients declined because of time conflict, severe toxicities, or exhausting visits. Besides, several subjects were excluded because of incomplete data or interrupted treatment (Fig. 1). The age of the 334 subjects was 53.5 ± 12.9 (18.0–88.0) years. They accepted one fraction of intensity-modulated radiation (IMRT) in each weekday. The planned RT schedule included 31.0 ± 2.2 (17–35) fractions with a total of 65.3 ± 5.0 (36–75) Gy. At T_2 ,

they received 12.38 ± 2.14 fractions RT, and 28.78 ± 2.68 fractions at T₃. Table 1 displayed subjects' general information.

Occurrence of NIS and symptom clusters

We found that pain, taste change, dry mouth, thick saliva, and difficulty swallowing were the top-five frequent and serious symptoms during RT, while pain, oral mucositis, difficulty swallowing, taste change, loss of appetite had the most impact on dietary intake in our population (Table 2).

Before EFA analysis, we dropped diarrhea (MSA = 0.485) as weak correlation with other symptoms. After conducting EFA with the other 16 symptoms, we deleted the symptom of constipation as it had low factor loadings on all factors (< 0.40). As a result, 15 symptoms were retained in the next EFA analysis. The KMO test value was 0.770 and Bartlett's test of sphericity has statistical significance ($\chi^2 = 1727.947$, $P < 0.001$). However, dry mouth and altered smell had loadings > 0.40 on two factors. Considering the factor loading and conceptual meaning, the dry mouth was placed with the first factor, and the altered smell was placed with the third factor. Finally, we extracted four clusters that explained 60.536% of the variance, as shown in Table 3. The RT-specific symptom cluster consisted of pain, difficulty swallowing, oral mucositis, thick saliva, difficulty chewing, and dry mouth (Cronbach's $\alpha = 0.813$). The psychological status cluster consisted of anxiety, depression, and lack of energy (Cronbach's $\alpha = 0.745$). The eating experience cluster consisted of altered smell, loss of appetite, taste change, and feeling full (Cronbach's $\alpha = 0.496$). The upper gastrointestinal symptom cluster consisted of vomiting and nausea (Cronbach's $\alpha = 0.698$). The composite scores of four symptom clusters were shown in Table 4.

Crucial NIS clusters

In the GEE models, the time point and four clusters were independent variables, while the WLR and global QoL were set as the dependent variable, respectively. The univariable model indicated that all the four clusters had a significant correlation with the WLR and global QoL. The multivariable GEE models were presented in Table 5. The RT-specific symptom and upper gastrointestinal symptom clusters were significantly correlated with both WLR and global QoL, so they were defined as crucial symptom clusters.

Predictive factors of crucial NIS clusters

As they had a significant correlation with WLR and global QoL; we analyzed their baseline predictive factors. In the GEE model, the independent variables included the time point, general information, nutritional risk, or nutritional status before RT. The RT-specific symptom cluster and upper gastrointestinal symptom cluster were used as dependent variables separately. The univariable model showed that the RT-specific symptom cluster was related to the time point, gender, age, baseline nutritional risk, and nutritional status; the upper gastrointestinal symptom cluster was associated with the time point, gender, age, tumor site, tumor stage, and RT type. Table 6 presents the predictive factors from multivariable models. The RT-specific symptom cluster was related to gender (Model 1: $\chi^2 = 4.915$, $P = 0.027$; Model 2: $\chi^2 = 4.827$, $P = 0.028$), age (Model 1: $\chi^2 = 7.642$, $P = 0.006$; Model 2: $\chi^2 = 7.870$, $P = 0.005$), tumor site (Model 1: $\chi^2 = 10.113$, $P = 0.006$; Model 2: $\chi^2 = 10.300$, $P = 0.006$), nutritional risk ($\chi^2 = 6.934$, $P = 0.008$) and nutritional status ($\chi^2 = 6.833$, $P = 0.009$). The upper

gastrointestinal symptom cluster had significant correlation with gender ($\chi^2 = 10.169, P = 0.001$) and RT type ($\chi^2 = 17.696, P = 0.001$).

Discussion

NISs are symptoms that can significantly impact patients' dietary intake and metabolic absorption, which is related to patients' nutritional status and clinical outcomes. However, previous research attached limited importance to it. This prospective longitudinal study using the HNSC, the NIS-specific tool, showed that patients with HNC experienced multiple aggravating NIS during RT, consistent with other investigations[9, 28]. As a result, the management of NISs should be brought to the forefront.

Four NIS clusters were extracted with the HNSC: RT-specific symptom cluster, psychological status cluster, eating experience symptom cluster and upper gastrointestinal symptom cluster. The RT-specific symptom cluster comprised pain, difficulty swallowing, oral mucositis, thick saliva, difficulty chewing, and dry mouth. Direct and indirect radiation injury resulted in mucosa and tissue damage. Thus, patients commonly experience acute toxicities like mucositis, dry mouth, and soft tissue edema. Studies showed that mucositis and its pain were key determinants of dysphagia in patients with HNC accepting RT[12, 29]. Also, xerostomia and thick saliva caused by the damaged salivary gland could impact swallowing function[30, 31]. The eating experience cluster included altered smell, loss of appetite, taste change, and feeling full. Smell and taste function are important for flavor awareness and food perception, so altered smell and taste could influence patients' food enjoyment and interest in eating [32]. However, its Cronbach α coefficient (0.496) was relatively low. One possible explanation is the different anatomical positions of smell and taste receptors and the different tumor sites. A prospective study indicated that HNC patients receiving RT all experienced taste change, but only 30% of them got altered smell. [33] Besides, chemotherapy can damage taste and smell function. In our follow-up subjects, some received chemotherapy and they might have different symptoms profiles. [32]

The RT-specific symptom and gastrointestinal symptom clusters were defined as crucial NIS clusters as they had significant relationships with both WLR and QoL. NISs within the former cluster were related to swallowing function and were prerequisite for good dietary intake and nutritional status [34, 35]. For QoL, the RT-specific symptom, gastrointestinal symptom, and psychological status cluster had a negative impact on it. On the one hand, the RT-specific symptom and gastrointestinal symptom clusters are related to more WLR, while more WLR is related to worse QoL [36]. On the other hand, severe symptom burden could directly influence patients' QoL [34, 36]. Anxiety and depression are also prevalent problems in cancer patients. The study conducted by Hortense et al. indicated that anxiety and depression also had correlations with participants' QoL [37]. The RT-specific symptom cluster and gastrointestinal symptom cluster were crucial clusters for managing HNC patients with RT, so healthcare professionals should focus limited medical resources on these NISs to improve patients' nutritional status and QoL. It is essential to explore their predictive factors for better symptom cluster management.

For the RT-specific symptom cluster, patients who were older, female, diagnosed with oral cavity cancer, and had nutritional risk or malnutrition at T₁ had more probability to experience severe symptoms. Previous research showed that female patients tended to get more severe dysphagia and mucositis. [38, 39] But the

study of Xiao et al.[17] in HNC patients with concurrent chemoradiotherapy did not find the correlation between gender and severity of HNC-specific symptom cluster. This may be due to different populations, evaluation instruments, symptoms within a cluster, and alternative predictive factors. A systematic review suggested that age, tumor stage, tumor site, therapy, and pretreatment oral function were related to oral toxicities [35]. A cross-sectional study with 2248 cancer patients showed that patients with nutritional risk got significantly more severe adverse events. [19] In addition, a retrospective study indicated that pretreatment nutritional status could predict severe adverse events in HNC patients with RT [40]. Therefore, healthcare professionals should identify patients with higher risk of severe RT-specific symptom cluster early and pay more attention to their management before RT. Especially, the pretreatment nutritional intervention should be put in the priority queue to reduce patients' nutritional risk and improve their nutritional status at T₁. So that we could mitigate their NIS cluster burdens, improve nutritional status and QoL during RT.

For the upper gastrointestinal symptom cluster, patients who were female, accepted intensive therapy (concurrent chemoradiotherapy with or without surgery) were more likely to get severe upper gastrointestinal symptom cluster. Xiao et al. [17] also found that women were more likely to get severe gastrointestinal symptom clusters. RT and chemotherapy drugs could both conduct an impact on the central nervous system (dorsal vagal complex) and elevate levels of 5-hydroxytryptamine that involves in the generation of nausea and vomiting [41, 42], so participants accepted concurrent chemoradiotherapy experienced severe upper gastrointestinal symptom clusters. As a result, clinical practitioners could identify patients at risk of severe upper gastrointestinal symptom cluster, and then provide early prevention measures for nausea and vomiting.

This study also had several limitations. Firstly, this was a monocentric study with a relatively high attrition rate, so this may limit the generalization of our findings. In the future, investigators could perform a multicenter study with larger sample to validate the NIS clusters and their predictors. Secondly, this study only recruited part of alternative predictive factors and researchers can take more factors into account that may relate to NIS burden like chemotherapy regimens or pretreatment NIS. Thirdly, we excluded patients with tube feeding and total parental nutrition. Futural studies could explore their relationship and effect on NIS clusters, nutritional status, and QoL.

Conclusions

In conclusion, this study identified two crucial NIS clusters in HNC patients receiving RT. The RT-specific symptom cluster and upper gastrointestinal symptom cluster both had a negative impact on WLR and QoL, so healthcare professionals should pay more attention to their management. For sociodemographic and clinical characteristics, female patients tended to report more severe symptom cluster burden. Patients at an older age and with oral cavity cancer were more likely to get severe RT-specific symptom cluster, while patients accepted intensive therapy would experience more severe upper gastrointestinal symptom cluster. Thus, we should recognize patients at risk and intervene early. In addition, patients with nutritional risk and malnutrition had a higher risk of getting severe RT-specific symptom cluster. Clinical practitioners should give early nutritional management before RT to improve HNC patients' NIS severity, nutritional status and QoL during treatment.

Declarations

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Conflict of interest:

None declares.

Availability of data and material:

The corresponding author should be contacted directly for any queries related to the availability of data and material.

Code availability:

Not relevant to this study.

Authors' contributions:

Yujie Wang: data analysis, interpretation of data and drafted the initial manuscript. Lichuan Zhang, Bing Zhuang, Tong Zhang, Sanli Jin, Zhou Huang, Dan Zhao, Shaowen Xiao, Baomin Zheng, Liqing Gong, Yan Sun: acquisition of data. Sanli Jin, Qian Lu: editing and proofreading. Yan Sun, Qian Lu: supervision.

Ethics approval:

This study had got approval from the Ethics Committee of the author's University (No. IRB00001052-17002).

Consent to participate:

All subjects were informed about the study.

Consent for publication:

Not relevant to this study.

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Tables

Table 1
General information at baseline (n = 334)

Variable	Category	n (%)	Variable	Category	n (%)
Gender	Male	211(63.2)	Marriage	Married	306(91.6)
	Female	123(36.8)		others	28(8.4)
Tumor site	Oral cancer	93(27.8)	Tumor stage	I	12(3.6)
	Nasopharyngeal cancer	80(24.0)		II	39(11.7)
	Salivary gland carcinoma	33(9.9)		III	68(20.4)
	Sinonasal malignant melanoma	27(8.1)		IV	202(60.5)
	Oropharyngeal cancer	20(6.0)		Unsure	13(3.9)
	Laryngeal cancer	20(6.0)	RT type	RT	38(11.4)
	Hypopharyngeal carcinoma	17(5.1)		Postoperative RT	125(37.4)
	Lymphoma	10(3.0)		CT + RT	100(29.9)
	Esophagus cancer	9(2.7)		Postoperative CT + RT	71(21.3)
	Thyroid cancer	6(1.8)	Nutritional risk	Yes	89(26.6)
Others	19(5.7)	No		245(73.4)	
BMI category	underweight	26(7.8)	Malnutrition	Yes	84(25.1)
	normal weight	176(52.7)		diagnosed by GLIM	No
	overweight	132(39.5)			

RT: radiation therapy; CT: chemotherapy.

Table 2
The occurrence of symptoms (n = 334)

Symptom	T ₂ - Prevalence (%)	T ₃ - Prevalence (%)	T ₂ - Severity (M ± SD)	T ₃ -Severity (M ± SD)	T ₂ -Interference (M ± SD)	T ₃ -Interference (M ± SD)
pain	91.3	94.6	3.36 ± 1.26	3.67 ± 1.21	3.25 ± 1.48	3.64 ± 1.43
dry mouth	89.5	91.6	3.07 ± 1.27	3.38 ± 1.32	1.58 ± 0.90	1.82 ± 1.08
thick saliva	88.0	92.2	3.09 ± 1.31	3.52 ± 1.31	1.43 ± 0.86	1.55 ± 0.96
taste change	78.1	89.2	3.28 ± 1.56	4.02 ± 1.41	2.14 ± 1.34	2.75 ± 1.55
difficulty swallowing	76.0	82.0	2.95 ± 1.45	3.30 ± 1.43	2.85 ± 1.57	3.27 ± 1.56
oral mucositis	72.2	80.5	2.74 ± 1.44	3.17 ± 1.47	2.57 ± 1.55	2.95 ± 1.60
lack of energy	57.2	68.3	1.91 ± 0.96	2.31 ± 1.16	1.10 ± 0.38	1.19 ± 0.58
loss of appetite	56.9	62.9	2.39 ± 1.47	2.67 ± 1.57	2.16 ± 1.46	2.50 ± 1.63
nausea	39.5	47.0	1.63 ± 0.94	1.81 ± 1.06	1.40 ± 0.89	1.62 ± 1.14
difficulty chewing	38.3	43.4	1.94 ± 1.39	2.09 ± 1.43	1.66 ± 1.20	1.78 ± 1.26
constipation	28.7	43.1	1.46 ± 0.85	1.83 ± 1.14	1.06 ± 0.32	1.09 ± 0.34
anxious	28.1	36.2	1.43 ± 0.79	1.58 ± 0.91	1.10 ± 0.40	1.15 ± 0.53
altered smell	21.3	20.1	1.47 ± 1.05	1.53 ± 1.19	1.11 ± 0.47	1.10 ± 0.47
depressed	16.5	22.2	1.25 ± 0.66	1.37 ± 0.81	1.05 ± 0.34	1.10 ± 0.40
feeling full	14.4	15.9	1.21 ± 0.58	1.28 ± 0.71	1.16 ± 0.56	1.20 ± 0.61
vomiting	10.5	22.5	1.17 ± 0.55	1.37 ± 0.79	1.15 ± 0.55	1.33 ± 0.87
diarrhea	2.1	2.4	1.03 ± 0.20	1.04 ± 0.26	1.00 ± 0.06	1.00 ± 0.05

Table 3
The factor matrix of symptom clusters (n = 334)

Variable	Standardized Factor Loadings			
	1	2	3	4
pain	0.848	0.154	0.054	0.046
difficulty swallowing	0.782	0.051	0.073	0.120
oral mucositis	0.702	0.290	-0.004	-0.112
thick saliva	0.677	-0.022	0.339	0.192
difficulty chewing	0.609	0.165	0.131	-0.268
dry mouth	0.508	-0.148	0.481	0.084
anxious	0.165	0.867	-0.048	0.166
depressed	0.128	0.850	-0.084	0.192
lack of energy	0.326	0.497	0.347	0.212
altered smell	-0.050	0.474	0.407	-0.378
loss of appetite	0.228	0.035	0.664	0.197
taste change	0.251	0.020	0.658	0.082
feeling full	-0.058	0.016	0.614	0.054
vomiting	0.049	0.208	0.107	0.801
nausea	-0.055	0.180	0.331	0.765

Table 4
The composite score of symptom clusters at T₂ and T₃ (n = 334)

	Cluster 1 RT-specific symptom	Cluster 2 Psychological status	Cluster 3 Eating experience	Cluster 4 Upper gastrointestinal symptom
Number of symptoms	6	3	4	2
T ₂	2.86 ± 0.93	1.53 ± 0.64	2.08 ± 0.77	1.40 ± 0.66
T ₃	3.19 ± 0.94	1.75 ± 0.80	2.37 ± 0.75	1.59 ± 0.81

Table 5

The multivariable GEE model of NIS cluster's correlation with WLR and Global QoL (n = 334)

Dependent variable	Item	Values	β	SE	95%CI		Wald χ^2	P
WLR	Time point	End = 1	3.576	0.381	2.830	4.322	88.219	< 0.001
		Mid = 2	0.226	0.292	-0.346	0.798	0.601	0.438
		Baseline = 3	0 ^a	-	-	-	-	-
	Cluster	RT-specific symptom	1.001	0.163	0.682	1.321	37.735	< 0.001
		Psychological status	0.387	0.272	-0.145	0.920	2.032	0.154
		Eating experience	0.146	0.201	-0.248	0.541	0.529	0.467
		Upper gastrointestinal symptom	0.789	0.188	0.421	1.157	17.647	< 0.001
Global QoL	Time point	End = 1	-6.050	2.352	-10.660	-1.441	6.619	0.010
		Mid = 2	-3.149	1.895	-6.862	0.564	2.763	0.096
		Baseline = 3	0 ^a	-	-	-	-	-
	Cluster	RT-specific symptom	-8.465	1.344	-11.099	-5.830	39.657	< 0.001
		Psychological status	-8.419	1.303	-10.973	-5.865	41.748	< 0.001
		Eating experience	0.551	1.072	-1.551	2.653	0.264	0.607
		Upper gastrointestinal symptom	-2.860	1.190	-5.192	-0.528	5.777	0.016

GEE: generalized estimating equations; NIS: nutrition impact symptom; WLR: weight loss rate; QoL: quality of life; SE: standard error; 95% CI: 95% confidence interval;

β : regression weight; 0^a: the reference group

Table 6

The multivariable GEE model of predictive factors for crucial symptom clusters (n = 334)

Dependent variable	Item	Values	β	SE	95%CI		Wald χ^2	P
The RT-specific symptom cluster-Model 1	Time point	End = 1	1.906	0.048	1.813	1.999	1604.777	< 0.001
		Mid = 2	1.577	0.048	1.483	1.671	1087.436	< 0.001
		Baseline = 3	0 ^a	-	-	-	-	-
	Gender	Male = 1	-0.165	0.074	-0.311	-0.019	4.915	0.027
		Female = 2	0 ^a	-	-	-	-	-
	Age		0.007	0.003	0.002	0.012	7.652	0.006
	Tumor site ^Δ	Pharynx = 1	0.112	0.086	-0.056	0.280	1.708	0.191
		Oral cavity = 2	0.280	0.090	0.104	0.457	9.668	0.002
		Other = 3	0 ^a	-	-	-	-	-
	Nutritional risk	No	-0.225	0.085	-0.392	-0.057	6.934	0.008
Yes		0 ^a	-	-	-	-	-	
The RT-specific symptom cluster-Model 2	Time point	End = 1	1.906	0.048	1.813	1.999	1604.950	< 0.001
		Mid = 2	1.577	0.048	1.483	1.671	1087.178	< 0.001
		Baseline = 3	0 ^a	-	-	-	-	-
	Gender	Male = 1	-0.163	0.074	-0.309	-0.018	4.827	0.028
		Female = 2	0 ^a	-	-	-	-	-
	Age		0.007	0.003	0.002	0.012	7.870	0.005
	Tumor site ^Δ	Pharynx = 1	0.117	0.086	-0.052	0.286	1.848	0.174
		Oral cavity = 2	0.283	0.090	0.107	0.460	9.911	0.002
		Other = 3	0 ^a	-	-	-	-	-
	Nutritional status	No	-0.231	0.088	-0.404	-0.058	6.833	0.009

Dependent variable	Item	Values	β	SE	95%CI	Wald χ^2	P	
		Yes	0 ^a	-	-	-	-	
The upper gastrointestinal symptom cluster	Time point	End = 1	0.498	0.048	0.404	0.592	107.742	< 0.001
		Mid = 2	0.308	0.038	0.234	0.382	65.949	< 0.001
		Baseline = 3	0 ^a	-	-	-	-	-
	Gender	Male = 1	-0.156	0.049	-0.251	-0.060	10.169	0.001
Female = 2		0 ^a	-	-	-	-	-	
	RT type	RT	-0.076	0.085	-0.243	0.091	0.794	0.373
		Postoperative RT = 2	-0.143	0.051	-0.243	-0.044	7.968	0.005
		CT + RT = 3	0.117	0.077	-0.033	0.267	2.322	0.128
		Postoperative CT + RT = 4	0 ^a	-	-	-	-	-

[△]The tumor sites were divided into three categories: (1) pharynx, including nasopharyngeal cancer, oropharyngeal carcinoma, hypopharyngeal carcinoma and laryngeal cancer; (2) oral cavity, including oral cancer and salivary gland carcinoma; and (3) all the others.

RT: radiotherapy; CT: chemotherapy; GEE: generalized estimating equations; SE: standard error; 95% CI: 95% confidence interval;

β : regression weight; 0^a: the reference group

Figures

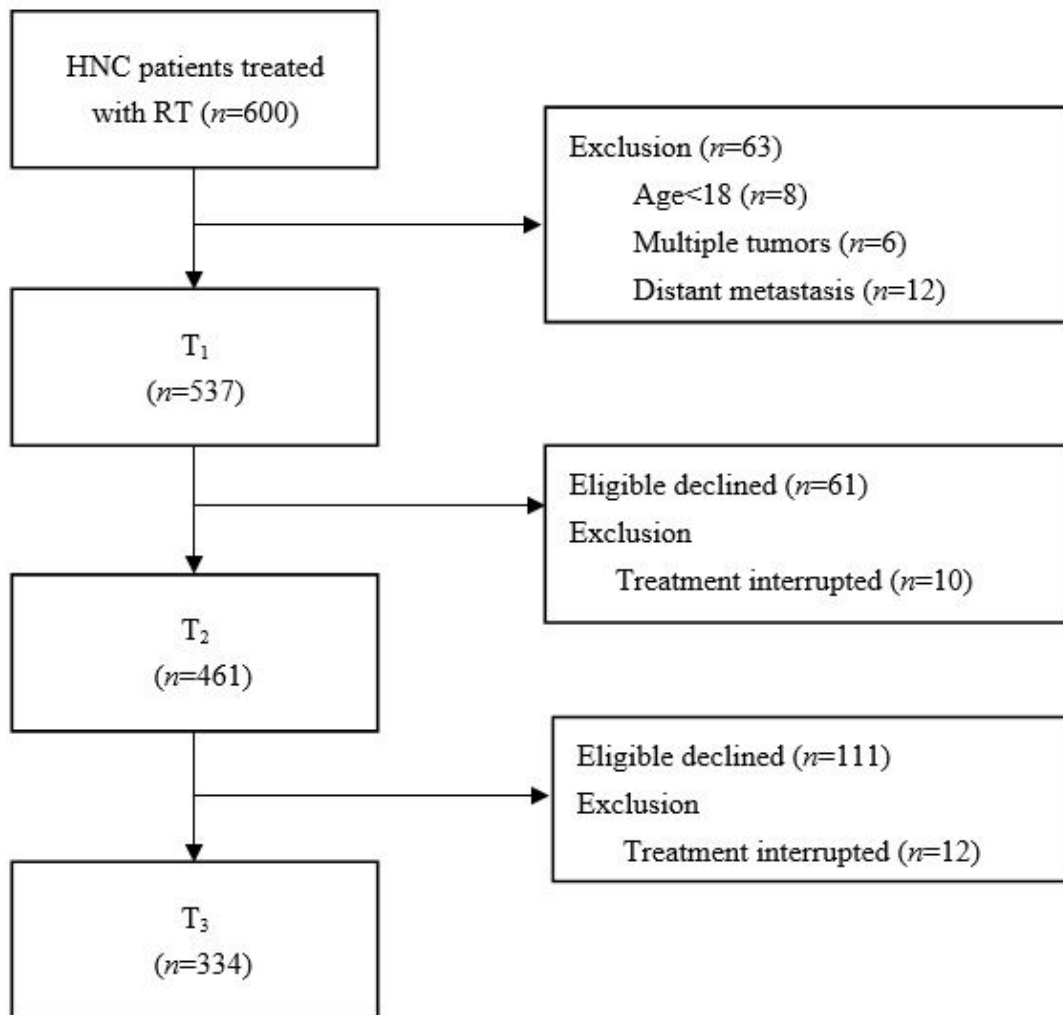


Figure 1

Patient eligibility within the studied cohort