Quality of life and Its Association With Radiation-Induced Oral Mucositis in Patients With Nasopharyngeal Carcinoma During Radiotherapy: A Prospective Study

Lei Wang
Department of Radiotherapy, Zhejiang Cancer Hospital, Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences

Xiaohui Liu
The Second Clinical Medical College of Zhejiang Chinese Medical University

Zekai Shu
Department of Radiotherapy, Zhejiang Cancer Hospital, Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences

Ziyi Zeng
Sun Yat-sen University Cancer Center

Bingqi Yu
Zhejiang Hospital

Shuang Huang
Department of Radiotherapy, Zhejiang Cancer Hospital, Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences

Yonghong Hua
Department of Radiotherapy, Zhejiang Cancer Hospital, Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences

Ting Jin
Department of Radiotherapy, Zhejiang Cancer Hospital, Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences

Changjuan Tao
Department of Radiotherapy, Zhejiang Cancer Hospital, Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences

Caineng Cao
Department of Radiotherapy, Zhejiang Cancer Hospital, Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences

Zumin Xu
Affiliated Hospital of Guangdong Medical University

Qifeng Jin

Department of Radiotherapy, Zhejiang Cancer Hospital, Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences

Feng Jiang
Department of Radiotherapy, Zhejiang Cancer Hospital, Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences

Xinglai Feng
Department of Radiotherapy, Zhejiang Cancer Hospital, Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences

Yongfeng Piao
Department of Radiotherapy, Zhejiang Cancer Hospital, Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences

Jing Huang
The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University

Xiaozhong Chen
Department of Radiotherapy, Zhejiang Cancer Hospital, Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences

Hui Wu
Affiliated Cancer Hospital of Zhengzhou University

Xiushen Wang
Affiliated Cancer Hospital of Zhengzhou University

Lixia Lu
State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Sun Yat-sen University

Rongliang Qiu
Affiliated Cancer Hospital of Zhengzhou University

Yuanyuan Chen (chenyy2@sysucc.org.cn)
Sun Yat-sen University Cancer Center

Research Article

Keywords: head and neck cancer, nasopharyngeal carcinoma (NPC), quality of life, radiation–induced oral mucositis, radiotherapy

Posted Date: February 3rd, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2539310/v1

Abstract

We aimed to investigate the quality of life of nasopharyngeal carcinoma (NPC) patients during treatment and association with radiation-induced oral mucositis (ROM). A prospective study of 173 patients with nasopharyngeal carcinoma was initiated. Quality of life (QoL) was evaluated using the self-reported quality of life questionnaire for Head and Neck (QLQ-H&N 35) and ROM was evaluated before treatment and weekly with the Common Terminology Criteria for Adverse Events dictionary (CTCAE 4.0). Patients were divided into three groups (mild, moderate, severe groups) according to the duration of ≥ 3 grade ROM. The ANOVA analysis was performed to investigate the change in life quality and its association with ROM. During the treatment process, there was a significant decrease in patient QoL from T0 to T1-6. There were also significant differences ($p < 0.05$) observed in most scales at several time points (especially between T4 and T6), between the groups (mild *vs.* severe group). The QoL for NPC patients deteriorated during treatment and was associated with ROM. Patients with severe ROM were likely to develop the poorest QoL. More supportive intervention should be carried out early particularly for those with severe ROM.

Introduction

Nasopharyngeal carcinoma (NPC) accounted for approximately 0.7% of incident cancers globally in 2020 [1]. Although the incidence rate is low compared with other cancers, its global prevalence is skewed, with over 70% of new cases diagnosed in east and southeast Asia. NPC can result in significant morbidity and mortality, as well as inflicting an economic burden on straining health services [2].

Radiotherapy (RT) is the main treatment modality for NPC. With the development of new technology like intensity-modulated radiotherapy and systemic therapy, 5-year survival rates have reached 82% for overall survival and exceed 90% for locoregional control [3–5]. Despite the successful treatment, toxicity from RT remains a significant problem. This includes acute toxicity such as radiation-induced oral mucositis (ROM), dermatitis, and long-term toxicity that can result in hearing loss, depression, and fatigue [6–8]. Intensity-modulated radiation treatment (IMRT) can reduce dose and consequent damage to normal tissue. However, no difference has been observed between patients treated with IMRT and 3D-CRT with respect to ROM and the incidence of grade ≥ 3 ranges from 30–60% [9–11]. Once severe ROM occurs, patients suffer extreme oral pain, dysphagia, and malnutrition [7, 12, 13]. In clinical practice, ROM is considered to have a great impact on life quality during RT. However, there are a lack of prospective studies regarding this. Our study was performed to help elucidate the correlation between oral mucositis and life quality in NPC patients during RT.

Materials And Methods

Study population

This study was conducted in five medical centers. The individuals were identified from an RCT (NCT03720340). The basic inclusion and exclusion criteria were the same as has previously been reported [12]. Briefly, study individuals were newly diagnosed NPC patients (as defined by 8th version of I-IVB of the AJCC; age ranger 18–75 y; 0 or 1 performance status; and without bone marrow, renal, hepatic dysfunction), who were willing to participate. Excluded patients were those treated with palliative intent; with previous malignancy; pregnancy or lactation; had previously received anti-cancer treatment for primary tumors or nodes; had oral mucositis and senile dry stomatitis before treatment; those with severe comorbidities; those receiving fluorouracil drugs; and those allergic to recombinant human interleukin-11. The QLQ-H&N 35 was given to patients who would self-report. Patients who failed to complete the questionnaire were excluded. However, if the questionnaire was completed from T0 to T6 on at least one occasion, the patient was included. The details of the radiotherapy plan have been described in our previous studies [12, 14].

Treatment Plan

The treatment plan was detailed in the previous study [14]. Briefly, patients received radiation five times per week, and eventually finished 32 episodes of radiotherapy over approximately 1.5 months. Most patients received 3 cycles of platinum-based neoadjuvant and between 0–2 cycles of concurrent chemotherapy. Concurrent nimotuzumab was also used in some patients.

Data Collection

The data from basic characteristics of patients was recorded before treatment. The questionnaire used for scoring oral mucositis was the Common Terminology Criteria for Adverse Events dictionary (CTCAE, version 4.0). The interview was completed before commencement of RT (T0), and every week during the RT process (T1-T6) by a clinical research coordinator. The QLQ-H&N 35 was self-completed by patients every week (T0-T6). Patients were divided into the mild ROM group, moderate group, and severe group when they experienced 0, 1–2, and ≥ 3 weeks of severe ROM, respectively.

Statistical Analysis

The paired Student's t-test was used to compare responses to 18 items between T0 and T1-T6 using the QLQ-H&N 35. The *post hoc* ANOVA tests were performed between three groups, and the Repeated Measures ANOVA was also performed for the 18 items among groups. A p value less than 0.05 ($p < 0.05$) was considered to be statistically significant. We performed analysis using SPSS software, version 24.0 (IBM Corp., NY, USA).

Results

Patient characteristics and subgroups

173 patients were eligible and included in this study and their characteristics are presented in Table 1. According to the categorization mentioned above 66, 77 and 30 patients were categorized into mild, moderate and severe groups, respectively.

Life quality in all patients undergoing RT

We compared scales of H&N 35 between T0 and T1-6 (Table 2). Most scales significantly worsened during the treatment process. The criteria for pain, swallowing, sensory problems, trouble with social eating, dry mouth, sticky saliva, coughing, feeling of illness, nutritional supplements, and weight loss were significantly different from T1 compared to T0 and continued thereafter. The scores for speech problems, trouble with social contact, loss of libido, dental health, opening of the mouth, use of analgesics, and use of a feeding tube also increased and was significantly different from T0 to the end of treatment. Weight gain was not significantly different from T0.

Association between life quality and oral mucositis during RT

Patients were divided into three groups according to the duration of severe ROM. As shown in Table 3, significant differences ($p < 0.05$) were observed at several time points (especially between T4 and T6) between the groups for the following H&N 35 categories: pain, swallowing, speech problems, sensory problems, social eating, inability in maintaining social contact, loss of libido, dental health, opening of the mouth, dry mouth, sticky saliva, coughing, feeling ill, and use of analgesics. For nutritional supplements, use of a feeding tube, weight loss, and weight gain, there were no significant differences observed except between T0 and T2, where nutritional supplements and weight loss significantly differed, respectively. Repeated Measures ANOVA showed that significant differences among the groups remained for pain ($p < 0.001$), swallowing ($p < 0.001$), sensory problems ($p = 0.042$), speech problems ($p = 0.025$), trouble with social eating ($p < 0.001$), inability in maintaining social contact ($p = 0.002$), loss of libido ($p = 0.009$), dental health ($p = 0.019$), opening of the mouth ($p < 0.001$), dry mouth ($p < 0.001$), sticky saliva ($p = 0.047$), coughing ($p = 0.017$), feeling ill ($p = 0.010$), and use of analgesics ($p = 0.007$). No significant differences were observed for use of nutritional supplements ($p = 0.289$), use of feeding tube ($p = 0.850$), weight loss ($p = 0.218$), and weight gain ($p = 0.693$).

Discussion

Although cancer is the leading cause of death worldwide, survival rates have improved in recent decades with the development of new treatment modalities and improved diagnosis. Therefore, the quality of life in cancer patients has been gaining increased attention, both during and after treatment. Quality of life questionnaires evaluate disease symptoms, adverse effects of treatment, psychological, social, and spiritual impact on patients [15]. The QLQ-H&N 35 module consists of 35 questions assessing symptoms, treatment side effects, social function, body image, and sexuality for patients with head and neck cancer [16].

As a primary treatment for cancer, chemotherapy and radiotherapy can lead to acute and late toxicity in multiple organ systems [17–19]. Acute toxicity includes myelosuppression, gastrointestinal symptoms, and acute inflammation, [17–20] which may impair QoL [19, 20]. Studies have revealed the association between baseline and change in QoL with disease prognosis [21–23], therefore the importance of improving QoL is essential. We hypothesize that better QoL at baseline may reflect a less advanced cancer stage. Furthermore, less deterioration in QoL during treatment could have less impact on patients' physical and psychological status, permitting patients to receive further life-extending treatment.

Chemoradiotherapy is the main treatment modality for nasopharyngeal carcinoma. Previous studies observed a general trend in QoL deterioration across most QoL criteria during, and at the end of radiotherapy [24–26]. In this study, we also demonstrated that weight gain did not show this trend. The scores for the remaining 17 criteria showed a generally increasing trend. Pain, swallowing, sensory problems, trouble with social eating, dry mouth, sticky saliva, coughing, feeling ill, nutritional supplements, and weight loss were significantly different between T0 compared with T1-T6. Although we noted a reduction in the use of the feeding tube at T2, we believe this may be the consequence of incompletion of the life quality questionnaire at this time point rather than an association with QoL improvement. The results present a continuous exacerbation of life quality for NPC patients throughout the entire course of radiotherapy. We believe this reflects a deterioration in the physical and mental condition of these patients, which has implications for the administration of radiotherapy and chemotherapy. Meanwhile, Fang and Huang et al. reported a gradual recovery in most of the criteria at 3 and 12 months post-treatment [24, 26]. A similar phenomenon has also been observed in other studies [25, 27].

ROM is a common and acute toxic complication of RT for NPC patients [7]. IMRT can reduce the dose to normal tissue compared with 3D-CRT, but no significant differences have been observed between these two RT technologies on overall incidence of ROM and its severity [10]. Considering severe oral pain, local infection, dysphagia, and consequent malnutrition caused by ROM, ROM has a significant role in affecting life quality. Only a few studies have been conducted on this topic, therefore we performed this study to assess the association between ROM and life quality during RT for NPC patients. As shown in Table 3, there were significant differences ($p < 0.05$) were found at most T4-T6 time points between groups (especially mild vs severe) in the most scales (pain, swallowing, speech problem, sensory problem, trouble with social eating, etc). The analysis of Repeated Measures ANOVA further supported this result. The above results indicated that ROM was related to life quality.

In our previous studies, we demonstrated that the severity of ROM developed as the treatment continued and reached a peak severity between T3-T6 [12], which accords with the data generated in this QoL study. We further illustrate the association between ROM and life quality, and we speculate that severe ROM is more detrimental to QoL. The underlying mechanism is unclear. Intolerable oral pain, local infection, dysphagia, and consequent malnutrition might lead to physical and psychological disorders, which may underpin the association. A retrospective study exploring QoL in oral cancer patients also found post-

treatment oral mucositis was significantly associated with physical disorders such as pain, psychological problems such as depression. In totality, this could result in bleak future prospects, social isolation, reduced well-being and QoL [28]. Therefore, early and considered supportive interventions should conducted during chemoradiotherapy for NPC patients, to reduce physical and psychological suffering, while also improving QoL and potentially prognosis.

The study had several limitations. Although the sample size was not small, some patients did not finish completing the QLQ-H&N 35 at some time points due to intensive follow-up during the entire treatment course. This led to the loss of some data. Furthermore, there were some significant differences in T0 and data fluctuation, and this could also be due to loss of some data. However, in our previous study, there was a significant difference observed at T0 with respect to the NRS2002 questionnaire score [12]. The reason for this is not known. Since the questionnaire evokes self reporting, its reliability will be affected by the patient's education level, which might be associated with ROM severity, where the well-educated generally have better oral hygiene[29, 30]. Finally, the study only used the QLQ-H&N 35 which focused mostly on symptoms, side effects, some degree of social function, and body image/sexuality, rather inclusion of multiple questionnaires like the QLQ C30.

Conclusion

This prospective study demonstrated that ROM was associated with QoL in NPC patients during treatment, and that patients with severe ROM tended to develop worsening QoL through RT. Considering the relationship between QoL and disease prognosis, we suggest more supportive interventions should be promptly introduced to alleviate both physical and psychological of patients.

Declarations

Data Availability Statement

The data used in the study analyses can be made available by the corresponding author on reasonable request.

Ethics Statement

The study was approved by the ethical committees of five medical centers, Zhejiang Cancer Hospital (IRB-2018-180), Sun Yat-sen University Cancer Center (B2019-069-01), Affiliated Cancer Hospital of Zhengzhou University (2019268), Affiliated Hospital of Guangdong Medical University (PJ2019-063), and Affiliated Huaian No.1 People's Hospital of Nanjing Medical University (YX-P-2019-059-01). Written informed consent was obtained from the patients in this study.

Author Contributions

Y.C. and R.Q. designed the research. L.W. drafted the manuscript; Other authors recruited the patients and finished the questionnaire; Z.S. perform the statistical analysis; All authors read and approved the final version of manuscript.

Funding

The work received financial support from Qilu Pharmaceutical Co., Ltd.

Conflict of Interest

The authors declare that this study received funding from Qilu Pharmaceutical Co., Ltd. The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

Acknowledgments

We would like to express our sincere appreciation to all patients and medical staffs who participated in this study for their great effort during the pandemic lockdown period.

References

1. Sung, H., et al., *Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries*. CA Cancer J Clin, 2021. **71**: p. 209–249.
2. Chen, Y.P., et al., *Nasopharyngeal carcinoma*. Lancet, 2019. **394**(10192): p. 64–80.
3. Wee, J., et al., *Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety*. J Clin Oncol, 2005. **23**(27): p. 6730–8.
4. Mao, Y.P., et al., *Prognostic factors and failure patterns in non-metastatic nasopharyngeal carcinoma after intensity-modulated radiotherapy*. Chin J Cancer, 2016. **35**(1): p. 103.
5. Zhang, B., et al., *Intensity-modulated radiation therapy versus 2D-RT or 3D-CRT for the treatment of nasopharyngeal carcinoma: A systematic review and meta-analysis*. Oral Oncol, 2015. **51**(11): p. 1041–1046.
6. McDowell, L.J., et al., *Long-Term Late Toxicity, Quality of Life, and Emotional Distress in Patients With Nasopharyngeal Carcinoma Treated With Intensity Modulated Radiation Therapy*. Int J Radiat Oncol Biol Phys, 2018. **102**(2): p. 340–352.
7. Elad, S., et al., *MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy*. Cancer, 2020. **126**(19): p. 4423–4431.
8. Fang, F.M., et al., *Concurrent chemoradiotherapy by simultaneously integrated boost volumetric-modulated arc therapy for nasopharyngeal carcinoma-toxicity/quality of life and survival*. Head Neck, 2019. **41**(5): p. 1282–1289.

9. Lee, A.W., et al., *Evolution of treatment for nasopharyngeal cancer–success and setback in the intensity-modulated radiotherapy era*. Radiother Oncol, 2014. **110**(3): p. 377–84.
10. Yao, Z., et al., *Radiation-induced acute injury of intensity-modulated radiotherapy versus three-dimensional conformal radiotherapy in induction chemotherapy followed by concurrent chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma: a prospective cohort study*. Sci Rep, 2021. **11**(1): p. 7693.
11. Orlandi, E., et al., *Multivariable model for predicting acute oral mucositis during combined IMRT and chemotherapy for locally advanced nasopharyngeal cancer patients*. Oral Oncol, 2018. **86**: p. 266–272.
12. Shu, Z., et al., *Nutritional Status and Its Association With Radiation-Induced Oral Mucositis in Patients With Nasopharyngeal Carcinoma During Radiotherapy: A Prospective Study*. Front Oncol, 2020. **10**: p. 594687.
13. Trotti, A., et al., *Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review*. Radiother Oncol, 2003. **66**(3): p. 253–62.
14. Li, K., et al., *Oral Mucosa Dose Parameters Predicting Grade ≥ 3 Acute Toxicity in Locally Advanced Nasopharyngeal Carcinoma Patients Treated With Concurrent Intensity-Modulated Radiation Therapy and Chemotherapy: An Independent Validation Study Comparing Oral Cavity versus Mucosal Surface Contouring Techniques*. Transl Oncol, 2017. **10**(5): p. 752–759.
15. Lewandowska, A., et al., *Quality of Life of Cancer Patients Treated with Chemotherapy*. Int J Environ Res Public Health, 2020. **17**(19).
16. Bjordal, K., et al., *Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-H&N35*. J Clin Oncol, 1999. **17**(3): p. 1008–19.
17. Schirrmacher, V., *From chemotherapy to biological therapy: A review of novel concepts to reduce the side effects of systemic cancer treatment (Review)*. Int J Oncol, 2019. **54**(2): p. 407–419.
18. Livshits, Z., R.B. Rao, and S.W. Smith, *An approach to chemotherapy-associated toxicity*. Emerg Med Clin North Am, 2014. **32**(1): p. 167–203.
19. Dilalla, V., et al., *Radiotherapy side effects: integrating a survivorship clinical lens to better serve patients*. Curr Oncol, 2020. **27**(2): p. 107–112.
20. Bukowinski, A.J., et al., *Toxicity of Cancer Therapy in Adolescents and Young Adults (AYAs)*. Semin Oncol Nurs, 2015. **31**(3): p. 216–26.
21. Carrillo, J.F., et al., *The impact of treatment on quality of life of patients with head and neck cancer and its association with prognosis*. Eur J Surg Oncol, 2016. **42**(10): p. 1614–21.
22. Kypriotakis, G., et al., *The longitudinal relationship between quality of life and survival in advanced stage cancer*. Psychooncology, 2016. **25**(2): p. 225–31.
23. Ishiyama, H., et al., *Quality of life score as a prognosticator for pharyngeal cancer patients treated with radiotherapy*. Sci Rep, 2022. **12**(1): p. 2387.

24. Fang, F.M., et al., *Quality of life and survival outcome for patients with nasopharyngeal carcinoma receiving three-dimensional conformal radiotherapy vs. intensity-modulated radiotherapy-a longitudinal study*. Int J Radiat Oncol Biol Phys, 2008. **72**(2): p. 356–64.
25. He, Y., et al., *Relationship Between the Comprehensive Nutritional Index and the EORTC QLQ-H&N35 in Nasopharyngeal Carcinoma Patients Treated with Intensity-Modulated Radiation Therapy*. Nutr Cancer, 2017. **69**(3): p. 436–443.
26. Huang, T.L., et al., *Quality of life and survival outcome for patients with nasopharyngeal carcinoma treated by volumetric-modulated arc therapy versus intensity-modulated radiotherapy*. Radiat Oncol, 2020. **15**(1): p. 84.
27. Chen, J., et al., *Influence of Intensity-Modulated Radiation Therapy on the Life Quality of Patients with Nasopharyngeal Carcinoma*. Cell Biochem Biophys, 2015. **73**(3): p. 731–6.
28. Jehn, P., et al., *Physical and Psychological Impairments Associated with Mucositis after Oral Cancer Treatment and Their Impact on Quality of Life*. Oncol Res Treat, 2019. **42**(6): p. 342–349.
29. Vano, M., et al., *The influence of educational level and oral hygiene behaviours on DMFT index and CPITN index in an adult Italian population: an epidemiological study*. Int J Dent Hyg, 2015. **13**(2): p. 151–7.
30. Paulander, J., P. Axelsson, and J. Lindhe, *Association between level of education and oral health status in 35-, 50-, 65- and 75-year-olds*. J Clin Periodontol, 2003. **30**(8): p. 697–704.

Tables

Table 1

		Mild group	Moderate group	Severe group
Age, mean ± SD	Years	49.24 ± 9.05	51.22 ± 10.21	53.07 ± 9.07
Sex ratio	M/F	45/21	54/23	18/12
Barthel index, mean ± SD		92.95 ± 5.11	91.30 ± 5.16	90.37 ± 5.37
T stage, 1–2 n (%)	T1-2/T3-4	16/50	14/63	7/23
N stage, n (%)	N0-2/N3	56/10	58/19	23/7
Neo-chemotherapy, n (%)	Yes/No	63/3	70/7	26/4
Concurrent chemotherapy, n (%)	Yes/No	63/3	71/6	23/7
Radiation technology, n (%)	IMRT/TOMO	43/23	55/22	26/4
Nimotuzumab, n (%)	Yes/No	41/25	47/30	21/9

Table 2

Items	T0	T1	T2	T3	T4	T5	T6
Pain	0.75 ± 2.90	3.14 ± 6.83$^{\&}$	15.67 ± 14.36$^{\&}$	27.16 ± 18.98$^{\&}$	27.58 ± 20.35$^{\&}$	27.91 ± 21.76$^{\&}$	30.93 ± 22.65$^{\&}$
Swallowing	0.91 ± 4.19	2.37 ± 6.73$^{\&}$	11.95 ± 15.11$^{\&}$	23.20 ± 23.21$^{\&}$	26.49 ± 27.09$^{\&}$	26.07 ± 25.28$^{\&}$	29.71 ± 25.46$^{\&}$
Sensory problems	2.89 ± 8.29	11.63 ± 15.55$^{\&}$	22.42 ± 18.87$^{\&}$	33.64 ± 20.05$^{\&}$	38.19 ± 19.25$^{\&}$	41.21 ± 20.31$^{\&}$	42.45 ± 22.28$^{\&}$
Speech problems	1.57 ± 6.37	1.78 ± 5.93^{+}	3.77 ± 9.56*	5.69 ± 13.91$^{\&}$	6.48 ± 13.23$^{\&}$	7.77 ± 14.67$^{\&}$	8.43 ± 16.64$^{\&}$
Trouble with social eating	3.95 ± 8.22	6.84 ± 9.24$^{\&}$	12.05 ± 11.85$^{\&}$	18.42 ± 15.36$^{\&}$	19.54 ± 14.22$^{\&}$	20.91 ± 17.26$^{\&}$	22.55 ± 18.24$^{\&}$
Inability in maintaining social contact	2.44 ± 5.77	3.58 ± 7.40^{+}	4.56 ± 9.82$^{\#}$	6.13 ± 12.74$^{\&}$	6.83 ± 13.71$^{\&}$	7.12 ± 14.63$^{\&}$	8.67 ± 16.71$^{\&}$
Loss of libido	13.46 ± 23.50	14.81 ± 23.50$^{\#}$	14.98 ± 23.19^{+}	15.54 ± 24.79^{+}	18.06 ± 26.77^{++}	18.20 ± 27.58^{+}	19.51 ± 28.61*
Dental Health	7.05 ± 15.15	8.85 ± 16.94*	9.52 ± 19.00^{++}	11.72 ± 21.17$^{\#}$	10.52 ± 19.00*	10.22 ± 18.27*	10.00 ± 17.71*
Opening of mouth	0.85 ± 6.50	3.29 ± 10.65*	4.76 ± 13.79$^{\#}$	12.76 ± 23.54$^{\&}$	12.90 ± 22.76$^{\&}$	17.38 ± 27.05$^{\&}$	18.63 ± 25.88$^{\&}$
Dry mouth	5.77 ± 14.25	27.98 ± 18.17$^{\&}$	44.05 ± 21.98$^{\&}$	49.79 ± 23.86$^{\&}$	52.98 ± 24.29$^{\&}$	57.06 ± 23.64$^{\&}$	56.67 ± 23.18$^{\&}$
Sticky saliva	2.78 ± 10.68	21.60 ± 21.49$^{\&}$	38.29 ± 25.18$^{\&}$	48.35 ± 26.28$^{\&}$	50.40 ± 25.27$^{\&}$	55.21 ± 24.95$^{\&}$	58.04 ± 24.94$^{\&}$
Coughing	1.71 ± 7.38	5.76 ± 13.69$^{\&}$	9.33 ± 17.47$^{\&}$	10.29 ± 18.68$^{\&}$	11.11 ± 19.19$^{\&}$	12.88 ± 20.06$^{\&}$	12.35 ± 21.70$^{\&}$
Feeling ill	13.25 ± 22.30	19.55 ± 21.87$^{\&}$	25.60 ± 20.63$^{\&}$	28.40 ± 21.73$^{\&}$	31.94 ± 21.38$^{\&}$	33.33 ± 22.83$^{\&}$	35.10 ± 20.27$^{\&}$
Analgesic consumption	3.85 ± 19.29	4.94 ± 21.73^{+}	5.95 ± 23.73^{+}	13.58 ± 34.36$^{\#}$	14.88 ± 35.70$^{\#}$	12.27 ± 32.91$^{\#}$	13.53 ± 34.30$^{\#}$
Nutritional supplements	12.82 ± 33.54	21.60 ± 41.28$^{\#}$	26.19 ± 44.10$^{\&}$	37.65 ± 48.60$^{\&}$	46.43 ± 50.02$^{\&}$	48.47 ± 50.13$^{\&}$	50.59 ± 50.14$^{\&}$

$^{+}p > 0.10$; $^{++}$ p = 0.05–0.10; *p < 0.05; $^{\#}p < 0.01$; $^{\&}p < 0.001$

Items	T0	T1	T2	T3	T4	T5	T6
Feeding tube	0.00 ± 0.00	1.23 ± 11.08^{+}	0.60 ± 7.72^{+w}	1.23 ± 11.08^{+}	1.19 ± 15.43^{+}	3.68 ± 18.89*	3.53 ± 18.51*
Weight loss	10.90 ± 31.26	25.93 ± 43.96$^{\&}$	47.02 ± 50.06$^{\&}$	59.88 ± 49.17$^{\&}$	68.45 ± 46.61$^{\&}$	62.58 ± 48.54$^{\&}$	61.18 ± 48.88$^{\&}$
Weight gain	5.13 ± 22.13	14.81 ± 35.63$^{\#}$	7.14 ± 25.83^{+}	4.32 ± 20.40^{+}	2.38 ± 15.29^{+}	4.91 ± 21.67^{+}	5.88 ± 23.60^{+}
$^{+}p > 0.10$; $^{++}$ p = 0.05–0.10; *p < 0.05; $^{\#}p < 0.01$; $^{\&}p < 0.001$							

Table 3

Items	Mild group	Moderate group	Severe group	*p* (Mild vs. Moderate)	*p* (Mild vs. Severe)	*p* (Moderate vs. Severe)
Pain						
T0	0.27 ± 1.50	0.72 ± 3.11	1.92 ± 4.29	0.371	**0.015**	0.071
T1	2.51 ± 4.88	2.55 ± 5.53	6.17 ± 11.69	0.977	**0.019**	**0.018**
T2	12.50 ± 15.07	15.46 ± 11.92	23.51 ± 16.21	0.212	**0.001**	**0.010**
T3	20.96 ± 17.31	28.05 ± 17.61	39.51 ± 20.36	**0.023**	**< 0.001**	**0.005**
T4	19.27 ± 17.37	28.33 ± 18.02	43.97 ± 22.26	**0.005**	**< 0.001**	**< 0.001**
T5	19.31 ± 18.01	29.63 ± 22.02	27.91 ± 21.76	**0.004**	**< 0.001**	**0.004**
T6	21.22 ± 20.03	33.11 ± 21.60	46.11 ± 21.30	**0.001**	**< 0.001**	**0.005**
* p < 0.05, **p < 0.01, ***p < 0.001 (Mild vs. Moderate);						
$^{\#}$ p < 0.05, $^{\#\#}$ p < 0.01, $^{\#\#\#}$ p < 0.001 (Mild vs. Severe);						
$^{\&}$ p < 0.05, $^{\&\&}$ p < 0.01, $^{\&\&\&}$ p < 0.001 (Moderate vs. Severe)						

Items	Mild group	Moderate group	Severe group	*p* (Mild vs. Moderate)	*p* (Mild vs. Severe)	*p* (Moderate vs. Severe)
Swallowing						
T0	0.68 ± 3.82	0.85 ± 3.82	1.60 ± 5.78	0.826	0.352	0.435
T1	1.06 ± 4.10	3.24 ± 8.10	3.09 ± 7.36	0.060	0.189	0.919
T2	7.94 ± 13.15	12.50 ± 14.81	19.64 ± 17.30	0.069	**0.001**	**0.029**
T3	16.54 ± 21.44	23.94 ± 20.36	37.04 ± 28.24	0.055	**< 0.001**	**0.010**
T4	17.19 ± 20.46	28.89 ± 30.03	40.80 ± 25.03	**0.009**	**< 0.001**	**0.037**
T5	17.72 ± 22.33	28.82 ± 25.52	37.80 ± 25.51	**0.009**	**< 0.001**	**0.099**
T6	22.14 ± 24.45	30.04 ± 23.46	45.00 ± 26.22	0.057	**< 0.001**	**0.005**

Items	Mild group	Moderate group	Severe group	*p* (Mild vs. Moderate)	*p* (Mild vs. Severe)	*p* (Moderate vs. Severe)
Speech Problems						
T0	1.09 ± 4.40	0.97 ± 4.95	4.27 ± 11.36	0.909	0.032	0.024
T1	1.41 ± 5.08	1.85 ± 5.90	2.47 ± 7.76	0.668	0.441	0.647
T2	3.47 ± 9.26	3.07 ± 9.53	6.35 ± 10.22	0.804	0.185	0.122
T3	5.56 ± 14.81	3.29 ± 8.27	12.35 ± 20.52	0.336	**0.031**	**0.004**
T4	3.65 ± 8.64	6.52 ± 12.80	12.64 ± 19.64	0.194	**0.002**	**0.032**
T5	4.41 ± 8.82	8.49 ± 16.52	13.49 ± 18.23	0.103	**0.006**	0.121
T6	5.56 ± 12.20	7.16 ± 13.78	17.78 ± 26.20	0.558	**0.001**	**0.003**

Items	Mild group	Moderate group	Severe group	*p* (Mild vs. Moderate)	*p* (Mild vs. Severe)	*p* (Moderate vs. Severe)
Sensory Problems						
T0	2.19 ± 7.12	3.14 ± 9.16	3.85 ± 8.57	0.515	0.395	0.713
T1	10.85 ± 16.98	13.89 ± 15.57	7.41 ± 10.67	0.256	0.335	0.065
T2	21.88 ± 17.79	22.37 ± 20.10	23.81 ± 18.39	0.878	0.653	0.732
T3	30.21 ± 16.77	33.33 ± 21.08	42.59 ± 22.33	0.359	**0.007**	0.039
T4	33.85 ± 15.42	39.33 ± 20.62	44.83 ± 21.41	0.091	**0.011**	0.187
T5	36.24 ± 18.34	41.89 ± 20.55	50.60 ± 21.02	0.100	**0.002**	0.050
T6	36.20 ± 17.95	44.08 ± 23.05	51.67 ± 25.28	0.034	**0.002**	0.107

Items	Mild group	Moderate group	Severe group	*p* (Mild vs. Moderate)	*p* (Mild vs. Severe)	*p* (Moderate vs. Severe)
Difficulty with Social Eating						
T0	3.28 ± 6.85	2.42 ± 5.91	9.62 ± 13.06	0.533	**0.001**	**< 0.001**
T1	5.42 ± 7.94	6.71 ± 9.03	10.49 ± 11.69	0.414	**0.017**	0.068
T2	7.94 ± 10.33	13.38 ± 11.55	17.86 ± 12.97	0.005	**< 0.001**	0.076
T3	14.71 ± 13.83	17.61 ± 13.62	29.32 ± 18.40	0.252	**< 0.001**	**0.001**
T4	14.45 ± 9.87	19.33 ± 13.64	31.32 ± 17.06	**0.029**	**< 0.001**	**< 0.001**
T5	14.95 ± 11.61	21.64 ± 17.56	32.44 ± 21.07	**0.018**	**< 0.001**	**0.003**
T6	15.49 ± 10.59	22.26 ± 16.80	38.33 ± 24.43	**0.017**	**< 0.001**	**< 0.001**

Items	Mild group	Moderate group	Severe group	*p* (Mild vs. Moderate)	*p* (Mild vs. Severe)	*p* (Moderate vs. Severe)
Difficulty maintaining Social Contact						
T0	2.19 ± 5.27	1.26 ± 3.66	6.15 ± 9.22	0.342	**0.003**	**< 0.001**
T1	3.17 ± 7.07	2.96 ± 6.89	6.17 ± 9.04	0.868	0.078	0.055
T2	4.06 ± 9.98	3.51 ± 9.27	8.57 ± 10.24	0.737	**0.042**	**0.019**
T3	5.94 ± 12.85	3.57 ± 8.34	13.33 ± 18.58	0.267	**0.010**	**0.001**
T4	4.69 ± 9.55	5.51 ± 14.09	14.94 ± 17.52	0.716	**0.001**	**0.001**
T5	3.92 ± 7.91	7.59 ± 18.09	13.10 ± 14.79	0.140	**0.006**	0.087
T6	5.31 ± 9.52	7.46 ± 17.14	18.89 ± 23.10	0.433	**< 0.001**	**0.001**

Items	Mild group	Moderate group	Severe group	*p* (Mild vs. Moderate)	*p* (Mild vs. Severe)	*p* (Moderate vs. Severe)
Loss of libido						
T0	10.66 ± 20.65	11.11 ± 20.35	26.28 ± 32.72	0.910	**0.004**	**0.005**
T1	12.70 ± 20.89	12.50 ± 20.89	25.93 ± 32.14	0.960	**0.014**	**0.011**
T2	11.98 ± 17.69	14.47 ± 23.62	23.21 ± 30.88	0.524	**0.033**	0.088
T3	11.72 ± 20.07	13.62 ± 21.88	29.63 ± 35.91	0.649	**0.001**	**0.004**
T4	13.02 ± 19.80	16.44 ± 25.63	33.33 ± 36.73	0.439	**0.001**	**0.003**
T5	14.29 ± 22.37	16.90 ± 27.62	30.36 ± 34.89	0.578	**0.010**	**0.027**
T6	15.36 ± 23.25	17.76 ± 28.20	32.78 ± 36.22	0.615	**0.006**	**0.014**

Items	Mild group	Moderate group	Severe group	*p*(Mild vs Moderate)	*p*(Mild vs Severe)	*p*(Moderate vs Severe)
Dental Health						
T0	5.46 ± 13.85	6.28 ± 13.13	12.82 ± 21.24	0.758	**0.038**	0.060
T1	7.41 ± 16.33	7.87 ± 15.31	14.81 ± 21.35	0.874	0.058	0.069
T2	9.90 ± 20.30	10.09 ± 18.87	7.14 ± 16.62	0.953	0.525	0.486
T3	8.33 ± 17.82	13.62 ± 22.24	14.81 ± 25.04	0.149	0.183	0.802
T4	5.73 ± 15.21	10.22 ± 18.15	21.84 ± 24.03	0.150	**< 0.001**	**0.004**
T5	6.88 ± 14.86	9.26 ± 17.89	20.24 ± 22.84	0.438	**0.001**	**0.006**
T6	9.90 ± 16.46	7.02 ± 16.61	17.78 ± 20.96	0.331	**0.042**	**0.005**

Items	Mild group	Moderate group	Severe group	*p*(Mild vs Moderate)	*p*(Mild vs Severe)	*p*(Moderate vs Severe)
Opening of Mouth						
T0	0.55 ± 4.27	1.45 ± 8.92	0.00 ± 0.00	0.432	0.721	0.336
T1	3.17 ± 11.54	3.24 ± 9.94	3.70 ± 10.68	0.971	0.830	0.848
T2	4.69 ± 15.56	3.95 ± 10.84	7.14 ± 16.62	0.753	0.434	0.297
T3	10.94 ± 21.46	8.92 ± 17.78	27.16 ± 34.64	0.608	**0.002**	**0.001**
T4	6.25 ± 14.40	10.22 ± 18.96	34.48 ± 32.71	0.257	**< 0.001**	**< 0.001**
T5	10.05 ± 19.52	18.52 ± 28.47	30.95 ± 32.62	0.063	**0.001**	**0.035**
T6	13.54 ± 21.18	16.23 ± 24.03	35.56 ± 32.68	0.524	**< 0.001**	**< 0.001**

Items	Mild group	Moderate group	Severe group	*p* (Mild vs. Moderate)	*p* (Mild vs. Severe)	*p* (Moderate vs. Severe)
Dry Mouth						
T0	4.37 ± 11.35	4.35 ± 12.67	12.82 ± 21.24	0.992	**0.011**	**0.009**
T1	26.98 ± 16.78	28.24 ± 19.10	29.63 ± 19.25	0.690	0.530	0.736
T2	40.10 ± 19.86	41.67 ± 18.95	59.52 ± 27.75	0.661	**< 0.001**	**< 0.001**
T3	47.40 ± 22.85	47.42 ± 23.68	61.73 ± 23.94	0.996	**0.008**	0.008
T4	46.88 ± 22.79	54.22 ± 24.37	63.22 ± 24.14	0.071	**0.002**	0.085
T5	49.21 ± 23.08	59.72 ± 24.35	67.86 ± 16.93	**0.008**	**< 0.001**	0.110
T6	50.00 ± 22.22	58.77 ± 24.26	65.56 ± 18.54	**0.023**	**0.002**	0.166

Items	Mild group	Moderate group	Severe group	*p* (Mild vs. Moderate)	*p* (Mild vs. Severe)	*p* (Moderate vs. Severe)
Sticky Saliva						
T0	2.19 ± 8.32	0.97 ± 5.63	8.97 ± 20.13	0.504	**0.006**	**0.001**
T1	20.63 ± 21.11	22.22 ± 20.93	22.22 ± 24.46	0.671	0.750	1.000
T2	36.46 ± 25.70	40.35 ± 24.53	36.90 ± 26.20	0.365	0.938	0.538
T3	45.83 ± 27.54	47.42 ± 24.98	56.79 ± 25.84	0.726	0.070	0.115
T4	47.92 ± 23.66	49.33 ± 27.05	58.62 ± 22.98	0.741	0.059	0.093
T5	50.26 ± 25.31	55.09 ± 25.12	66.67 ± 20.29	0.254	**0.004**	**0.035**
T6	53.65 ± 25.63	58.77 ± 24.26	65.56 ± 23.95	0.224	**0.031**	0.205

Items	Mild group	Moderate group	Severe group	*p* (Mild vs. Moderate)	*p* (Mild vs. Severe)	*p* (Moderate vs. Severe)
Coughing						
T0	1.09 ± 5.99	0.97 ± 5.63	5.13 ± 12.26	0.921	**0.019**	**0.014**
T1	5.29 ± 14.4391	5.56 ± 12.51	7.41 ± 14.12	0.911	0.505	0.552
T2	9.38 ± 18.28	7.89 ± 16.21	13.10 ± 18.90	0.618	0.349	0.180
T3	9.90 ± 18.48	8.92 ± 16.86	14.81 ± 23.27	0.762	0.253	0.165
T4	8.33 ± 15.71	9.78 ± 18.80	20.69 ± 24.26	0.652	**0.004**	**0.009**
T5	8.47 ± 15.80	13.43 ± 21.42	21.43 ± 22.62	0.146	**0.004**	0.070
T6	9.90 ± 16.46	10.53 ± 21.92	22.22 ± 29.14	0.862	**0.010**	**0.012**

Items	Mild group	Moderate group	Severe group	*p* (Mild vs. Moderate)	*p* (Mild vs. Severe)	*p* (Moderate vs. Severe)
Feeling ill						
T0	10.38 ± 19.76	10.63 ± 20.21	26.92 ± 28.31	0.948	**0.001**	**0.001**
T1	16.93 ± 20.63	18.98 ± 20.80	27.16 ± 26.21	0.585	**0.042**	0.097
T2	23.44 ± 21.97	26.32 ± 19.10	28.57 ± 21.69	0.413	0.274	0.622
T3	24.48 ± 19.91	27.70 ± 19.51	39.51 ± 27.79	0.380	**0.002**	**0.015**
T4	29.69 ± 18.89	30.22 ± 20.63	41.38 ± 26.21	0.882	**0.014**	**0.017**
T5	30.16 ± 22.17	34.26 ± 21.65	38.10 ± 26.78	0.299	0.127	0.451
T6	31.25 ± 17.69	35.53 ± 19.88	42.22 ± 24.66	0.210	**0.014**	0.123

Items	Mild group	Moderate group	Severe group	*p* (Mild vs. Moderate)	*p* (Mild vs. Severe)	*p* (Moderate vs. Severe)
Analgesic consumptions						
T0	4.92 ± 21.80	2.90 ± 16.90	3.85 ± 19.61	0.554	0.814	0.832
T1	3.17 ± 17.67	5.56 ± 23.07	7.41 ± 26.69	0.528	0.400	0.707
T2	3.13 ± 17.54	5.26 ± 22.48	14.29 ± 35.63	0.593	**0.038**	0.085
T3	12.50 ± 33.33	9.86 ± 30.02	25.93 ± 44.66	0.654	0.088	**0.039**
T4	7.81 ± 27.05	16.00 ± 36.91	27.59 ± 45.49	0.174	**0.013**	0.135
T5	4.76 ± 21.47	12.50 ± 33.30	28.57 ± 46.00	0.164	**0.001**	**0.026**
T6	4.69 ± 21.30	14.47 ± 35.42	30.00 ± 46.61	0.085	**0.001**	**0.032**

Items	Mild group	Moderate group	Severe group	*p* (Mild vs. Moderate)	*p* (Mild vs. Severe)	*p* (Moderate vs. Severe)
Nutritional Supplement						
T0	8.20 ± 27.66	11.59 ± 32.25	26.92 ± 45.23	0.560	**0.017**	**0.046**
T1	20.63 ± 40.79	22.22 ± 41.87	22.22 ± 42.37	0.825	0.868	1.00
T2	26.56 ± 44.52	23.68 ± 42.80	32.14 ± 47.56	0.702	0.579	0.389
T3	39.06 ± 49.17	35.21 ± 48.10	40.74 ± 50.07	0.648	0.881	0.617
T4	45.31 ± 50.17	42.67 ± 49.79	58.62 ± 50.12	0.756	0.236	0.146
T5	47.62 ± 50.34	45.83 ± 50.18	57.14 ± 50.40	0.837	0.406	0.314
T6	51.56 ± 50.37	48.68 ± 50.31	53.33 ± 50.74	0.737	0.874	0.669

Items	Mild group	Moderate group	Severe group	*p* (Mild vs. Moderate)	*p* (Mild vs. Severe)	*p* (Moderate vs. Severe)
Feeding Tube						
T0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	-	-	-
T1	0.00 ± 0.00	2.78 ± 16.55	0.00 ± 0.00	0.147	1.00	0.267
T2	0.00 ± 0.00	1.32 ± 11.47	0.00 ± 0.00	0.317	1.00	0.443
T3	1.56 ± 12.50	1.41 ± 11.87	0.00 ± 0.00	0.936	0.542	0.577
T4	3.13 ± 17.54	0.00 ± 0.00	3.45 ± 18.57	0.168	0.913	0.236
T5	4.76 ± 21.47	2.78 ± 16.55	3.57 ± 18.90	0.545	0.783	0.851
T6	6.25 ± 24.40	2.63 ± 16.11	0.00 ± 0.00	0.250	0.128	0.510

Items	Mild group	Moderate group	Severe group	*p* (Mild vs. Moderate)	*p* (Mild vs. Severe)	*p* (Moderate vs. Severe)
Weight loss						
T0	9.84 ± 30.03	8.70 ± 28.38	19.23 ± 40.19	0.836	0.201	0.145
T1	28.57 ± 45.54	25.00 ± 43.61	22.22 ± 42.37	0.640	0.533	0.781
T2	34.38 ± 47.87	57.89 ± 49.70	46.43 ± 50.79	**0.005**	0.281	0.293
T3	60.94 ± 49.17	60.56 ± 49.22	55.56 ± 50.64	0.965	0.636	0.655
T4	64.06 ± 48.36	74.67 ± 43.78	62.07 ± 49.38	0.182	0.849	0.218
T5	58.73 ± 49.63	63.89 ± 48.37	67.86 ± 47.56	0.540	0.411	0.715
T6	59.38 ± 49.50	61.84 ± 48.90	63.33 ± 49.01	0.768	0.716	0.888

Items	Mild group	Moderate group	Severe group	*p* (Mild vs. Moderate)	*p* (Mild vs. Severe)	*p* (Moderate vs. Severe)
Weight gain						
T0	3.28 ± 17.96	2.90 ± 16.90	15.38 ± 36.79	0.921	0.019	0.014
T1	11.11 ± 31.68	16.67 ± 37.53	18.52 ± 39.58	0.369	0.369	0.819
T2	9.38 ± 29.38	5.26 ± 22.48	7.14 ± 26.23	0.351	0.704	0.743
T3	3.13 ± 17.54	2.82 ± 16.67	11.11 ± 32.03	0.930	0.088	0.073
T4	1.56 ± 12.50	2.67 ± 16.22	3.45 ± 18.57	0.673	0.584	0.816
T5	4.76 ± 21.47	5.56 ± 23.07	3.57 ± 18.90	0.833	0.810	0.683
T6	10.94 ± 31.46	3.95 ± 19.60	0.00 ± 0.00	0.080	0.036	0.434
Repeated ANOVA measurements: Pain $p < 0.001$; Swallowing $p < 0.001$; Sensory problems $p = 0.042$; Speech problems $p = 0.025$; Trouble with social eating $p < 0.001$; Inability to maintain social contact $p = 0.002$; Loss of libido $p = 0.009$; Dental health $p = 0.019$; Opening of mouth $p < 0.001$; Dry mouth $p < 0.001$; Sticky saliva $p = 0.047$; Coughing $p = 0.017$; Feeling ill $p = 0.010$; Analgesia consumption $p = 0.007$; Nutritional supplement $p = 0.289$; Feeding tube $p = 0.850$; Weight loss $p = 0.218$; Weight gain $p = 0.693$						