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Original Article

Oral dose-volume parameters as independent predictors of severe radiation-induced mucositis in nasopharyngeal carcinoma patients: a retrospective study

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Abstract: Objective: To investigate the association between clinical factors, oral dose-volume parameters during radiotherapy for nasopharyngeal carcinoma (NPC), and the development of severe radiation-induced oral mucositis (ROM). It also aims to identify predictive risk factors for severe ROM to support preventive strategies. Methods: Clinical data from 175 NPC patients treated at Jiangxi Cancer Hospital between July 2023 and February 2024 were analyzed. The associations between clinical factors, oral dose-volume parameters, and severe ROM were assessed using univariate and multivariate logistic regression analyses. Results: The incidence of severe ROM was 34.3% (60/175). Univariate analysis demonstrated significant correlations between severe ROM and dose-volume parameters, including V_{30} (t = 2.497, P = 0.013), V_{35} (t = 3.348, P = 0.001), V_{40} (t = 3.344, P = 0.001), V_{45} (t = 3.289, P = 0.001), V_{50} (t = 3.291, P = 0.001), and the mean dose (D_{mean}) (t = 3.863, P < 0.001). Multivariate analysis identified oral mucosal V_{35} and D_{mean} as independent risk factors for severe ROM. Receiver operating characteristic (ROC) curve analysis determined a cutoff value of 37.38% for oral V_{35}, with an area under the curve (AUC) of 0.652 (95% CI: 0.565-0.738, P = 0.044). For D_{mean}, the cutoff value was 3471.4 cGy, with an AUC of 0.666 (95% CI: 0.580-0.751, P < 0.001). Conclusion: The irradiated oral mucosa volume at V_{35} and D_{mean} are independent predictors of severe oral mucositis in NPC patients undergoing radiotherapy. These findings highlight the importance of optimizing oral dose constraints to mitigate ROM severity and improve treatment tolerability.

Keywords: Nasopharyngeal carcinoma, radiotherapy, severe oral mucositis, risk factors, dose-volume parameters

Introduction

Nasopharyngeal carcinoma (NPC) is one of the most prevalent malignancies in China, with its incidence demonstrating notable geographical variation worldwide. The highest rates are reported in regions such as Southeast Asia and North Africa, with southern China also recognized as a high-prevalence area [1]. Radiotherapy remains the cornerstone of NPC treatment, playing a critical role in tumor control, metastasis prevention, and improving both survival rates and quality of life [2]. However, radiotherapy is often associated with significant adverse effects, particularly mucositis. Studies show that over 90% of cases develop mucositis to varying degrees during radiotherapy, with nearly all affected when undergoing concurrent chemoradiotherapy [3].

Radiation-induced oral mucositis (ROM) is the most common radiotherapy-related adverse effect, manifesting as inflammation, erythema, swelling, erosion, and ulceration of the oral mucosa. These symptoms severely impair functions such as eating, chewing, swallowing, and speaking. ROM is also associated with complications including malnutrition, pain, infections, and bleeding, all of which collectively diminish patients' quality of life and compromise treatment outcomes [4, 5]. The severity and progression of ROM are influenced by multiple factors, including radiation dose, treatment duration, delivery techniques, and irradiated vol-

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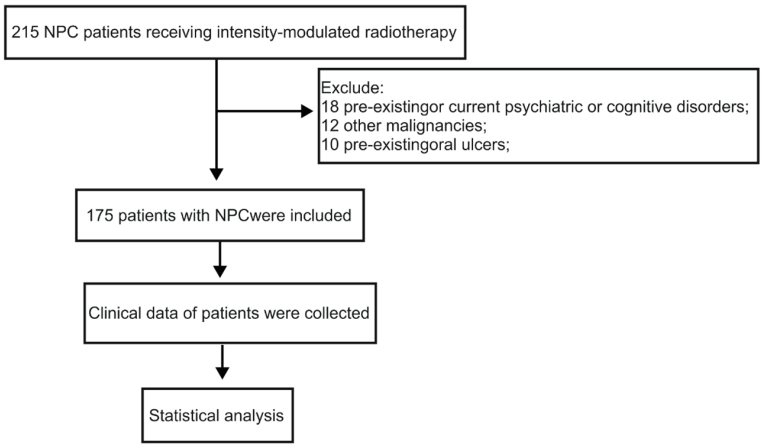

Figure 1. Patient selection process for this study.

ume, as well as patient-specific variables such as comorbidities, genetic predisposition, and oral hygiene practices [6].

In recent years, increasing attention has been paid to factors influencing ROM during radiotherapy for nasopharyngeal cancer, particularly the oral irradiated dose. This refers to the radiation absorbed by the oral mucosa, commonly expressed as the mean oral cavity dose (MOCD) or the oral cavity dose-volume histogram (OCDVH). Previous research has demonstrated a strong correlation between higher radiation doses to the oral cavity and increased incidence and severity of ROM [7]. Studies on patients with head and neck malignancies have shown that restricting the cumulative oral cavity radiation dose to below 32 Gray (Gy) significantly reduces the risk of severe mucositis (grade 2: 25%; grade 3: 0%) [8, 9]. These findings highlight the importance of optimizing dose constraints to minimize ROM-related morbidity.

Despite these advances, no consensus has been reached regarding the specific dosimetric thresholds that effectively reduce the risk of ROM in NPC patients. This study systematically investigated the influence of oral dose-volume parameters on ROM severity, aiming to identify key dose constraints that could inform and refine radiotherapy protocols. By providing novel insights into the relationship between oral cavity irradiation and ROM, this study seeks to enhance treatment strategies and offer practical guidance for optimizing NPC radiotherapy to improve patient outcomes.

Materials and methods

Source of cases and basic information

This study enrolled 175 patients with NPC who were admitted to Jiangxi Cancer Hospital between July 2023 and February 2024. All patients underwent CT simulation for radiotherapy planning and received intensity-modulated radiotherapy (IMRT) at a dose of 2.12 Gy per fraction, administered five days per week, for a total dose of 69.96 Gy. Inclusion criteria: age between 18 and 70 years; newly diagnosed, histopathologically confirmed, and previously untreated NPC; an Eastern Cooperative Oncology Group performance status (ECOG PS) score of ≤ 1; and stage I to IVA disease, according to the 8th edition of the Union for International Cancer Control (UICC) staging system [10]. Exclusion criteria: pre-existing or current psychiatric or cognitive disorders; concurrent malignancies; pre-existing oral ulcers before radiotherapy; a history of prior radiotherapy to the head and neck region. A flow chart illustrating the patient selection process is presented in **Figure 1**. This study was approved by the Ethical Review Committee of Jiangxi Cancer Hospital (Approval No. 2023ky080).

Data extraction

Clinical factors assessed in this study included patient sex, age, body mass index (BMI), smoking history, alcohol consumption history, clinical stage, and whether the patients received induction chemotherapy (IC), concurrent chemotherapy (CCRT), immunotherapy, or targeted therapy. Oral cavity contours were delineated based on contrast-enhanced CT images. The anatomical boundaries of the oral cavity were defined as follows: the hard palate (the upper border), the buccal mucosa surrounding the teeth (the anterior border), the floor of the mouth (the lower border), and the surface of the tongue and the position of the uvula (the posterior border). To evaluate the dosimetric impact on the development of severe oral mucositis (SOM), the following dose-volume parameters were analyzed: V_{20} (%), V_{25} (%), V_{30}

(%), V_{35} (%), V_{40} (%), V_{45} (%), and V_{50} (%), as well as the mean dose to the oral cavity (D_{mean}, in centigray (cGy)) and the maximum dose (D_{max}, cGy).

Outcome measures

The primary outcome was the incidence of severe radiation-induced ROM, defined as grade ≥ 3 according to the Radiation Therapy Oncology Group (RTOG). ROM severity was assessed using the RTOG grading scale for acute radiation injury, which classifies ROM into five grades (0-4). Grade 0: no observable changes; Grade 1: mucosal congestion with mild pain not requiring analgesics; Grade 2: patchy mucositis with inflammatory or bloody exudate, moderate pain, requiring analgesics; Grade 3: confluent fibrinous mucositis, severe pain, requiring narcotic analgesics; Grade 4: ulceration, hemorrhage, and necrosis.

Secondary outcomes included the analysis of dose-volume parameters (V_{30}-V_{50}, D_{mean}, D_{max}) and their association with ROM severity.

Statistical analysis

Statistical analyses were performed using IBM SPSS version 25.0 and GraphPad Prism version 9. Continuous variables that followed a normal distribution were presented as mean ± standard deviation and were analyzed by independent samples t-tests. For data that did not follow a normal distribution, the Mann-Whitney U test (rank-sum test) was applied. Categorical variables were expressed as frequencies and percentages, with group comparisons conducted using the chi-square test. Multivariate analysis was conducted using binary logistic regression. Receiver operating characteristic (ROC) curve analysis was used to determine optimal cutoff values for key dosimetric parameters. A *P*-value < 0.05 was considered statistically significant.

Results

Incidence of ROM and patient characteristics

Among the 175 patients with NPC, 40 cases experienced mild ROM (grade 0-1), 75 cases developed moderate ROM (grade 2), and 60 cases had severe ROM (grade 3). Notably, no cases of grade 4 ROM were observed. The overall incidence of severe ROM (≥ grade 3) was 34.3% (60/175), underscoring the substantial burden of this adverse effect during radiotherapy. To identify potential risk factors, various clinical parameters were assessed, including sex, age, BMI, T category, N category, clinical stage, IC, CCRT, targeted therapy, immunotherapy, smoking history, and alcohol consumption. The distribution of these variables is detailed in **Table 1**. Univariate and multivariate logistic regression analyses revealed no significant differences in baseline clinical characteristics between the severe and non-severe ROM groups (all P > 0.05). Specifically, factors such as gender, age, BMI, tumor staging (T and N categories), clinical stage, treatment modalities (IC, CCRT, targeted therapy, and immunotherapy), as well as lifestyle factors like smoking and alcohol consumption, were not significantly associated with the development of severe ROM (**Tables 1**, **2**). These findings suggest that while ROM is a prevalent side effect, its severity may be influenced by factors beyond conventional clinical and demographic parameters.

Effect of dose-volume parameters on severe ROM

Univariate analysis demonstrated a significant association between several oral dose-volume parameters and the development of severe ROM in NPC patients undergoing radiotherapy. Specifically, higher values of V_{30} (t = 2.497, P = 0.013), V_{35} (t = 3.348, P = 0.001), V_{40} (t = 3.344, P = 0.001), V_{45} (t = 3.289, P = 0.001), V_{50} (t = 3.291, P = 0.001), and D_{mean} (t = 3.863, P < 0.001) were significantly correlated with an increased risk of severe ROM (**Table 3**).

Analysis of the mean dose-volume histogram further supported these findings, revealing that patients who developed severe ROM were more likely to have received higher radiation dose volumes. A dose-dependent trend was observed, with the incidence of severe ROM increasing progressively with higher radiation exposure (**Figure 2**). This pattern underscores the importance of precise dose-volume control in reducing the risk of ROM during radiotherapy.

Multivariate analysis provided additional insight, indicating that even small increments in radiation exposure significantly elevated the

Table 1. Associated between clinical factors with severe ROM analyzed by univariate analysis

Variable		ROM(n = 115) No. (%)	Severe ROM (n = 60) No. (%)	X^2	*P* value
Sex	Male	87 (75.7)	46 (76.7)	0.022	0.881
	Female	28 (24.3)	14 (23.3)		
Age (year)	≤ 52	63 (54.8)	27 (45)	1.511	0.219
	> 52	52 (45.2)	33 (55)		
BMI (kg/m^2)	< 22.8	58 (50.4)	28 (46.7)	0.224	0.636
	≥ 22.8	57 (49.6)	32 (53.3)		
T category	T_1-T_2	12 (10.4)	7 (11.7)	0.062	0.804
	T_3-T_4	103 (89.6)	53 (88.3)		
N category	N_0-N_1	67 (58.3)	38 (63.3)	0.423	0.516
	N_2-N_3	48 (41.7)	22 (36.7)		
Clinical stage	I-III	60 (52.2)	29 (48.3)	0.233	0.630
	IV	55 (47.8)	31 (51.7)		
IC	Yes	84 (73)	39 (65)	1.221	0.269
	No	31 (27)	21 (35)		
CCRT	Yes	98 (85.2)	48 (80)	0.776	0.378
	No	17 (14.8)	12 (20)		
Target therapy	Yes	89 (77.4)	48 (80)	0.158	0.691
	No	26 (22.6)	12 (20)		
Immunotherapy	Yes	15 (13)	7 (11.7)	0.068	0.794
	No	100 (87)	53 (88.3)		
Smoking	Yes	40 (34.8)	22 (36.7)	0.061	0.805
	No	75 (65.2)	38 (63.3)		
Drinking	Yes	26 (22.6)	16 (26.7)	0.365	0.551
	No	89 (77.4)	44 (73.3)		

ROM: radiation-induced oral mucositis; BMI: body mass index; IC: induction chemotherapy; CCRT: concurrent chemoradiotherapy.

risk of severe ROM. Specifically, each 1% increase in V_{35}, the risk of severe ROM increased by 0.074-fold (P = 0.015, 95% CI: 1.014-1.137). Likewise, for each additional cGy in D_{mean}, the likelihood of severe ROM increased by 0.02-fold (P = 0.002, 95% CI: 1.007-1.033) (**Table 4**). These findings emphasize the critical need for careful radiation dose planning to minimize the risk of severe mucositis and improve patient outcomes.

Volume-response curve analysis

ROC curve analysis identified a critical threshold of 37.38% for oral V_{35}, above which the risk of severe ROM significantly increased. At this cutoff, specificity was 49.6% (57/115), sensitivity reached 78.3% (47/60), and overall accuracy was 59.4% (104/175). The corresponding positive and negative likelihood ratios were 1.554 and 0.437, respectively. The area under the curve (AUC) was 0.652 (P = 0.044, 95% CI: 0.565-0.738), indicating moderate predictive value (**Figure 3**).

Similarly, analysis of D_{mean} revealed a critical threshold of 3471.4 cGy. Exceeding this value was associated with a specificity of 51.3% (59/115), sensitivity of 75.0% (45/60), and an overall accuracy remained of 59.4% (104/175). The corresponding positive and negative likelihood ratios were 1.540 and 0.487, respectively. The AUC for D_{mean} was slightly higher at 0.666 (P < 0.001, 95% CI: 0.580-0.751), indicating a stronger predictive capability (**Table 5**).

These findings suggest that patients with an oral V_{35} > 37.38% and a D_{mean} exceeding 3471.4 cGy are at a significantly elevated risk of developing severe ROM. These thresholds emphasize the importance of careful dose optimization in radiotherapy planning to mitigate ROM

Table 2. Univariate and multivariate analyses of factors influencing severe ROM

Variable		Univariable analyses		Multivariate analyses	
		OR (95% CI)	*P* value	*OR (95% CI)*	*P* value
Sex	Male vs. Female	0.95 (0.45-1.97)	0.881		
Age (year)	≤ 52 vs. > 52	1.48 (0.79-2.77)	0.220	1.50 (0.80-2.82)	0.205
BMI (kg/m^2)	< 22.8 vs. ≥ 22.8	1.16 (0.62-2.17)	0.636		
T category	T_1-T_2 vs. T_3-T_4	0.88 (0.33-2.37)	0.804		
N category	N_0-N_1 vs. N_2-N_3	0.81 (0.43-1.54)	0.516		
Clinical stage	I-III vs. IV	1.17 (0.62-2.18)	0.630		
IC	No vs. Yes	0.69 (0.35-1.34)	0.270	0.67 (0.34-1.32)	0.251
CCRT	No vs. Yes	0.69 (0.31-1.57)	0.380		
Target therapy	No vs. Yes	1.17 (0.54-2.52)	0.691		
Immunotherapy	No vs. Yes	0.88 (0.34-2.29)	0.794		
Smoking	No vs. Yes	1.09 (0.57-2.08)	0.805		
Drinking	No vs. Yes	1.25 (0.61-2.56)	0.551		

ROM: radiation-induced oral mucositis; BMI: body mass index; IC: induction chemotherapy; CCRT: concurrent chemoradiotherapy.

Table 3. The effect of oral dose volume parameters on severe ROM indicated by univariate analysis ($\bar{x} \pm s$)

Parameters	ROM	Severe ROM	*t* value	*P* value
V_{20} (%)	92.46 ± 8.50	94.25 ± 6.64	1.415	0.159
V_{25} (%)	73.96 ± 16.47	78.66 ± 16.14	1.802	0.073
V_{30} (%)	55.57 ± 18.12	62.78 ± 18.20	2.497	0.013
V_{35} (%)	39.95 ± 15.35	48.44 ± 16.99	3.348	0.001
V_{40} (%)	29.08 ± 12.75	37.01 ± 15.90	3.344	0.001
V_{45} (%)	21.34 ± 11.09	28.52 ± 14.90	3.289	0.001
V_{50} (%)	15.17 ± 9.65	21.70 ± 13.68	3.291	0.001
D_{mean} (cGy)	3469.62 ± 461.09	3778.60 ± 573.59	3.863	0.000
D_{max} (cGy)	6872.31 ± 575.39	7033.46 ± 564.62	1.770	0.079

D_{mean}: mean dose to the oral cavity; D_{max}: maximum dose to the oral cavity.

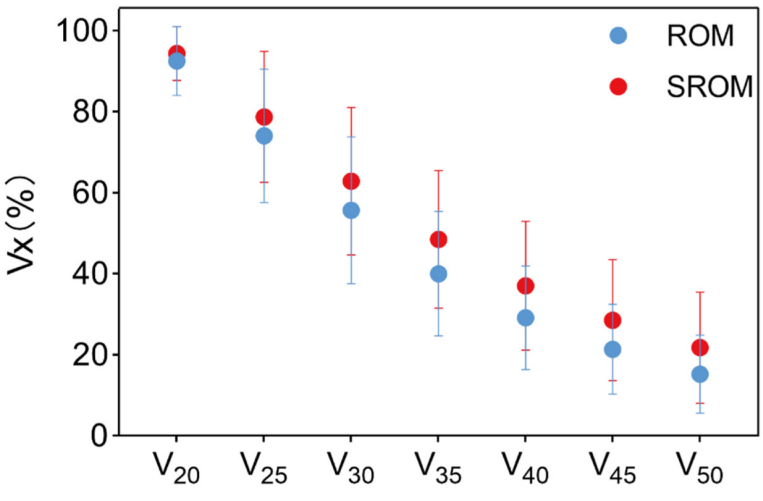

Figure 2. Mean dose-volume parameters in the ROM and SROM groups. SROM: severe radiation-induced oral mucositis.

severity and improve patient outcomes (**Table 6**).

Discussion

Nasopharyngeal carcinoma (NPC) is one of the most prevalent head and neck malignancies in China, with radiotherapy serving as the cornerstone of its treatment [11]. However, radiation-induced oral mucositis (ROM) is a frequent and debilitating side effect, significantly impairing patients' quality of life [12]. Despite advances in radiotherapy techniques, research

Table 4. The effect of oral dose volume parameters on severe ROM indicated by multivariate analysis

Parameters	Univariable analyses		Multivariate analyses	
	OR (95% CI)	*P* value	*OR (95% CI)*	*P* value
V_{20} (%)	1.032 (0.988-1.078)	0.162	0.928 (0.831-1.035)	0.178
V_{25} (%)	1.018 (0.998-1.039)	0.075	0.906 (0.799-1.028)	0.125
V_{30} (%)	1.023 (1.004-1.041)	0.015	0.858 (0.714-1.032)	0.103
V_{35} (%)	1.034 (1.013-1.055)	0.002	1.074 (1.014-1.137)	0.015
V_{40} (%)	1.041 (1.017-1.065)	0.001	0.796 (0.454-1.396)	0.426
V_{45} (%)	1.045 (1.018-1.072)	0.001	1.027 (0.481-2.192)	0.944
V_{50} (%)	1.050 (1.021-1.080)	0.001	0.718 (0.412-1.250)	0.241
D_{mean} (cGy)	1.001 (1.001-1.002)	0.000	1.020 (1.007-1.033)	0.002
D_{max} (cGy)	1.001 (1.000-1.001)	0.083	1.000 (0.999-1.001)	0.508

D_{mean}: mean dose to the oral cavity; D_{max}: maximum dose to the oral cavity.

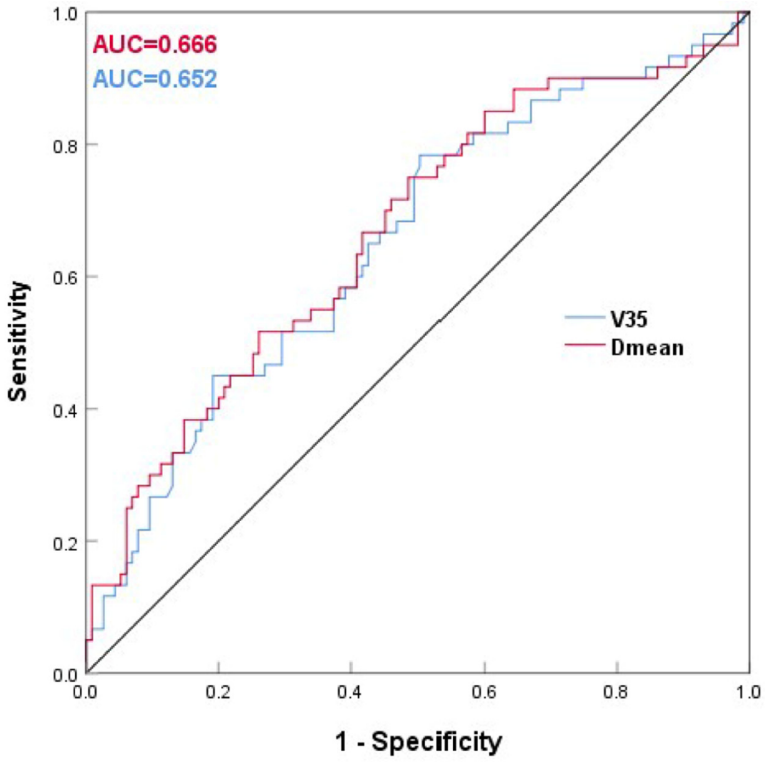

Figure 3. Predictive performances for V_{35} and D_{mean} for severe ROM analyzed using ROC curve. ROM: radiation-induced oral mucositis; ROC: receiver operating characteristic.

Table 5. The predictive value of V_{35} for severe ROM

V_{35} determination results	Actual number of ROM cases		Total
	ROM	Severe ROM	
ROM	57	13	70
Severe ROM	58	47	105
Total	115	60	175

indicates that nearly all head and neck cancer patients treated with IMRT develop some degree of acute ROM, with approximately half experiencing severe ROM [13-16]. A key contributing factor to the high incidence of ROM is the lack of strict dose constraints for the oral cavity during treatment planning [17]. Additionally, the use of induction and concurrent chemotherapy, immunotherapy, and targeted therapies further exacerbates ROM risk [18]. Identifying reliable predictors for severe ROM is essential for early intervention, optimizing treatment strategies, and improving patient management [19].

Previous studies have identified factors such as age, N stage, and the number of induction chemotherapy cycles as independent predictors of severe ROM [20]. However, in this study, no significant association was found between severe ROM and clinical parameters, including sex, age, BMI, T stage, N stage, clinical stage, smoking history, alcohol consumption history, induction chemotherapy, or concurrent chemotherapy. This discrepancy may be due to the lower relative incidence of severe ROM in our cohort, as well as proactive monitoring and timely management

Table 6. The predictive value of D_{mean} for severe ROM

D_{mean} determination results	Actual number of ROM cases		Total
	ROM	Severe ROM	
ROM	59	15	74
Severe ROM	56	45	101
Total	115	60	175

of adverse reactions in our institution. The progression of ROM primarily leads to pain and discomfort, severely impairing oral intake and, in severe cases, causing treatment interruptions [21]. While pain management and nutritional support are critical, identifying predictive factors remains critical to mitigating ROM severity and improving treatment tolerance. Our findings demonstrate that oral dose-volume parameters, particularly V_{35} and D_{mean}, are independent risk factors for severe ROM. These findings align with prior research showing a strong correlation between radiation dose, irradiated volume, and ROM severity.

Ebert et al. reported that head and neck cancer patients with grade 3 mucositis had significantly higher D_{max} and V_{30} values compared to those without severe ROM [22]. Similarly, Li et al. found that in patients receiving carbon ion radiotherapy, severe ROM was significantly associated with dosimetric parameters, and proposed dose constraints for D_{max}, D_{10}, D_{15}, and D_{20} [23]. While different studies suggest varying threshold values, our findings identified V_{35} > 37.38% and D_{mean} > 3471.4 cGy as critical cutoffs, beyond which the incidence of severe ROM increases significantly. These findings further underscore the importance of optimizing dose-volume parameters to reduce ROM risk while maintaining treatment efficacy.

Several strategies have been explored to mitigate radiotherapy-induced ROM. A randomized clinical trial demonstrated that the probiotic *Streptococcus salivarius* K12 significantly reduced both the incidence and severity of ROM [24]. Nutritional interventions, such as early oral nutritional supplementation, have also been identified as protective factors against severe ROM [25, 26]. Moreover, adjunctive treatments, including Yunnan Baiyao and Kangfuxin solutions, have shown efficacy in suppressing inflammatory responses and alleviating mucositis severity [27]. Emerging evidence also suggests that cognitive behavioral therapy (CBT) may help alleviate radiation-induced toxicities, including xerostomia, fatigue, and insomnia, while improving patients' psychological well-being [28].

In our study, BMI was not significantly differ between the non-severe and severe ROM groups. This may be attributed to the relatively small sample size, as well as the early implementation of nutritional support and standardized symptomatic management, which likely mitigated significant weight changes. Nevertheless, early intervention remains crucial for improving patient prognosis and minimizing ROM-related complications.

Despite the valuable insights gained, this study has several limitations. First, the relatively small number of cases with severe ROM may have limited the statistical power of our findings. Second, potential selection bias may have occurred during patient enrollment. Third, we only documented the highest grade of mucositis during radiotherapy, without tracking its progression or evaluating post-treatment outcomes. Future large-scale, multi-center studies are needed to validate these findings and further investigate the relationship between predictive factors and the development of severe ROM.

Conclusion

This study investigated the relationship between clinical factors, oral dose-volume parameters, and the risk of severe ROM in NPC patients undergoing radiotherapy. The findings identified V_{35} and D_{mean} as independent predictive indicators for severe ROM, reinforcing the importance of dose constraints to the oral mucosa. Optimizing dose-volume parameters during radiotherapy planning may help reduce the incidence of severe ROM, enhance patient tolerability, and improve treatment outcomes. Further research with larger sample sizes and multi-center validation [29] is warranted to refine predictive models and develop targeted intervention strategies.

Disclosure of conflict of interest

None.

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