

# Impact of Factors on Acute Radiation Oral Mucositis for Nasopharyngeal Carcinoma Patients Treated with Concurrent Intensity-Modulated Radiation Therapy and Chemoradiotherapy: A Retrospective Study

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## Research article

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# Abstract

## Background

To retrospectively studied the medical records in the latest 4 years in order to investigate the occurrence and influencing factors of radiation-induced oral mucositis in patients with nasopharyngeal carcinoma treated with concurrent intensity-modulated radiation therapy and chemoradiotherapy.

## Methods

Between January 2014 and December 2018, 262 patients with non-metastatic nasopharyngeal carcinoma treated with concurrent intensity-modulated radiation therapy and chemoradiotherapy were enrolled in the study. The patients' age, gender, body mass index, smoking, diabetes, clinical stage, hematological parameters before radiotherapy (leukocyte count, erythrocyte count, hemoglobin level, platelet count, lymphocyte count, neutrophil count), PGTV, PCTV1, PCTV2, induction chemotherapy, concurrent chemotherapy interval (weekly or three-weekly chemotherapy) and the concurrent chemotherapeutic drugs (single cisplatin or single lobaplatin or docetaxel plus cisplatin regimen) were examined, and the associations of variables with oral mucositis were analyzed by multivariate logistic regression analysis.

## Results

Only platelet count before radiotherapy is the risk factor for grade 2 and higher acute oral mucositis ( $p = 0.028$ ) with an odds ratio of 1.005 (95% CI: 1.001–1.009). There was no difference in the risk of grade 2 and higher oral mucositis between the single platinum regimen and docetaxel plus cisplatin regimen. The study also found similar responses to oral mucositis between weekly regimen and three-weekly regimen.

## Conclusion

The present retrospective study demonstrated that certain factor may predispose patients with with nasopharyngeal carcinoma treated with concurrent intensity-modulated radiation therapy and chemoradiotherapy to develop oral mucositis.

## Background

Nasopharyngeal carcinoma (NPC) is one of the head and neck tumors with an unbalanced epidemic distribution, with >70% of new cases occurring in East and Southeast Asia[1]. For many years, concurrent chemoradiotherapy (CCRT) with or without adjuvant chemotherapy has been considered the standard treatment for locally advanced NPC[2]. The results of the meta-analysis by Blanchard et al.[3] also showed that CCRT had a better survival benefit for patients with locally advanced NPC. However, concurrent

chemoradiotherapy also aggravates the toxicity, the most severe of which is acute radiation-induced oral mucositis (OM)[4].The incidence and severity of acute radiation-induced oral mucositis is usually not significantly reduced by the application of advanced radiotherapy techniques such as Intensity Modulated Radiation Therapy(IMRT)[5].

Acute radiation-induced oral mucositis can affect the patient's oral function, resulting in problems such as dysphagia, dysgeusia, anorexia, and pain[6]. OM also increases the need for narcotic analgesics, gastric tubes, gastrostomy tubes, and total parenteral nutrition, prolongs hospital stay, and increases the risk of local and systemic infections, and in severe cases causes radiotherapy delay or interruption, which not only affects the treatment outcome, but also causes a serious decrease in the patient's quality of life and increases the cost of medical care[7, 8].

OM results from the interaction of patient, tumor, and treatment-related factors[9]At present, there are few studies on radiation-induced oral mucositis caused by intensity-modulated radiotherapy combined with different concurrent chemotherapy regimenst. This study retrospectively studied the data in the latest 4 years in order to investigate the occurrence and influencing factors of radiation-induced OM in patients with NPC treated with concurrent intensity-modulated radiation therapy and chemoradiotherapy.

## Methods

### Patients

A total of 262 patients with newly diagnosed nasopharyngeal carcinoma were enrolled in the Cancer Center of the First Affiliated Hospital of University of South China, Hengyang City, Hunan Province,China, from January 2014 to December 2018. All patients were required to meet the following conditions: histopathological diagnosis of NPC; complete the whole process of IMRT without interruption; receive intensity-modulated radiotherapy combined with concurrent chemotherapy; no distant metastasis; KPS(Karnofsky Performance Status) of more than 70 points; no other sites of tumors; patients with oral mucosal diseases before radiotherapy were excluded according to the case data. The study was approved by the institutional ethics committee.

### Variables

Patient data were collected from the electronic medical record system, and selected variables included age, gender, body mass index(BMI), smoking, diabetes, clinical stage.In this study, the hematological parameters of patients before radiotherapy were collected, including leukocyte count,erythrocyte count,hemoglobin level,platelet count,lymphocyte count, neutrophil count.The study also collected planning gross target volume(PGTV), planning clinical target volume 1(PCTV1), planning clinical target volume 2(PCTV2), induction chemotherapy, and the concurrent chemotherapy interval (weekly or three-weekly chemotherapy ), and chemotherapeutic drugs (single cisplatin or single lobaplatin or docetaxel plus cisplatin regimen) .

### Radiotherapy

All patients were treated with 6-MV photon IMRT using a Varian23EX, 600C/D linear accelerator, and 120 motorized gratings in the United States to complete IMRT. The patient was placed in supine position, hands were placed on the side of the body. The head, neck and shoulder were fixed with thermoplastic film. All patients were positioned using the Computer Tomography (CT) simulator of General Electric Company(GE). The scanning range was from the top of the head to 1 cm below the clavicular head, the scanning slice thickness was 3 mm, and the slice distance was 3 mm. After scanning, the CT image was transmitted to the Eclipse treatment planning system. The physician in charge delineated the target area and organs at risk layer by layer based on the definition in documents 50 and 62 of the International Radiation Unit and Measurement Committee[10, 11]and determined the dose to the tumor target area and the tolerated dose to the surrounding organs at risk. Nasopharynx gross tumor volume(GTV-nx) and cervical metastatic lymph nodes gross tumor volume(GTV-nd) were delineated based on the boundaries of the primary tumor and cervical metastatic lymph nodes shown by CT and Magnetic Resonance Imaging(MRI). Clinical target volume 1 (CTV1) is GTV plus 5 ~ 10 mm, including the whole nasopharyngeal mucosa (submucosal 5 mm), clinical target volume 2 (CTV2) nasopharyngeal range is nasopharyngeal cavity, posterior nasal cavity, posterior maxillary sinus, pterygopalatine fossa, partial posterior ethmoid sinus, parapharyngeal space, skull base, partial cervical vertebra or clivus. Lesions exceeding the above structures were defined as GTV plus 10 mm. Neck range is the region of positive lymph nodes and 1–2 neck regions downward. In patients with N0, the lower boundary of CTV2 is at the level of the cricoid cartilage. For patients with positive unilateral lymph nodes, CTV2 included ipsilateral zone II, III, IV, and V lymph nodes, and zone II, III, and Va lymph nodes contralateral. For patients with positive lymph nodes bilateral, CTV2 includes lymph nodes in regions II, III, IV, and V. Whether zone I lymph nodes are irradiated depends on the situation. The same intensity-modulated plan was performed for the upper neck plus lower neck plus supraclavicular region and the primary tumor. Mandatory delineations of vital organs are the spinal cord, brainstem, temporal lobe, pituitary gland, parotid gland, lens, optic nerve and chiasm, temporomandibular joint, and mandible.

The prescribed dose to the target area was 66 to 70 Gy, 2.10 to 2.25 Gy/f for GTV-nx, 66 Gy, 2.00 to 2.25 Gy/f for GTV-nd; 60 to 62 Gy, 1.8 to 2.05 Gy/f for CTV-1; and 50 to 56 Gy, 1.7 to 1.8 Gy/f for CTV-2. The physicist designed the IMRT plan as required, and the treatment was performed using a 9-field split protocol, with all patients treated on a Varian IX treatment machine at a frequency of once a day, five times a week for three times.

## Chemotherapy

The weekly regimen was weekly chemotherapy during radiotherapy, and all of them received platinum chemotherapy, with a dose of 25 to 30 mg/m<sup>2</sup> per week for cisplatin, a dose of 15 to 20 mg/m<sup>2</sup> per week for lobaplatin, and a dose of 30 to 40 mg/m<sup>2</sup> per week for nedaplatin.

The three-week regimen was concurrent chemotherapy starting on days 1 to 3 from the start of radiotherapy, 21–28 days per cycle, until the end of radiotherapy. Platinum regimen is cisplatin 25 to 30 mg/m<sup>2</sup> or lobaplatin 15 to 20 mg/m<sup>2</sup> or nedaplatin 30 to 40 mg/m<sup>2</sup> on days 1 to 3. The docetaxel plus

cisplatin regimen (DP regimen) was 60 to 75 mg/m<sup>2</sup> on day 1 combined with cisplatin 25 to 30 mg/m<sup>2</sup> on days 1 to 3.

During chemotherapy, closely monitor the patient's blood routine, liver and kidney function electrolytes, and if the white blood cell count is less than 3000 mm<sup>3</sup> or the platelet count is less than 75,000 mm<sup>3</sup>, delay or discontinue the administration until recovery is observed.

## **Basic Oral Care And Management**

Oral care was routinely performed in all patients during radiotherapy. When oral mucositis occurs, sodium bicarbonate mouthwash, 0.9% normal saline (NS) 100 ml plus lidocaine 5 ml plus dexamethasone 5 mg, and 0.9% NS 100 ml plus recombinant human interleukin-11 3 mg can be used topically to gargle, 3 to 5 times a day, 10 ml/time, containing 5 to 10 minutes before spitting up. Then according to the severity of oral mucositis, 5 ml of lidocaine plus 20 ml of 0.9% NS was given for oxygen nebulization; or topical epidermal growth factor was sprayed to promote mucosal inflammatory surface healing. When oral bacterial culture was positive, antibiotic therapy was implemented on a case-by-case basis, and radiotherapy was suspended if necessary.

## **Acute Toxicity Assessment**

Oral mucositis toxicity was consistently scored three times a week by the physician in charge using the Raditon Therapy Oncology Group/European Organization of Research on Treatment of Cancer RTOG/EORTC scale, and only the highest grade of acute OM in each patient's toxicity assessment was used in the analysis. Oral mucositis is classified as moderate to severe (maximum toxicity score of grade 2 and above) and none/mild (maximum toxicity score of grade 1 or less) because more than grade 2 radiation stomatitis can cause oral pain and has an impact on the patient's quality of life.

## **Statistical analysis**

Statistical analyses were performed using SPSS software (version 26.0). The association between each variable and oral mucositis of grade 2 and above was analyzed by univariate and multivariate logistic regression. In multivariate analysis, stepwise selection was used to enter the regression model for all variables. A p-value < 0.05 was considered statistically significant in all analyses. Categorical variables were tested for association with acute grade 2 and above OM by use of Pearson's test. Independent-samples T test was used to identify difference between continuous variables from patients with and without acute grade 2 and above OM. Parameters statistically significant on the test and t test analysis were considered for a binary logistic regression analysis to identify determined factors for acute grade 2 and above OM. In multivariate analysis, stepwise selection was used to enter the regression model for all variables. A p-value < 0.05 was considered statistically significant in all analyses.

## **Results**

### **Demographic factors of the patients**

Table 1 shows patient characteristics of the cohort. This cohort had 262 NPC patients, including 194 men and 68 women. The median age was 51 years. Based on criteria of the American Joint Committee on Cancer/International Union Against Cancer-5(AJCC/UICC-5),11 patients in phase II, 146 in phase III and 105 in phase IV. All patients received intensity-modulated radiotherapy in combination with concurrent chemotherapy, and 44 patients received induction chemotherapy. The median radiation dose was 70 Gy, and the dose between the 25th to 75th percentiles was 70 to 70 Gy. A total of 96 patients received single cisplatin, 43 followed by single lobaplatin, 123 patients received DP regimen.

A total of 97 patients received weekly chemotherapy, of whom 79.12% (72/91) completed 4 or more cycles of chemotherapy, and the 20.88% (19/91)received 2 or 3 cycles of chemotherapy. Patients on the weekly regimen all received platinum chemotherapy.A total of 171 patients received three-week chemotherapy, of whom 62.57% (107/171)received at least two or more cycles of chemotherapy and the 37.43%(64/171) received one cycle of chemotherapy. In the three-week regimen, 48 patients received single-agent platinum chemotherapy and 123 patients received DP regimen.

### **Table 1**

Demographic factors of the 262 patients

<b>Variable</b>		<b>Number of patients or median (25–75% tile)</b>
Age		51.00(44.00–60.00)
Gender	Male	194
	Female	68
Body mass index (BMI)		21.88(19.95–24.02)
Diabetes	(+)	11
	(-)	251
Smokers	(+)	75
	(-)	187
Clinical Phase	Phase II	11
	Phase III	146
	Phase IV	105
Concurrent chemotherapy interval	Weekly chemotherapy	91
	Three-weekly chemotherapy	171
Concurrent chemotherapeutic drugs	single-agent cisplatin	96
	single-agent lobaplatin	43
	DP regimen	123
Induction chemotherapy	(+)	44
	(-)	218
Leukocyte ( $\times 10^9/L$ )		6.36(5.17–7.51)
Erythrocyte ( $\times 10^9/L$ )		4.49(4.15–4.85)
Hemoglobin (g/L)		132.00(122.00-143.00)
Platelet ( $\times 10^9/L$ )		222.00(179.00-263.25)
Lymphocyte( $\times 10^9/L$ )		1.60(1.25–1.95)
Neutrophil ( $\times 10^9/L$ )		3.97(3.11–4.91)
PGTV (Gy)		70.00(70.00–70.00)
PCTV1 (Gy)		62.00(60.00–62.00)



Variable	Number of patients or median (25–75% tile)
PCTV2 (Gy)	54.00(54.00–54.00)

### Factors related to development of grade 2 and higher acute OM during RT

Oral mucositis occurred in 251 (95.80%) of the 305 patients, and mucositis was grade 1, 2, and 3 in 60 (22.90%), 178 (67.90%), and 13 (5.00%) patients, respectively, and no grade 4 OM was found. Table 2 and Table 3 show clinical factors and hematological parameters tested for association with toxicity. Concurrent chemotherapy interval, chemotherapeutic drugs and platelet count before radiotherapy were significantly associated with grade 2 and higher acute OM. Logistic regression analysis was performed for all statistically significant parameters and as Table 4 suggests, only platelet count before radiotherapy is the risk factor for grade 2 and higher acute OM ( $p = 0.028$ ) with an odds ratio of 1.005 (95%CI: 1.001–1.009).

### Table 2

Patient characteristics and association with grade 2 and higher acute OM in 262 patients (Categorical variables).

Characteristic		oral mucositis				p value
		Grade 0-1		Grade2-3		
		n	%	n	%	
Gender	Male	53	27.3%	141	72.7%	0.892
	Female	18	26.5%	50	73.5%	
Diabetes	(+)	5	45.5%	6	54.5%	0.163
	(-)	66	26.3%	185	73.7%	
Smokers	(+)	22	29.3%	53	70.7%	0.606
	(-)	49	26.2%	138	73.8%	
Clinical Phase	Phase II	2	18.2%	9	81.8%	0.268
	Phase III	46	31.5%	100	68.5%	
	Phase IV	23	21.9%	82	78.1%	
Concurrent chemotherapy interval	Weekly chemotherapy	36	39.6%	55	60.4%	0.001*
	Three-weekly chemotherapy	35	20.5%	136	79.5%	
Concurrent chemotherapeutic drugs	single-agent cisplatin	28	29.2%	68	70.8%	0.006*
	single-agent lobaplatin	19	44.2%	24	55.8%	
	DP regimen	24	19.5%	99	80.5%	
Induction chemotherapy	(+)	8	18.2%	36	81.8%	0.145
	(-)	63	28.9%	155	71.1%	
*p < 0.05						

**Table 3**

Patient characteristics and association with grade 2 and higher acute OM in 262 patients(Continuous variables)

Characteristic	Oral mucositis				p value
	Grade 0–1		Grade2-3		
	Mean	SD	Mean	SD	
Age	52.69	9.751	50.90	9.920	0.191
Body mass index (BMI)	22.01	3.04	22.14	3.00	0.744
Leukocyte count (×10 <sup>9</sup> /L)	6.64	2.11	6.59	1.86	0.849
Erythrocytes count (×10 <sup>9</sup> /L)	4.51	0.61	4.51	0.51	0.999
Hemoglobin count (g/L)	133.32	18.91	131.18	17.92	0.410
Platelet count (×10 <sup>9</sup> /L)	209.63	68.05	229.36	65.02	0.032*
Lymphocyte count (×10 <sup>9</sup> /L)	1.71	0.62	1.61	0.51	0.195
Neutrophil count (×10 <sup>9</sup> /L)	4.17	1.686	4.27	1.66	0.669
PGTV (Gy)	69.49	1.08	69.61	1.09	0.429
PCTV1(Gy)	61.46	2.44	61.85	1.65	0.141
PCTV2(Gy)	53.94	2.14	53.99	1.03	0.789
*p < 0.05					

**Table 4**

Multivariate Logistic regression analysis of predictors of acute severe ROM.

Variable	B	S.E.	Wald	OR	95% CI	p value
Concurrent chemotherapy interval	0.654	0.440	2.212	1.924	0.812–4.556	0.137
Concurrent chemotherapeutic drugs			1.219			0.544
Concurrent chemotherapeutic drugs(1)	-0.190	0.417	0.209	0.827	0.365–1.871	0.648
Concurrent chemotherapeutic drugs(2)	-0.593	0.566	1.097	0.553	0.182–1.676	0.295
Platelet count	0.005	0.002	4.806	1.005	1.001–1.009	0.028*
Logistic regression (stepwise selection) Abbreviation: SD = Standard deviation						
*p < 0.05						

## Discussion

For locally advanced nasopharyngeal carcinoma, concurrent chemoradiotherapy has become a well-established and effective treatment modality, and platinum-based concurrent chemoradiotherapy regimens are the most commonly used[12].At present, there is no effective treatment for radiation-induced oral mucositis, and the risk factors of radiation-induced oral mucositis should be clarified to prevent or reduce oral mucositis as much as possible.

However, there are few studies on the relationship between platelet count and mucositis.In our study, we found that the higher the platelet count, the more severe the OM. Previous studies have shown that lymphocytes and platelets may play an important role in tumor-induced systemic inflammatory responses[13].Elevated platelet count can promote the pathogenesis of mucositis through its proinflammatory properties,such as the release and recruitment of inflammatory mediators and the regulation of other inflammatory cells[14].Some scholars also believe that the initiation mechanism of radiation-induced oral mucositis is related to the initiation and release of a series of inflammatory factors[15].

This study also found that was no difference in the risk of grade 2 and higher OM between the single platinum regimen and DP regimen.This is inconsistent with previous studies[5, 16, 17].It may be related to the chemotherapy interval in this study. Of the patients in this study who received single-agent platinum chemotherapy, 97 received weekly therapy, 48 received three-week therapy, and all received three-week therapy with the DP regimen.

The current National Comprehensive Cancer Network (NCCN) guidelines recommend concurrent chemotherapy with a 3-week regimen of single-agent cisplatin or a weekly regimen of single-agent cisplatin based on the 0099 trial and the study by Chan et al[18].Some scholars have compared weekly and three-week concurrent chemotherapy regimen for nasopharyngeal carcinoma, and the results showed that dose-density therapy significantly improved the clinical outcome[19, 20].However, current studies on the toxicity of two regimens have focused on nausea, vomiting and myelosuppression, and there are few reports of oral mucosal toxicity. In only a few studies,the results of studies on oral mucosal toxicity of the two regimens are also inconsistent.The results of a retrospective study of 83 patients with head and neck cancer by Geeta et al.[21]showed that patients who received three-week chemotherapy regimen had lower mucosal toxicity than those who received weekly regimen.In the study by Ho et al.[20]found that the toxicity was similar between the two groups.Our study also found similar toxic responses to OM for both regimens.

However, because a retrospective study may have potential bias due to the nature of retrospective study and the limited scope of this study, the results should be cautiously generalized, and more multicenter, large-sample, prospective studies are needed for verification in the future.

## Conclusion

Our data demonstrate for the first time the relationship between platelet count before radiotherapy and oral mucositis in patients with NPC treated with IMRT concurrent chemotherapy.

## Abbreviations

NPC:Nasopharyngeal carcinoma;CCRT:concurrent chemoradiotherapy;OM:oral mucositis;IMRT:Intensity Modulated Radiation Therapy;KPS:Karnofsky Performance Status;BMI:body mass index;PGTV:planning gross target volume;PCTV: planning clinical target volume;CT:Computer Tomography;GE:General Electric Company;GTV-nx:Nasopharynx gross tumor volume;GTV-nd:lymph nodes gross tumor volume;CTV: Clinical target volume;MRI:Magnetic Resonance Imaging;DP regimen:docetaxel plus cisplatin regimen;NS:normal saline;RTOG/EORTC:Radition Therapy Oncology Group/European Organization of Research on Treatment of Cancer;AJCC/UICC:American Joint Committee on Cancer/International Union Against Cancer;NCCN:National Comprehensive Cancer Network

## Declarations

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### Authors'contributions

YY planned, coordinated and conducted the initial data collection. All authors(YY, SQ,HW,XL,DT,QT,XL,JG,JZ) worked together to design the study.YY analyzed data. All authors contributed to data interpretation. YY and JZ drafted the manuscript. All authors revised the manuscript critically andapproved the final manuscript.

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### Availability of data and materials

Public availability of data might compromise the respondents'privacy.According to the approval from The Committee for Medical Research Ethics, the data are to bestored properly.However, anonymized data are freely available to interested researchers upon request, pending ethical approval from the Ethics committee.Interested researchers can contact project leader Prof. Zhang(jpzhang1965@csu.edu.cn) with requests for the data underlying these findings.

### Ethics approval and consent to participate

The study was ethically reviewed and approved by the Ethics Review Committee of Nursing and Behavioral Medicine Research, School of Nursing, Central South University, China. The Ethics Review No.E202034 .

### **Competing interests**

The authors declare that they have no competing interests.

### **Consent for publication**

Not applicable.

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