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# Factors associated with acute oral mucosal reaction induced by radiotherapy in head and neck squamous cell carcinoma

## A retrospective single-center experience

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**Abstract**

To investigate risk factors for acute oral mucosal reaction during head and neck squamous cell carcinoma radiotherapy.

A retrospective study of patients with head and neck squamous cell carcinoma who underwent radiotherapy from November 2013 to May 2016 in Anhui Provincial Cancer Hospital was conducted. Data on the occurrence and severity of acute oral mucositis were extracted from clinical records. Based on the Radiation Therapy Oncology Group (RTOG) grading of acute radiation mucosal injury, the patients were assigned into acute reaction (grades 2–4) and minimum reaction (grades 0–1) groups. Preradiotherapy characteristics and treatment factors were compared between the 2 groups. Multivariate logistic regression analysis was used to detect the independent factors associated with acute oral mucosal reactions.

Eighty patients completed radiotherapy during the study period. Oral mucosal reactions were recorded as 25, 31, and 24 cases of grades 1, 2, and 3 injuries, respectively. Significant differences between acute reaction and minimum reaction groups were detected in cancer lymph node (N) staging, smoking and diabetes history, pretreatment platelet count and T-Helper/T-Suppressor lymphocyte (Th/Ts) ratio, concurrent chemotherapy, and total and single irradiation doses.

Multivariate analysis showed that N stage, smoking history, single dose parapharyngeal irradiation, and pretreatment platelet count were independent risk factors for acute radiation induced oral mucosal reaction. Smoking history, higher grading of N stage, higher single dose irradiation, and lower preirradiation platelet count may increase the risk and severity of acute radiation oral mucosal reaction in radiotherapy of head and neck cancer patients.

**Abbreviations:** OM = oral mucositis, PAF = platelet activating factor, PDGF = platelet derived growth factor, ROM = radiation-induced oral mucositis, RTOG = Radiation Therapy Oncology Group.

**Keywords:** acute oral toxicity, correlated factors, head and neck squamous cell carcinoma, radiotherapy, retrospective

## 1. Introduction

Head and neck cancers are among the major malignant tumors, accounting for approximately 3% of all cancer incidence.[1,2] Squamous cell carcinoma is the major pathological type. Radiotherapy is one of the primary treatments of head and neck squamous cell carcinoma. Utilized to kill cancer cells and control tumor growth, radiation exposure may simultaneously induce oral mucosal inflammation through multiple mechanisms,[3–5] causing tissue damage and other side effects.

Patients with head and neck cancer undergoing radiotherapy may develop acute treatment-induced oral mucosal reactions. Oral mucositis (OM) is one of the most common complications that head and neck cancer patients experience during radiotherapy, with an incidence rate of nearly 100%.[6–8] Common manifestations include pain, bleeding, dysphagia, infections, and impaired oral intake. In addition to causing patient suffering, when oral mucosal reaction interferes with eating it may lead to malnutrition and decreased immunity. In addition, occurrence of OM may increase the hospitalization rate and interrupt the planned treatment regimen.[9] Furthermore, the damaged mucosal barrier increases the risk of infection, the need for analgesia, and enteral nutrition, thus greatly increasing the human and financial costs of treatment.[10–13] Current treatment methods for radioactive oral mucosal reaction include conventional oral care, drug treatment (cytokines, analgesics, vitamins, traditional Chinese medicine, etc.), and gastric tube feedings to improve nutrition. Clinical management methods for mucositis are still inefficient; therefore, mucositis remains a major limiting factor in head and neck cancer treatment. In the clinical setting, reducing the occurrence and severity of oral mucosal reaction would be a more practical and efficient goal. Understanding the risk factors for oral mucosal reactions could facilitate accurate clinical

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evaluation and planning for treatment to minimize the incidence and severity of reactions. Currently many factors have been associated with OM. The most commonly recognized risk factors for OM include poor oral hygiene and periodontal disease,[14] chronic alcohol consumption, cigarette smoking,[15] hyposalivation,[16] low body mass index (BMI $< 18.5$),[17] as well as concurrent diseases such as diabetes mellitus. In addition, age, sex and therapeutic regimen have been suggested as risk factors.[18] However, due to the limited number of studies and controversial results, there is still no clear consensus on the evaluation of risk for radiotherapy-induced oral mucosal reactions in head and neck cancer patients.

In this study, the records of patients with head and neck squamous cell carcinoma who received radiotherapy in our center between 2013 and 2016 were retrospectively analyzed. The interrelationship between pretreatment characteristics, the treatment regimen, and the occurrence of acute oral mucosal inflammation was statistically analyzed using single and multivariate analysis.

## 2. Methods

### 2.1. Study setting and patients

This was a retrospective study of consecutive patients who underwent radiotherapy for head and neck cancer in the department of Radiation Oncology, Anhui Provincial Cancer Hospital from November 2013 to May 2016. Medical records were reviewed to screen the study subjects. The inclusion criteria were: pathologically diagnosed head and neck squamous cell carcinoma; intact records of pretreatment physical examination, blood biochemical tests, MRI/CT examination, and abdominal ultrasonography; pretreatment Karnofsky score ≥70; and completed conformal intensity modulated radiation therapy regimen, with intact records of acute radiation injury mucosal evaluation. The exclusion criteria were: pretreatment oral diseases such as chronic oral ulcers and periodontitis and no oral mucosal irradiation. The study was approved by the Ethical Committee of Anhui Provincial Cancer Hospital. Since the study was a retrospective chart review the committee waived the requirement for informed consent.

### 2.2. Treatment

Conformal intensity modulated radiation therapy was delivered to the patient at a fixed supine position using a 6 MV x ray medical linear accelerator (Varian company). Irradiation was delivered in five fractions per week, once a day. Normal tissue dose limits were set according to RTOG standards (RTOG0225 and RTOG0615).[19] Total dosages of Gross tumor volume of nasopharynx and involved lymph nodes (GTVnx/GTVnd) were 50 to 70 Gy with a single dose ranging from 2 to 2.3 Gy. Mean doses ($D_{mean}$) in the pharyngeal space were recorded ranging 20.69 to 68 Gy, with a single dose in the parapharyngeal space ranging 1.63 to 2.2 Gy. The study subjects all completed the standard treatment, with more than 95% of the tumor volume receiving the prescription dose. The maximum and mean doses were also limited to the doses for the tissues and organs in the head and neck regions. The normal tissues were exposed to doses within the tolerable range (according to RTOG0225 and RTOG0615 normal tissue limit).

There were 64 patients who received concurrent chemotherapy of either a single platinum regimen (cisplatin/nedaplatin 40 mg/$m^2$ D1, 1 times a week, total 3–5 times) or platinum + fluorouracil regimen (cisplatin/nedaplatin 80 mg/$m^2$ D1 + 5 Fu 0.5/$m^2$ D1–5, for a period of 21 days).

**Table 1**

**RTOG standard for acute radiation injury of mucosa.**

| Grade | Oral mucosa reaction |
|---|---|
| Grade 0 | Basically no change |
| Grade 1 | Irritation/may experience mild pain not requiring analgesic |
| Grade 2 | Patchy mucositis that may produce an inflammatory serosanguinous discharge/may experience moderate pain requiring analgesia |
| Grade 3 | Confluent fibrinous mucositis/may include severe pain requiring narcotic |
| Grade 4 | Ulcer, hemorrhage or necrosis |

### 2.3. Radiotherapy response evaluation

Acute radiation injury of the mucosa was graded according to RTOG standards[20] (also shown in Table 1). OM, inflammation of the oral mucosa resulting from chemotherapeutic agents or ionizing radiation[21] was the primary adverse effect investigated in the current study.

### 2.4. Management of oral mucosal reaction

The mouth of the patient was kept clean before and during radiotherapy. An acute oral mucosal reaction was treated with sodium bicarbonate gargle, and/or mannitol (250 mL) + lidocaine (0.2 g) + dexamethasone (10 mg) gargle, and/or oral He–Ne laser irradiation. For severe pain, patients were treated either with oxycodone hydrochloride prolonged-release tablets or fentanyl transdermal system analgesic therapy. In extreme situations, radiation therapy was suspended for 2 to 3 days, and then resumed after local symptoms were relieved.

### 2.5. Data collection

Demographic and clinical characteristics of patients were collected from medical records, including: age; sex; history of diabetes, hypertension, smoking, and alcohol use; tumor stage; chemotherapy regimen; radiotherapy dose; and hematology indices etc.

### 2.6. Statistical analysis

SPSS 13 (IBM, Armonk, NY) software was used for statistical analysis. Continuous quantitative data were presented as mean ± standard deviation. Differences among groups were compared using the Student *t* test. Categorical data were presented as rate (percentage) with differences among groups analyzed using Chi-square test. Nonconditional multivariate logistic analysis was performed to test the independent correlated factors of acute oral mucosal reaction. Statistical analysis was tested on two-sided settings, with $P < .05$ considered as statistically significant.

## 3. Results

Total 80 patients were included in the study, with 58 males and 22 females (male: female 2.6:1). The ages of patients ranged 14 to 81 years (median age 53). Diagnosis of head and neck cancer included: nasopharyngeal (50), oropharyngeal (2), laryngeal

(15), hypopharynx (9), nasal/sinus (2), and oral (2). Among them, 6 patients received oral site surgery. Patients' histories included: hypertension (17), diabetes (10), smoking (27 [smoking for 5–40 years, with average 20–40 cigarettes/day]), and alcohol use (30 [ranging 5–40 years, with average 100–250 mL alcohol drinks consumed each day]).

All 80 patients who completed radiotherapy treatment had various degrees of oral mucosal reaction with 25, 31, and 24 cases of grades 1, 2, and 3 respectively. The grades were categorized into two groups, the acute reaction group (grades 2–4 – there was no one with a grade 4) and the minimum reaction group (grades 0–1—there was no one with a grade 0). The characteristics were then compared between the two groups (as shown in Table 2). The results showed that significant differences existed between the two groups in diabetes and smoking history, cancer N staging, concurrent chemotherapy, pretreatment ratio between T helper and T-suppressor lymphocytes (Th/Ts), platelet counts, as well as irradiation in the parapharyngeal space and pharyngeal irradiation single dose.

The significant different characteristics between the two groups were then analyzed using multivariate logistic regression to determine independent correlated factors of radiation induced oral mucosal reactions. The results (Table 3) indicated that cancer N staging, smoking history, pharyngeal irradiation single dose, and pretreatment platelet count were associated with radiation induced oral mucosal reactions.

**Table 2**

**Comparison of characteristics between patients with acute and minimum reaction groups.**

| Influence factor | | Minimum reaction (grades 0–1, n = 25) | Acute reaction (grades 2–4, n = 55) | $X^2/t$ | P |
|---|---|---|---|---|---|
| Gender | Male | 20 | 38 | 1.026 | .311 |
| | Female | 5 | 17 | | |
| KPS | < 90 | 16 | 26 | 1.928 | .165 |
| | 90–100 | 9 | 29 | | |
| History of hypertension | Yes | 6 | 11 | 0.164 | .658 |
| | No | 19 | 44 | | |
| History of diabetes | Yes | 0 | 10 | 5.195 | .026 |
| | No | 25 | 45 | | |
| Smoking history | Yes | 4 | 23 | 5.124 | .024 |
| | No | 21 | 32 | | |
| Drinking history | Yes | 10 | 20 | 0.097 | .755 |
| | No | 15 | 35 | | |
| History of oral surgery | Yes | 2 | 4 | 0.013 | 1.000 |
| | No | 23 | 51 | | |
| T staging | T1 | 2 | 6 | 3.492 | .322 |
| | T2 | 2 | 5 | | |
| | T3 | 6 | 23 | | |
| | T4 | 15 | 21 | | |
| N staging | N0 | 11 | 6 | 15.847 | .001 |
| | N1 | 3 | 2 | | |
| | N2 | 8 | 25 | | |
| | N3 | 3 | 22 | | |
| Clinical stages | I | 2 | 2 | 0.954 | .812 |
| | II | 1 | 2 | | |
| | III | 4 | 12 | | |
| | IV | 18 | 39 | | |
| Synchronous chemotherapy | No | 9 | 7 | 6.114 | .047 |
| | Single platinum | 10 | 26 | | |
| | Platinum+5Fu | 6 | 22 | | |
| CRP, mg/L | Normal | 14 | 40 | 2.192 | .139 |
| | Raise | 11 | 15 | | |
| Th/Ts | Normal | 11 | 9 | 10.202 | .006 |
| | Reduce | 5 | 30 | | |
| | Raise | 9 | 16 | | |
| Age, years | | 58.36 ± 9.95 | 54.11 ± 12.83 | 1.466 | .147 |
| GTV total amount, Gy | | 64.320 ± 6.675 | 67.04 ± 5.506 | −1.916 | .059 |
| GTV single dose, Gy | | 2.094 ± 0.049 | 2.108 ± 0.269 | −0.271 | .787 |
| The total dose of parapharyngeal space, Gy | | 53.722 ± 9.610 | 58.511 ± 4.837 | −2.360 | .025 |
| Single dose of irradiation dose in the parapharyngeal space, Gy | | 1.807 ± 0.087 | 1.888 ± 0.114 | −3.494 | .001 |
| BMI, $kg/m^2$ | | 21.784 ± 3.12486 | 20.7309 ± 2.84507 | 1.488 | .141 |
| White blood cell count, $\times 10^9/L$ | | 6.04 ± 1.64 | 5.72 ± 2.70 | 0.546 | .586 |
| Neutrophil absolute value, $\times 10^9/L$ | | 6.19 ± 12.43 | 4.43 ± 6.08 | 0.258 | .396 |
| Red blood cell count, $10^{12}/L$ | | 4.0308 ± 0.46392 | 4.1462 ± 4.0980 | −1.120 | .266 |
| Hemoglobin value, g/L | | 120.56 ± 15.058 | 126.04 ± 13.630 | −1.612 | .111 |
| Platelet count, $10^9/L$ | | 231.48 ± 96.243 | 187.09 ± 57.688 | 2.138 | .040 |
| Albumin value, g/L | | 40.104 ± 3.37818 | 41.7582 ± 4.03864 | −1.782 | .079 |

**Table 3**

**Multivariate logistic regression analysis of correlated factors with acute radiation oral mucosal reaction.**

| Factor | OR | *P* | 95%CI |
|---|---|---|---|
| Smoking history | 8.562 | .028 | 1.258–58.253 |
| Platelet count | 0.989 | .042 | 0.978–1.000 |
| N staging | 4.616 | .007 | 1.524–13.980 |
| Single dose of irradiation dose in the pharyngeal space | 1.182 | .007 | 1.047–1.335 |

## 4. Discussion

In this current study, by retrospectively reviewing 80 records of head and neck cancer patients, we found that oral mucosal reactions were common during radiotherapy. All the study subjects had a certain amount of oral mucosal reactions, with grades 2 to 3 occurring in 69% of patients. Single and multivariate analyses demonstrated that smoking history, disease staging, pharyngeal space irradiation dose, and pretreatment platelet counts were risk factors for acute radiation induced oral mucosal reaction.

Radiation can cause tissue damage; therefore, the irradiation dose is the most well-recognized risk factor for acute oral mucosal reactions. Previous reports have shown that at 1 week of radiation therapy (usually with radiation dose of 20 Gy), oral mucosal reactions such as dry and/or sore throat were noticed. The reaction usually spread to all regions of the oral mucosa when the dose reached 30 to 40 Gy.[22] A radiation dose of 50 Gy can significantly reduce the secretion of saliva, resulting in obvious stomatitis with swallowing and eating difficulties.[23] The results of the current study showed that higher single pharyngeal space irradiation doses were significantly associated with acute mucosal reaction. The results indicated that a higher single dose may initiate early irradiation injury that causes more sensitivity to further irradiation exposure. Indeed, it has been shown that a higher single dose in a short time period tends to cause more significant early reaction and aggravate tissue damage.[24] At the same time, since diseases with lymph node involvement usually require higher treatment dosage, resulting in a higher dose in the pharyngeal space, the patients with higher N stage grading tend to have more severe oral mucosal reactions. Therefore, the irradiation dose, especially for patients with higher N stage, should be the risk factor of primary concern for radiation induced oral mucosal reactions.

Smoking has been recognized as an important risk factor for acute radiation oral mucosal reaction. During combustion, tobacco releases phenols, aldehydes, and other chemical substances that may invade oral mucosa and cause damage. These substances could also reduce the level of epidermal growth factor in saliva; therefore reduce cell proliferation and inhibit healing of mucosal injury.[25,26] In addition, nicotine in tobacco causes vasoconstriction, and decrease inflammatory and immune response, thus enhancing infection risk. These effects may further heighten oral mucosal reactions.[27] In addition, during combustion, tobacco produces carcinogenic and corrosive chemicals, as well as radioactive polonium 210, and releases alpha particles. Long-term smoking, therefore, may cause radiation-induced damages in perennial oral mucosa.[28] Thus, smokers are more likely to have severe radiation induced oral mucosal reactions during radiotherapy. The results in our study that smoking history is a significant correlated factor for oral mucosal reaction were consistent with the previous findings.

Platelets play an important role in the injury repair of ulcers. Studies have shown that a variety of cytokines released by the platelet, such as platelet activating factor (PAF) and platelet derived growth factor (PDGF), are important to promote wound healing.[29–31] PDGF has been used in various wound healing treatments such as chronic venous ulcer, diabetic ulcer, bedsore, and radioactive ulcer.[32] These results indicate that the platelet count may be an important sign for wound healing capability. Results from the current study have shown that the patients with higher pretreatment platelet count tended to have relatively milder oral mucosal reactions. These results suggested that platelet levels may be considered in the analysis of oral mucosal reaction risk factors. The exact mechanism of platelet influence on oral mucosal reaction needs to be further investigated in future studies.

Although not identified as independent risk factors in multivariate analysis, significant higher oral mucosal reactions were noticed in patients with diabetes, receiving concurrent chemotherapy especially a fluorouracil (5-FU) regimen, and lower ratio of Th/Ts. Whether these factors are independently correlated with radiation induced acute oral mucosal reaction needs to be further confirmed in studies with larger sample sizes. Previous studies have suggested hemoglobin levels and body mass index are correlated with the severity of radiotherapy induced OM severity.[17,33] In contrast, this current study did not detect association of these factors with oral mucosal reaction. These results may be due to the fact that most study subjects had relatively normal hemoglobins and BMIs.

Concurrent treatments may influence the incidence of adverse effects. It has been suggested that the incidence of radiation-induced oral mucositis (ROM) was 97% in patients with conventional radiotherapy of head and neck tumors, with 34% incidences of grade 3 and higher. The addition of chemotherapy resulted in a 43% incidence of grade 3 or higher OM, and the incidence even reached 56% with unconventional radiotherapy.[34,35] Chemotherapy drugs can inhibit DNA synthesis and cell regeneration, and the maturation and repair process, directly causing oral ulcers. Indirectly, chemotherapy may also cause injury through various mechanisms such as oral flora disturbance, bone marrow suppression, and inhibition of immune function leading to increased infection. In addition, the toxicity of chemotherapy reagents may cause reduced intake of food and water, decreased secretion of saliva, dysfunction of oral self-cleaning, and release of indole and amine substances. These effects may further damage the oral environment, leading to oral mucosal ulcers. In addition to chemotherapy, other concurrent treatments such as targeted therapy may also aggravate ROM.[36] Furthermore glucocorticoid application as part of supportive therapy may also cause oral flora disturbance that facilitates development of oral ulcers. Due to the limited sample size, the association of supportive care was not included in the current study. This warrants further exploration in the future.

This current study has certain limitations, including the retrospective design, and relatively small sample size. Despite these limitations, with the relatively intact baseline characteristic data, as well as the multivariate analysis, the results may provide some solid evidence for clinical consideration.

In conclusion, the current study has further confirmed pharyngeal space irradiation dose, disease N staging, and smoking history as important risk factors for radiotherapy induced oral mucosal reactions in head and neck cancer patients. In addition, pretreatment platelet counts may be taken into consideration in evaluation of risks. Radiotherapy is an

important treatment of head and neck squamous cell carcinoma, and acute radiation OM is the most common complication during radiotherapy; corresponding intervention should be implemented according to the patient's risk profile in order to reduce the severity of the acute oral mucosal reaction.

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