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Original Article

Clinical observations and relevant factors of acute skin and oral mucosal reactions in patients with nasopharyngeal carcinoma undergoing concurrent radiochemotherapy

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Abstract: Objective: To examine acute skin and oral mucosal reactions and identify their major influencing factors in patients with nasopharyngeal carcinoma (NPC) undergoing concurrent radiochemotherapy. Methods: The study enrolled 85 NPC patients who were treated with concurrent radiochemotherapy. Fifteen clinical and laboratory indices were examined, including blood mass index (BMI), weekly radiation dose, degree of acute oral mucosal and neck skin reactions, and blood routine test. Univariate and multivariate regression analyses were performed to assess the major influencing factors and identify the independent risk factors. Results: The risk factors closely related to the occurrence of acute radiation oral mucosal reactions were smoking (OR = 3.467, P < 0.05) and single dose for gross tumor volume > 2.15 Gy (OR = 3.393, P < 0.05), while those closely related to the occurrence of acute radiation skin reactions were diabetes mellitus (OR = 87.859, P < 0.05) and hemoglobin level one-week before radiotherapy > 130 g/L (OR = 21.404, P < 0.05). Conclusions: In NPC patients undergoing concurrent radiochemotherapy, smoking and single dose for gross tumor volume (GTVnx) are independent risk factors for acute radiationoral mucosal reactions, while diabetes mellitus and hemoglobin values one-week before radiotherapy are independent factors for acute radiation skin reactions.

Keywords: Nasopharyngeal carcinoma, intensity-modulated radiotherapy, acute mucosal reaction, acute skin reaction

Introduction

The nasopharyngeal cavity has a complex anatomy in which various parts of the organs are intertwined, limiting surgical operations. Radiotherapy can better preserve normal functions of organs and help improve the quality of life of patients [1, 2]. Although most patients with nasopharyngeal carcinoma (NPC) choose intensity-modulated radiotherapy (IMRT), this treatment can not completely avoid the occurrence of acute radiation reactions. Acute radiation skin and oral mucosal reactions commonly occur, which can be affected by a variety of factors. However, few studies have analyzed these relevant factors of acute radiation reactions. To this end, this study analyzed clinical and laboratory indices in NPC patients undergoing IMRT, in order to identify relevant factors influencing acute radiation skin and oral mucosal reactions. The results will provide a reference for clinical prevention and treatment of acute radiation skin and mucosal reactions.

Materials and methods

General clinical data

This study enrolled 85 NPC patients who were treated with concurrent radiochemotherapy at the Department of Radiotherapy, Affiliated Tumor Hospital of Zhengzhou University, Henan Province, China (March 2012 to May 2013). The patients included 57 males and 28 females, aged 13 to 80 years old, with a median age of 50 years. Regarding the medical history, 12 patients were associated with diabetes mellitus, 15 associated with hypertension, 34 asso-

Table 1. Evaluation criteria for acute radiation skin and mucosal reactions (RTOG)

Grade	Acute radiation skin reactions	Acute radiation oral mucosal reactions
0	Generally unchanged	Generally unchanged
1	Blisters, pale erythema, hair loss, dry desquamation, and decreased sweating	Congestion/possibly associated with mild pain; no analgesics required
2	Skin tenderness, obvious erythema, flaky moist desquamation, and moderate edema	Flaky mucositis, or inflammatory serum or blood secretions/or moderate pain, analgesics required
3	Integrative moist desquamation (except skin folds), and severe edema	Fused fibrous mucositis which can be accompanied by severe pain; anesthetics required
4	Ulcers, bleeding, and necrosis	Ulcers, bleeding, and necrosis.

ciated with smoking, and 30 associated with drinking.

Inclusion criteria: stage II-IV$_a$ NPC treated for the first time (refer to 2009UICC/AJCC TNM staging); poorly differentiated squamous cell carcinoma confirmed by pathological observation; absence of distant metastasis confirmed by relevant inspection; and Karnofsky score ≥ 70, with normal results of blood routine test as well as liver and kidney function test. Exclusion criteria: history of oral diseases such as chronic oral ulcers and periodontitis; and on-going anti-tumor therapy. Before the start of the therapy, all patients signed an informed consent form.

Therapeutic method

All patients underwent conformal IMRT with 6 MV X-ray from a medical linear accelerator (Varian Clinac 600 CD, Varian Medical Systems, Palo Alto, CA, USA). Radiotherapy was performed once daily, five times per week. The radiation dose for GTVnx and prescribed dose for GTVnd were 69.96-75.50 Gy, with a single dose of 2.0-2.25 Gy. The prescribed doses for clinical target volume (CTV) were 60-64 Gy in the nasopharynx and 50 Gy in the neck, with single doses of 1.8-2.0 Gy in the nasopharynx and upper neck and 1.7-2.0 Gy in lower neck. Concurrent chemotherapy involved intravenous infusion of 30 mg/m^2 cisplatin on days 1-3 and 60 mg/m^2 docetaxel on day 1. One treatment cycle lasted 21 d.

Radiation oral mucosal and skin reactions were treated as follows: Prior to and during radiotherapy, patients were asked to maintain oral hygiene and ware loose clothing for reducing skin friction in the radiation field. Acute oral mucosal reactions were treated by daily oral care and aerosol inhalation of compressed compound vitamin B12 solution. Grade 3 (or higher) acute radiation skin and mucosal reactions were treated with local application of compound vitamin B12 solution to promote skin or mucosal repair, combined with anti-inflammatory, symptomatic, and supportive treatments. Severe pain was treated with fentanyl transdermal patches. If the pain seriously affected feeding, then, radiotherapy was interrupted for 3-5 d and continued after remission of local symptoms.

Evaluation criteria for reactions to radiotherapy

Reactions to radiotherapy were evaluated using the Radiation Therapy Oncology Group (RTOG) acute radiation dermatitis grading system [3], as shown in **Table 1**.

Outcome measures

The outcome measures are listed in **Table 2**.

Statistical analysis

Data were statistically analyzed in SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Univariate analysis was first performed using χ^2 test for qualitative data and *t* test for measurement data. Thereafter, relevant factors of statistical significance were screened out and used for non-conditional multivariate logistic analysis. A *P*-value less than 0.05 was considered statistically significant.

Results

Clinical outcomes

All the 85 patients completed concurrent radiochemotherapy. Totally 83 patients had acute radiation oral mucosal reactions, including 30, 25, 25, and 3 cases of grade 1 to 4, respectively. There are 34 patients showing acute radiation skin reactions, including 14, 8, 11, and 1 cases of grade 1 to 4, respectively.

Table 2. Univariate analysis of factors influencing acute radiation skin and oral mucosal reactions

Factors		Acute radiation oral mucosal reaction		χ^2/t	*P*	Acute radiation skin reaction		χ^2/t	*P*
		Grade 0-1 (n = 32)	Grade 2-4 (n = 53)			Grade 0-1 (n = 32)	Grade 2-4 (n = 53)		
Gender	Male	18	39	2.714	0.099	43	14	0.102	0.749
	Women	14	14			22	6		
Diabetes mellitus	No	31	42	5.115	0.024	63	10	27.774	<0.001
	Yes	1	11			2	10		
Hypertension	No	28	42	0.936	0.333	52	18	1.052	0.3.5
	Yes	4	11			13	2		
Drinking	No	20	35	0.109	0.741	44	11	1.079	0.299
	Yes	12	18			21	9		
Smoking	No	26	25	9.656	0.002	44	7	6.811	0.009
	Yes	6	28			21	13		
Tumor staging	State I	1	8	4.582	0.205	6	3	2.882	0.410
	State II	13	18			23	8		
	State III	8	17			18	7		
	State IV	10	10			18	2		
Node staging	State I	4	5	4.767	0.190	9	0	3.205	0.361
	State II	6	17			17	6		
	State III	14	26			29	11		
	State IV	8	5			10	3		
BMI				2.631	0.10			2.697	0.008
Neutrophil count (10^9/L)									
1-week before the start of radiotherapy				-0.185	0.854			-0.295	0.768
1-week after the start of radiotherapy				0.896	0.373			0.583	0.561
2-week				1.819	0.072			0.374	0.071
3-week				0.101	0.920			-0.804	0.424
4-week				1.255	0.213			-0.110	0.912
5-week				-0.576	0.566			-0.690	0.492
6-week				-1.446	0.152			-1.997	0.051
> 6-week				-1.175	0.243			0.973	0.333
Hemoglobin (g/L)									
1-week before the start of radiotherapy				-2.221	0.029			-2.678	0.009
1-week after the start of radiotherapy				-2.364	0.020			-2.288	0.038
2-week				-1.882	0.063			-2.288	0.025
3-week				-1.526	0.131			-1.974	0.052
4-week				-1.246	0.216			-1.376	0.173
5-week				-0.921	0.360			-1.569	0.120
6-week				-0.503	0.616			-1.692	0.094
> 6-week				-0.208	0.836			-1.767	0.081
Total dose for primary gross tumor volume (Gy)				-1.068	0.289			-1.404	0.164
Single dose for primary gross tumor volume (Gy)				-2.908	0.005			-2.314	0.023
Single dose for clinical target volume of upper neck (Gy)				-0.892	0.375			-2.026	0.046
Single dose for clinical target volume of lower neck (Gy)				-1.070	0.288			-2.048	0.044

Univariate analysis

The results of univariate analysis are shown in **Table 2**.

Multivariate analysis

Relevant factors of statistical significance in the univariate analysis were chosen for multivariate analysis. The results showed that factors closely related to the occurrence of grade 2 (and above) acute radiation oral mucosal reactions were smoking and single dose for primary GTV > 2.15 Gy (**Table 3**). Additionally, factors closely related to the occurrence of grade 2 (and above) acute radiation skin reactions were diabetes mellitus and hemoglobin level

Table 3. Multivariate logistic regression analysis of factors affecting acute radiation oral mucosal reactions

Factors	*OR* value	*P* value
Smoking	3.467	0.003
Diabetes mellitus	4.222	0.217
BMI	0.735	0.602
Hemoglobin level before the start of radiotherapy (g/L)	1.966	0.301
Hemoglobin level 1-week after the start of radiotherapy (g/L)	0.989	0.987
Single dose for primary gross tumor volume (Gy)	3.393	0.043

Table 4. Multivariate logistic regression analysis of factors affecting acute radiation skin reactions

Factors	*OR* value	*P* value
Diabetes mellitus	87.859	0.001
BMI	0.925	0.916
Hemoglobin level before the start of radiotherapy (g/L)	21.404	0.017
Hemoglobin level 1-week after the start of radiotherapy (g/L)	0.387	0.437
Hemoglobin level 2-week after the start of radiotherapy (g/L)	2.113	0.482
Single dose for clinical target volume of upper neck (g/L)	1.167	0.834
Single dose for clinical target volume of lower neck (g/L)	3.321	0.108

one-week before the start of radiotherapy > 130 g/L (**Table 4**).

Discussion

Concurrent radiochemotherapy is the standard therapeutic regimen for mid-advanced NPC. Radiation oral mucosal and skin reactions are most commonly seen during the radiochemotherapy. The degree of such radiation reactions directly affects whether patients can complete the radiotherapy within the stipulated time, thus influencing the therapeutic effect. The above two types of radiation reactions show dose dependence in the same patients but exhibit difference between individual patients. What factors cause this individual difference? In the present study, clinical data showed that smoking and single dose for primary GTV were independent risk factors for acute radiation oral mucosal reactions, whereas diabetes mellitus and hemoglobin level one-week before radiotherapy were independent risk factors of acute radiation skin reactions in patients with NPC undergoing concurrent radiochemotherapy.

Tobacco ingredients include phenols, aldehydes, organic matter, and other substances. During smoking, tobacco poisons directly stimulate the oral mucosa and damage epithelial cells, leading to lesion development. In smokers, oral mucosal epithelial cells have poor proliferative ability and cell proliferation occurs late after radiochemotherapy, resulting in slow repair of oral mucosal reactions. Additionally, the smoking population has low levels of epidermal growth factor in saliva. Because epidermal growth factor can promote the regeneration of mucosal and skin lesions, decrease in oral epidermal growth factor slows down the repair of oral mucosal lesions, facilitating the occurrence of severe oral mucositis [4, 5]. Moreover, nicotine contained in tobacco can cause epidermal vasoconstriction, thus affecting wound healing.

In patients with diabetes mellitus, lesions in capillary vessels and peripheral nerves often cause skin nutritional disorders. Vessel wall damage and atherosclerosis existing in the skin and mucosa of the radiation field are possible reasons for which hyperglycaemia aggravates radiation dermatitis and mucositis. In the present study, there were 12 NCP patients associated with diabetes mellitus, who had an incidence of grade 2 (or above) acute radiation oral mucosal reactions of 91.7% (11/12) and an incidence of grade 2 (or above) acute radiation skin reactions of 83.3% (10/12), significantly higher than those of non-diabetic patients ($P < 0.02$). However, in these 12 patients, the incidences of grade 4 acute oral mucosa and skin reactions were both 8.3% (1/12), lower than the results reported by Yang et al. [6]. This difference might be related to the small sample size in the present study. Whether concurrent radiochemotherapy can increase the degree of acute radiation reactions in patients with diabetes mellitus needs to be further studied.

The oxygen effect plays an important role in radiotherapy of tumors. Hypoalbuminemia caused by reduction in hemoglobin level affects

the quality of life of patients. More importantly, anemia-hypoalbuminemia can aggravate hypoxia in tumor cells, allowing them to resist against radiation and thus reducing the therapeutic effect of radiotherapy [7]. Elevation of hemoglobin level through clinical intervention can not only improve the therapeutic effect but also increase the radiosensitivity of normal tissues. Henke et al. [8] reported that hemoglobin level was positively correlated with the incidence and severity of acute radiation reactions such as radiation mucositis and dermatitis. Kong et al. [9] carried out a retrospective analysis on 167 NPC patients undergoing radical radiotherapy. It was found that hemoglobin level before radiotherapy was an influencing factor of early oral mucosal reactions, while hemoglobin level during radiotherapy had no statistical significance. In the present study, we analyzed the relationships between acute radiation reactions and weekly hemoglobin levels before and after the start of radiotherapy. Results suggested that patients with grade 2 (or above) acute skin and oral mucosal reactions had significantly higher hemoglobin levels than those with grade 0-1 acute skin and oral mucosal reactions one-week before and after the start of radiotherapy. Additionally, patients with grade 2 (and above) acute skin reactions had significantly higher hemoglobin levels than those with grade 0-1 acute skin reactions two-week after the start of radiotherapy. These observations, which have not been reported in previous studies, need to be further verified.

Factors such as radiation energy, radiation dose, and split mode can affect the extent of radiation mucosal and skin reactions. Modern linear accelerators have a protective effect on the skin and make the maximum dose point beneath the basal cell layer of skin. However, the use of thermoplastic film for fixation of the head and neck can increase the radiation dose received by the skin, increasing skin reactions. Few studies have been reported on the relationship between single dose for clinical target volume and acute radiation reactions in concurrent radiochemotherapy. The results obtained in the present study showed that patients with grade 2 (and above) acute oral mucosal reactions had significantly higher single dose for GTVnx than those with grade 0-1 acute oral mucosal reactions. Additionally, patients with grade 2 (and above) acute skin reactions received significantly higher single dose for neck CTV than those with grade 0-1 acute skin reactions. These results suggest that mucosal and skin lesions are more worthy of consideration when increasing single radiation dose, shortening treatment time, and enhancing the biological effect.

Disclosure of conflict of interest

None.

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