Correlated factors of acute oral mucosal and skin reaction induced by radiotherapy in hypopharyngeal carcinoma

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Abstract

Background This present retrospective single center study was intended to investigate the factors associated with acute radiation oral mucositis or dermatitis during hypopharyngeal carcinoma radiotherapy.

Methods From May 2012 to December 2018, previously untreated 93 patients with hypopharyngeal squamous cell carcinoma received radiotherapy in Affiliated Cancer Hospital of Zhengzhou University were enrolled. Radiation Therapy Oncology Group (RTOG) scoring criteria were used for assessing the severity of toxicities. Patients are therefore classified into “mild reaction group” (G0~G1) and “acute reaction group” (G2~G4). Single variate was applied to screen out factors with significant difference between mild and acute reaction groups, multivariate analysis was used to detect independent risk factors from those related. A total of 16 medical and laboratory indexes were included to examine, i.e., gender, age, smoking history, primary site, history of hypotension and diabetes, treatment modalities, dose, T (tumor) staging, N (regional lymph node) staging, as well as hemoglobin value (1 week before radiotherapy). Relevant data used for the study were collected from clinical records.

Results Total of 93 subjects completed radiotherapy. Acute mucositis occurred in 75 patients, and 27 cases developed acute radiation dermatitis. Smoking history, post-operative radiotherapy, concurrent chemotherapy, T staging, N staging, total dose (Gy) for GTV, single fraction dose (Gy) for GTV, and hemoglobin value (1 week before radiotherapy) showed significant differences between G0~G1 and G2~G4 groups of oral mucosa reaction; significant differences between mild and acute dermatitis reaction groups were found in diabetes history, hemoglobin value, age, total dose (Gy). Multivariate analysis showed that higher hemoglobin value (OR = 1.120, P = 0.031), smoking history (OR = 0.070, P = 0.031) were independent risk factor of acute OM; significant relationships for acute skin reaction were found with hemoglobin value (OR = 1.059, P = 0.034) and older age (OR = 1.068, P = 0.036).

Conclusion Multivariate analysis showed higher hemoglobin value and smoking history to be the most relevant factors independently predicting grades 2 or higher OM; higher hemoglobin value and older age were found to be significantly associated with acute skin reaction.

1. Background

Patients with hypopharyngeal squamous cell carcinoma (HSCC) are often diagnosed at advanced stages, and accounts for 3 ~ 5% of head and neck cancer suffers^[1]. Radiotherapy has well been acknowledged as a major or indispensable measure in the curative treatment of head and neck cancer. However, even with the benefits of conformal IMRT (intensity modulated radiation therapy) technique, up to 90% of patients are inclined to experience different toxicities of various degrees^[2], especially the radiation oral mucositis and dermatitis, which are the most common complications. Therefore, great number of patients are expected to experience oral mucosa and skin reaction during RT treatment. Patient's ability to eat and drink can be temporarily or permanently impaired, as the result, the quality of patient's life was

lowered heavily^[3]. Even worse, in severe conditions, radiation oral mucositis and dermatitis can lead to super infection and interrupted treatment. The effectiveness of treatment was consequently interfered^[4]. Many clinic characteristics or concurrent diseases history have been suggested as potential risk factors for acute radiation oral mucosa and skin reaction of head and neck cancer, such as smoking history, diabetes history, higher hemoglobin value, dosage, as well as sex, age et al. However, there is still no consensus on the predictors of adverse effects due to the limited sample size and controversial results. In addition, there are few reports on the predictors of adverse effects of hypopharyngeal cancer radiotherapy. The purposes of this study were intended to investigate the risk factors that contribute to increased severity of radiation skin and mucosal reaction and to provide theoretical basis and important considerations for clinical practice.

2. Methods

2.1 Patient and the study setting:

From May 2012 to December 2018, a total of 93 patients with hypopharyngeal cancer who were undergoing radiotherapy were identified. They were staged IIB-IVA (8th edition AJCC Hypopharyngeal cancer TNM staging standard was referenced for staging). Patients inclusion criteria: previously untreated with hypopharyngeal cancer, staging IIB-IVA; completed radiotherapy and the records of acute toxicities were available; pathologically diagnosed hypopharyngeal cancer squamous cell carcinoma; there were no distant organ metastasis proved by MRI/CT examination; KPS (pretreatment Karnofsky score) ≥ 70 ; blood tests, kidney and liver function were in normal range. Patients exclusion criteria: patients have history of drug allergy; patients with others tumor. Clinical characteristics and relative data of patients were collected from the records. All subjects in present study had signed informed consent before they accepted treatment. This study was approved by the Ethical Committee of Affiliated Cancer Hospital of Zhengzhou University.

2.2 Variables

Patient's gender, age, BMI, history of cigarettes smoking and alcohol consumption, hypotension, diabetes mellitus, treatment regimens (RT alone, IC, CCRT, IC+ CCRT), post-operative radiotherapy, T staging, N staging, subsite (posterior pharyngeal, post cricoid region, pyriform sinus), GTV total dosage (Gy), GTV fraction dosage (Gy), as well as hemoglobin value (1 week before radiotherapy) were extracted from clinical records for investigation.

2.3 Treatment:

Radiotherapy Treatment: Patients were all accepted for conformal intensity modulated radiation therapy using 6MV x-ray medical linear accelerator (Varian company) as standard treatment modality. The prescription dose for gross tumor volume, including prime site of tumor and involved lymph nodes (GTVnx / GTVnd), ranges from 60 to 70Gy, with daily fraction dose of 2.0 - 2.2 5Gy, and 5 fractions per

week. Prescription dose of clinical target volume (CTV) ranges from 50.4Gy to 60Gy. Normal tissues were managed with tolerable RTOG0615 and RTOG0225 normal tissue limit dosage^[5].

Chemotherapy Treatment: Chemotherapy protocols include induction chemotherapy alone (IC), concurrent chemotherapy (CRT), and induction chemotherapy + concurrent chemotherapy (IC + CRT). 2 ~ 3 cycles chemotherapy were prescribed with each modality. Chemotherapy regimens include “TP”, “DF”, “P”. (TP: Cisplatin: 70~80mg-/m², d1, Docetaxel: 100~120mg, d1; DF: cisplatin: 70~80mg/m², d1, 5-Fu: 750mg/m², d1-5; P: Cisplatin 70~80mg/m², d1).

2.4 Management of radiation induced oral toxicities

Oral care was delivered to subjects with OM (once a day); compound VitminB12 solution was compressed and used for atomization inhalation; recombinant fibroblast growth factor 1(Acidic, FGF1) local spraying and antibiotic were used for patients of G3 OM. Antibiotics usage was based on throat swab culture results. Oxycodone hydrochloride prolonged-release tablets was administered when pain score of patients was up to 4. In severe situations, fentanyl would be applied for patients, and patients would be suggested to discontinue RT for 2 to 3 days (no more than 5 days) if even worse.

2.5 Radiation reaction and criteria

RTOG standard for acute radiation mucositis and dermatitis were used for grading ^[6, 7] (Table 1); G0 ~ G1was defined as mild adverse reaction; G2 ~ G4 was defined as acute adverse reaction (there is no one with grade 4 in this study).

2.6 Statistical analysis

Statistical analysis were carried out using SPSS 25 (IBM, Armonk, NY). Each variable was analyzed by univariate Cox regression, Student T-Test and Chi square test (or Fisher’s exact test) for continuous quantitative data and categorical variables respectively. The variables were considered correlated with oral mucositis when $p < 0.05$, and these variables were put into the multivariable Cox regression model to identify independent risk factors. Two-tailed test $p < 0.05$ were considered statistically significant.

Table 1 RTOG Standards for radiation mucositis and radiation dermatitis

Grade	Oral mucosa reaction	Acute radiation dermatitis
Grade 0	no change	No change over baseline
Grade 1	Irradiation/ may experience mild pain not requiring analgesic	Follicular, faint or dull erythema /epilation /dry desquamation/decreased sweating
Grade 2	Patchy mucositis that may produce an inflammatory serosanguinous discharge may experience moderate pain re-quiring narcotic	Tender or bright erythema, patchy moist desquama moderate edema
Grade 3	Confluent fibrinous mucositis may induce severe pain requiring narcotic	Confluent, moist desquamation other than skin folds, pitting edema
Grade 4	Ulcer, hemorrhage or necrosis	Ulceration, hemorrhage, necrosis

3. Results

Patient's characteristics and clinical indexes were shown in Table 2. Total 93 patients were enrolled in this study, with 79 males and 14 females. The ages of these patient ranged from 40-80 years old with a median age of 62 years. Sites of diagnosed hypopharyngeal carcinoma include posterior pharyngeal wall (16), post cricoid region (10), and pyriform sinus (67). The numbers of patient with history of smoking, diabetes, alcohol consumption, and hypotension were 56, 12, 48, 23 respectively. (Smoking cessation over half a year was defined as negative factor). Among them, 29 patients received concurrent chemotherapy (CRT), 28 patients accepted induction chemotherapy (IC), and 8 patients underwent (IC) + (CRT). 37 cases received post-operative radiotherapy. All subjects completed conformal intensity radiotherapy and developed various degrees of toxicities. Numbers of patients with oral mucositis ranging from G1-G3 were 18, 49, 26 respectively. Acute radiation skin reaction occurred in nearly 60% of 93 patients. The incidences of grades 1, 2, and 3 were 30, 20, and 7, respectively. 36 cases had no skin reaction. There is no one with grades 4 of oral mucositis or dermatitis.

Univariate analysis showed that smoking history, post-operative radiotherapy, fraction dose (Gy), total prescription dose (Gy), T staging, and N staging, were significant characteristics between "mild" and "acute" OM; hemoglobin value, fraction dose (Gy) and age were significant factors between the two groups of skin reaction. (as shown the Table 2). These significant different characteristics between the two groups were put into the multivariable cox regression model to identify independent risk factors. The result showed that hemoglobin value and CRT were independent factors of OM (Table 3), and that hemoglobin value, age, total dose have influence on grades of acute radiation dermatitis independently (Table 4).

Table 2 Clinical characteristics of 93 patients with hypopharyngeal carcinoma

Table 3 Multivariate logistic regression analysis of related factors with radiation dermatitis

Table 4 Multivariate logistic regression analysis of elated factors with radiation mucositis

Influence factor	OR value	P value
GTV total dose	1.044	0.629
GTV single dose	205.684	0.385
Chemotherapy		0.117
(IC)	1.886	0.525
(CRT)	28.560	0.020
(IC +CRT)	1.347	0.741
T stage	1.746	0.252
N stage	1.594	0.270
Hemoglobin value	1.120	0.031
Post-operative RT	0.668	0.944
Smoking history	0.070	0.031

4. Discussions

Post-operative radiotherapy, radiotherapy alone or in conjunction with concurrent chemotherapy have well

Influence factor		Oral mucositis		X^2/t value	P	Acute radiation		X^2/t	P value
		G0+G1 n=7	G2+G3 n=86			G0+G1 n= 66	G2+G3 n=27		
Gender	Female	2	12	0.176	0.737	10	4	0.002	0.620
	Male	15	64			56	23		
Diabetes history	No	16	65	0.912	0.456	61	29	5.741	0.023
	Yes	1	11			5	7		
Smoking history	No	9	21	4.072	0.044	22	8	0.464	0.120
	Yes	8	55			44	19		
Hypotension history	No	15	55	1.869	0.224	50	20	0.029	0.530
	Yes	2	21			16	7		
Drinking history	No	9	36	0.173	0.790	23	8	0.235	0.409
	Yes	8	40			43	19		
T stage	T1	2	2	11.590	0.005	4	0	7.103	0.064
	T2	12	27			31	8		
	T3	2	35			25	12		
	T4	0	13			6	7		
N stage	N0	8	9	7.421	0.041	14	3	1.764	0.639
	N1	2	8			6	4		
	N2	6	49			38	17		
	N3	2	9			2	9		
Sub-site	PPW	4	12	0.887	0.697	14	2	3.430	0.195
	PS	13	54			44	23		
	PR	1	9			8	2		
Chemotherapy	RT	10	16	15.197	0.001	22	4	4.089	0.261
	IC	4	15			14	5		
	CCRT	1	39			25	5		
	IC + CRT	2	6			5	3		

Post-operative	NO	6	51	5.926	0.026	37	20	2.621	0.082
radiotherapy	Yes	11	25			29	7		
Age		61.588±10.422	61.855±9.760	-0.101	0.920	60.439±9.747	65.148±9.371	-2.183	0.035
BMI		22.998±2.728	23.269±2.727	-0.371	0.711	23.042±2.787	23.655±2.524	-0.990	0.325
GTV total dose		61.788±2.794	64.914±4.638	-2.900	0.005	62.680±4.379	65.963±4.505	-2.263	0.026
GTV single dose		2.046±0.073	2.095±0.840	-2.239	0.028	2.072±0.090	2.094±0.094	-1.028	0.307
Hemoglobin		120.941±10.461	128.789±10.597	-2.767	0.007	125.303±10.707	132.370±10.038	-2.941	-0.004

Influence factor	OR value	P value
Age	1.068	0.036
GTV total dose	1.121	0.075
GTV single dose	174.290	0.117
Hemoglobin value	1.059	0.034
History of diabetes	0.247	0.078

been acknowledged as standard curative treatment for patient with head and neck cancer^[8]. OM and acute skin reaction are the most common complications, which always posed great challenge to clinical physician. Previous studies indicated that the two adverse effects showed dose and individual dependent. We retrospectively analyzed 93 patients and identified that higher hemoglobin value and smoking history are independent risk factors of OM; higher hemoglobin value, elder age and higher total dose are significantly associated with the severity of radiation skin reaction.

Smoking are shown to be positively correlated with OM in present study. It's always been known that tobacco comprised of aldehydic, phenolic and other organics. These compounds of toxic would be released during combustion and do damage to the oral mucosa, and the ability of proliferation of epithelia cell would be affected as a result. Besides, these substances could reduce the level of epidermal growth factor in saliva as well. Therefore, the epithelial cell of oral mucosa proliferation and repair was delayed, and the healing process was impeded directly. Moreover, nicotine could shrink skin capillary^[9], which contributes to increased severity of OM also.

Diabetic patients' skin is often in poor nutritional status due to microvascular and peripheral nerve disease. Peripheral vascular suffered from injury and atherosclerosis within radiated area may induce severe mucositis and radiation skin reaction. The body is in a state of stress when patient was exposed to radiotherapy, in which more glucagon, adrenal corticosteroid, growth hormones were released to blood. Moreover, the stress condition can reduce the sensitivity of tissue cell to insulin, resulting in aggravated disorder of glucose metabolism^[10]. Previously reports indicated that higher blood glucose is significantly associated with acute skin reaction and OM. In present study diabetes is not a risk factor of acute skin reaction. It can be explained by well controlled blood glucose level during radiotherapy treatment.

Oxygenation plays crucial role in radiotherapy of tumor. It is well been accepted that the reduction of blood hemoglobin concentration can induce impaired tumor oxygenation and increased X-ray resistance. Therefore, the effectiveness of radiotherapy was impeded. Increased blood hemoglobin level can increase

radio-sensitivity of tumor and the normal tissue. Cheng H et al reported that patients with higher value of blood hemoglobin at 1 week before radiotherapy were more inclined to develop acute skin reaction and OM, in consistent with this study^[11].

Chemotherapy and radiotherapy can complement each other and exert synergistic action on treatment of tumor because RT is significant on local control while chemotherapy is particularly important to systemic metastasis^[12, 13]. However, the normal tissues couldn't be spared totally when chemo-therapeutic drugs destroying tumor cells. DNA synthesis and cell regeneration can be inhibited by chemotherapy drugs and x-ray, resulting in oral ulcers and damaged normal tissue and organs. It has been well documented that some chemo-therapeutic drugs can enhance the biological effects of ionizing radiation ^[14–16]. In addition, chemotherapy can lead to bone marrow suppression (such as thrombocytopenia, neutropenia) and decreased immune-defense ability, indirectly impairing normal tissue healing. It has been reported by Bonomo P ^[17] that cisplatin-based regimen were potentially more susceptible to the development of acute toxicity and concurrent chemotherapy could increase the incidence of OM or acute skin reaction. Although not identified as independent risk factors in this study, significant higher (39/40, 40 patients received CCRT, 39 patients developed G2 or above OM) oral mucositis were observed in patients receiving CCRT, which may due to the smaller samples size.

Radiation of high energy particles can cause DNA damage directly or indirectly. Total GTV dose and single fraction dose have been well-recognized as risk factors to develop severe OM. A previous report indicated that a radiation dose of 30 Gy is a related factor of severe OM^[18]. Doctor Vera-Lionch M^[19] reported that risk increased when dose reached 50 Gy. Dose-volume parameters can also successfully predict acute skin reactions^[20]. The current study demonstrates that total dose and fraction dose are associate with Grade 2 or above OM and acute skin reaction.

Patients with higher N staging were administered with a larger radiation field and more dosage, and therefore were more likely to develop G2 or worse radiation mucositis. This has previously been reported^[6, 21]. One of the limitations of present study was that the sample size is small, partially due to that the incidence of hypopharyngeal cancer was low. In the current study, nearly all (13/14) patients with T4 staging developed G2 or above OM. There are few researches about it and the extensive efforts are needed for further investigation.

There is still no consent on how age impacts on radiation dermatitis. The aging of cell lines leads to thinning of the epidermis, losing of collagen and decreasing of capillary network^[16]. In addition, older patients often have poor nutrition status, which increases the difficulty in healing. That may explain that aging significantly increases the possibility of acute skin reaction., This result was also demonstrated in the paper of Dr Porcked ^[22].

Conclusions

The current study indicates that risk factors of OM and dermatitis should be taken into consideration in clinical practice by physician when making decisions on therapeutic time, fraction dose and biological effects.

Abbreviations

RT: Radiotherapy

CCRT: Concurrent Chemoradiotherapy

ICT: Induction Chemotherapy

OM: Oral Mucositis

RTOG: Radiation Therapy Oncology Group

Declarations

Ethics declarations

The current study was approved by the Ethical Committee of Affiliated Cancer Hospital of Zhengzhou University.

Ethics approval and consent to participate

The current study was approved by the Ethical Committee of Affiliated Cancer Hospital of Zhengzhou University.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon request.

Competing interests

No conflict of interest for this study have been declared by all authors.

Founding

Affiliated Cancer Hospital of Zhengzhou University provided all financial support.

Authors' contributions

Data collection, statistics analysis, and the initial draft were carried out by WY. HW contributed to the design of the study, supervised the research and modified the manuscript. XXL, RH, TT, WHL and TYL revised the manuscript. The submitted version of the manuscript have been read and approved by all authors.

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