Original Article

Risk factors for oral mucositis in patients with malignant tumors: a prospective cohort study

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Background: To investigate the incidence and risk factors of oral mucositis in patients with malignant tumors.

Methods: A total of 74 patients with malignant tumors who were hospitalized in the Affiliated Hospital of Nantong University from January 2020 to December 2020 were selected and divided into two groups according to whether oral mucositis occurred (n=45) or not (n=29). Chi-square test was used to compare the general data between the two groups, and multivariate logistic regression analysis was used to investigate the risk factors of oral mucositis in patients with malignant tumors.

Results: Oral mucositis occurred in 45 of 74 malignant tumor patients (60.8%), and the incidence in patients with head and neck tumors was significantly higher than in those with chest and abdomen tumors ($P<0.05$). A significantly higher incidence was also seen in patients with poor oral cleanliness in comparison to those with high oral cleanliness; in radiotherapy patients in comparison to non-radiotherapy patients; in patients who received Nituzumab during radiotherapy in comparison to those who did not, and in patients receiving eight cycles of chemotherapy in comparison to those not receiving chemotherapy. Multivariate logistic regression analysis showed that oral cleanliness, radiotherapy, and duration of radiotherapy were independent risk factors for oral mucositis in patients with malignant tumors ($P<0.05$).

Conclusions: Poor oral cleanliness, radiotherapy, and longer duration of radiotherapy lead to the occurrence of oral mucositis in patients with malignant tumors, and these risk factors should be targeted for intervention to reduce the occurrence of oral mucositis.

Keywords: Malignant tumor; oral mucositis; risk factor

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Introduction

Malignant tumors are newly generated abnormal tissues formed by the abnormal proliferation of clones caused by loss of the normal regulation of cell growth at the gene level under the action of various carcinogenic factors. The worldwide incidence of cancer is on the rise and according to statistics, every year more than 10 million people suffer from malignant tumors, and more than 9 million die, making this the second leading cause of death (1). Surgery, chemotherapy, and radiotherapy are the main treatment methods for patients with malignant

tumors, and can improve local control, reduce metastatic spread, and improve survival rates (2). However, while both chemotherapy and radiotherapy kill cancer cells, they also affect normal cells, which may lead to adverse reactions and complications. Oral mucositis is a common complication of radiotherapy and chemotherapy in patients with malignant tumors (3), and in severe cases, treatment must be interrupted or reduced, which has a negative impact on the therapeutic effect and prognosis (4,5). Oral mucositis is an inflammatory or ulcerative lesion of oral mucosa (6) which often manifests as local pain affecting chewing and eating. This may lead to malnutrition and decreased quality of life (7,8), as well as the risk of infection (9).

Shouval *et al.* found that age, lower body mass index, smoking, and the use of antibiotics and methotrexate were associated with the development of moderate to severe oral mucositis in allogeneic hematopoietic stem cell transplantation recipients (10). Çakmak *et al.*'s study (11) on cancer patients undergoing outpatient chemotherapy found that the incidence of oral mucositis was 51.7%, and advanced age, loss of appetite and long duration of chemotherapy were its risk factors. Dodd *et al.* (12) estimated the incidence of oral mucositis in chemotherapy patients to be 25.1% but found its causes and risk factors were not clear. Therefore, this study investigated the incidence of oral mucositis in patients with malignant tumors and explored the impact of factors, including age, gender, educational level, tumor diseases, tumor staging, radiotherapy, radiotherapy duration, chemotherapy, denture, smoking history, white blood cell count, oral cavity cleanness, body mass index, hemoglobin, creatinine, urea nitrogen, blood glucose, vomiting, diarrhea, and other factors on its risk. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1675).

Methods

Participants

Patients with malignant tumors who were hospitalized in the Department of Oncology Radiotherapy of the Affiliated Hospital of Nantong University from January 2020 to December 2020 were selected as the research subjects.

Inclusion criteria: (I) the diagnosis of malignant tumor was made according to the National Comprehensive Cancer Network (NCCN) guidelines; (II) the patient was over 18 years old; (III) the patient has no disturbance of consciousness and could communicate normally; (IV) the patient was fully informed and signed informed consent for their participation.

Exclusion criteria: patients with blood disease.

Sample size calculation

The calculated sample size was 60 cases, and the data of 74 patients were collected.

Assessment of oral mucositis and pH value

Patients who met the inclusion criteria signed the informed consent after admission, and data on their general condition was collected. The oral pH value of patients was then measured to evaluate the occurrence and grading of oral mucositis.

This saw the use of Geshan Precision Test Paper (Shanghai Linlei electronics co., LTD, China) in the morning before gargling and drinking water, before lunch, after siesta, and at night before bedtime (four times per day). A precision test paper was pasted on the median of the patient's tongue surface and under the tongue, and after the paper was soaked, its color was observed, and its average value was taken to determine the pH value. Abnormal results were considered as those exceeding the normal value range (6.5–7.0).

Ethical considerations

The study was approved by the ethics board at the Affiliated Hospital of Nantong University and informed consent was taken from all the patients. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Research scales

Questionnaire on general information of inpatients

General information of inpatients was obtained through direct inquiry and through consulting medical records, and included gender, age, educational level, tumor type, clinical stage, denture, oral pH value, presence of oral diseases, smoking history, oral cleanliness, and chemotherapy drugs.

Oral mucositis grading scale

The oral mucositis grading scale (13) is based on the grading

standard developed by the American Society of Radiotherapy Oncology (RTOG), and was divided into 0-IV grades according to the severity of oral mucositis as follows: Grade 0: no oral mucositis; Grade I: erythema of oral mucosa accompanied by mild pain; Grade II: oral mucosa erythema, ulceration, but the patient could eat; Grade III: oral mucosal ulcer, the patient could eat semi-liquid food; Grade IV: the ulcer was severe and the patient could not eat.

Oral cleanliness grading scale

The oral cleanliness score (14) was evaluated from eight aspects: mucous membrane, gums, tongue, odor, teeth, lips, injury, and palate. For grading the mucous membrane, 1point was awarded for wet and intact mucosa, 2 points for dry and intact mucosa, and 3 points for dry, abrased, or ulcerated mucosa. The condition of the gums was scored as 1 point for no bleeding and atrophy of the gums, 2 points for mild atrophy and hemorrhage, and 3 points when gums were atrophied, easily bled, and swollen. A wet tongue with a small amount of tongue coating was allocated 1 point, a dry or medium amount of tongue coating scored 2 points, and a dry or wet tongue with a large amount of coating, or a coating of yellow and black colour scored 3 points. An odorless or flavorful oral cavity odor attracted 1 point, an unpleasant odor attracted 2 points, and a pungent odor scored 3 points. Teeth or dentures without white spots or caries, and a suitable denture scored 1 point, a medium amount of white scale, no caries or interdental pus, or an unsuitable denture scored 2 points, and a large amount of dental calculi, many cavities, cracks, an unsuitable denture, and interdental pus scored 3 points. Moist, soft, lips without cleft were given 1 point, rough, dry lips or those having a few scabs, cleft, or hemorrhagic tendency attracted 2 points, and lips which were dry, were cleft, had many scabs, secretions, and were prone to easy bleeding, were given 3 points. No oral injury or ulcers attracted 1 point, the presence of lip injury scored 2 points, and oral injury scored 3 points. Finally, a wet palate or having a small amount of debris scored 1 point, a dry palate with a small or moderate amount of debris scored 2 points, and a dry palate with a large amount of debris scored 3 points. All items were scored on a scale of 8 to 24, with 8 being a normal oral condition. And the higher the score, the worse the oral cleanliness.

Collected data

Differences in age, gender, educational level, tumor types, tumor stage, radiotherapy, radiotherapy duration, chemotherapy, dentures, smoking history, white blood cell count, oral cleanliness, body mass index, hemoglobin, creatinine, urea nitrogen, blood glucose, vomiting, diarrhea, and other general information were compared between the oral mucositis group and the no oral mucositis group with univariate analysis. The indicators with significant differences in univariate analysis were included in the multivariate logistic regression model, and the independent risk factors affecting oral mucositis in malignant tumor patients were screened out.

Statistical analysis

SPSS 17.0 software was used for statistical analysis, and the enumeration data were displayed by percentage (%). Chi-square test or analysis of variance was used for comparison, and $P<0.05$ indicated that the difference was statistically significant. Logistic regression analysis was used to analyze risk factors.

Results

Univariate analysis of oral mucositis in patients with malignant tumors (Table 1)

As can be seen in *Table 1*, after radiotherapy and chemotherapy in the 74 malignant tumor patients, 45 cases developed oral mucositis of varying degrees, while 29 cases did not, with an incidence of 60.8%. The incidence of oral mucositis in patients with head and neck tumors was significantly higher than that in patients with chest and abdomen tumors and was significantly higher in the group with a high oral cleanliness score than in the group with a low oral cleanliness score. The incidence of oral mucositis in radiotherapy patients was significantly higher than that in non-radiotherapy patients, and the longer the radiotherapy time, the higher the incidence. The incidence of oral mucositis in patients treated with Nituzumab during radiotherapy was significantly higher than that in non-users and significantly higher in patients receiving 1–3 cycles or more than 8 cycles of chemotherapy than that in patients not receiving chemotherapy.

Multivariate logistic regression analysis of oral mucositis in patients with malignant tumors (Table 2)

As can be seen in *Table 2*, multivariate logistic regression

Table 1 Univariate analysis of oral mucositis in patients with malignant tumors

Factors	Constituent ratio (%)	Oral mucositis		χ^2/F	P
		Yes	No		
Gender				0.003	0.959
Male	51.4	23	15		
Female	48.6	22	14		
Age				0.396	0.821
<40 years	5.4	3	1		
40–60 years	45.9	20	14		
>60 years	48.7	22	14		
Education				1.167	0.761
<Junior high school	75.7	36	20		
Senior high school or technical secondary school	16.2	6	6		
Junior college	2.7	1	1		
≥Bachelor	5.4	2	2		
BMI				3.064	0.216
18.5–22.9 kg/m^2	48.6	19	17		
<18.5 kg/m^2	14.9	17	10		
≥23 kg/m^2	36.5	9	2		
Tumor site				8.638	0.013
Head and neck	67.6	36	14		
Chest	14.9	5	6		
Abdomen	17.5	4	9		
Stage				1.691	0.429
II	18.9	10	4		
III	54.1	25	15		
IV	27	10	10		
Oral disease				2.315	0.128
Yes	27	15	5		
No	73	30	24		
Denture				0.015	0.903
Yes	28.4	13	8		
No	71.6	32	21		
Smoking history				0.493	0.483
Yes	36.5	15	12		
No	63.5	30	17		

Table 1 (*continued*)

Table 1 (*continued*)

Factors	Constituent ratio (%)	Oral mucositis		χ^2/F	P
		Yes	No		
Oral cleanliness (points)				10.935	0.001
8	41.9	12	19		
>8	58.1	33	10		
Oral pH				1.216	0.544
<6.5	52.7	26	13		
6.5–7	37.8	15	13		
>7	9.5	4	3		
Radiotherapy history				0.161	0.688
Yes	33.8	16	9		
No	66.2	29	20		
Ongoing radiotherapy				10.781	0.001
Yes	51.4	30	8		
No	48.6	15	21		
Days of radiotherapy (days)				17.467	0.001
<7	23	3	14		
7–13	18.9	11	3		
14–21	23	12	5		
>21	35.1	19	7		
Single dose of radiotherapy				4.741	0.192
≤2	56.8	24	18		
2.1–5	17.6	6	7		
5.1–8	13.5	7	3		
≥8	12.1	8	1		
Number of times using nimotuzumab during radiotherapy				9.958	0.007
0	73	27	27		
1–3	8.1	5	1		
≥4	18.9	13	1		
Chemotherapy cycle				9.297	0.026
0	24.3	10	8		
1–3	54.1	29	11		
4–8	16.2	3	9		
>8	5.4	3	1		

Table 1 (*continued*)

Table 1 (*continued*)

Factors	Constituent ratio (%)	Oral mucositis		χ^2/F	P
		Yes	No		
WBC (×10^9/L)				3.805	0.149
4–10	62.2	24	22		
<4	27	15	5		
>10	10.8	6	2		
Hemoglobin (g/L)				0.161	0.803
110–150	66.2	29	20		
<110	33.8	16	9		
Blood urea (mmol/L)				1.471	0.479
2.8–7.6	87.8	38	27		
<2.8	8.1	5	1		
>7.6	4.1	2	1		
Serum creatinine (μmol/L)				0.841	0.657
49–90	55.4	26	15		
<49	39.2	16	13		
>90	5.4	3	1		
Blood glucose (mmol/L)				1.422	0.348
3.9–6.0	82.4	39	22		
>6	17.6	6	7		
Nausea and/or vomit				0.39	0.844
Yes	29.7	13	9		
No	70.3	32	20		
Diarrhea				0.094	0.759
Yes	6.8	4	1		
No	93.2	41	28		

Table 2 Risk factors of oral mucositis in patients with malignant tumors

Factor	B	Standard error	Wald	P	95% CI
Tumor site	−0.477	0.439	1.179	0.278	0.262–1.468
Oral cleanliness	2.528	0.733	11.886	0.001	2.976–52.698
Radiotherapy	−2.272	0.878	6.7	0.01	0.018–0.576
Radiotherapy duration	0.075	0.032	5.381	0.02	1.012–1.148
Number of times using nimotuzumab	0.389	0.703	0.307	0.579	0.372–5.851
Chemotherapy cycle	0.204	0.267	0.586	0.444	0.727–2.069

analysis showed that the independent risk factors for oral mucositis in patients with malignant tumors were oral cleanliness, radiotherapy, and radiotherapy duration (P<0.05). Logistic regression analysis included independent variables such as tumor site, oral cleanliness, radiotherapy, radiotherapy duration, times of use of Nimotuzumab, and chemotherapy cycle to clarify the factors that affect the incidence, and the factors excluded by statistical analysis were tumor location, chemotherapy cycle, and times of use of Nimotuzumab.

Discussion

Incidence of oral mucositis in patients with malignant tumors

In this study, 45 of 74 malignant tumor patients developed oral mucositis of varying degrees, with an incidence of 60.8%. According to the study of Çakmak *et al.* (11) the incidence of oral mucositis in cancer patients undergoing outpatient chemotherapy is 51.7%. This is higher than the 25% seen by Dodd (12), and may be due to the higher proportion of radiotherapy patients in the present study (51.4%). The incidence of oral mucositis was also significantly higher in patients with head and neck tumors (72%) than that in patients with chest and abdomen tumors. Zahn *et al.* found the incidence of oral mucositis after radiotherapy and chemotherapy for oropharyngeal tumors was as high as 99% (15), which may be because head and neck tumors in that study were not further divided into head tumors and oropharyngeal tumors. The results of these studies show attention should be paid to the oral mucosa of patients with malignant tumors, especially those with head and neck tumors, and timely detection of problems and early intervention should be given to reduce the incidence and degree of oral mucositis. The use of an anti-inflammatory mouthwash can help reduce symptoms of oral mucositis in head and neck tumor patients treated with radiotherapy (16), and in the present study the incidence of oral mucositis was significantly higher in the group with high oral cleanliness score than in the group with low oral cleanliness score. The oral cleanliness score was evaluated from eight aspects: mucous membrane, gums, tongue, odor, teeth, lip, injury, and palate. A higher score indicated worse oral cleanliness, and the more prone the patient was to oral mucositis. Poor oral cleanliness is conducive to the growth and reproduction of bacteria in the oral cavity. Bacteria in the oral cavity play an important role in the occurrence of oral mucositis, and affect its duration and severity (17,18). In clinical work, it is necessary to strengthen oral care, improve oral cleanliness, reduce bacterial reproduction, and reduce the incidence of oral mucositis.

The incidence of oral mucositis in radiotherapy patients was significantly higher than in patients not receiving radiotherapy. The mechanism by which this occurs is the direct cytotoxic effect of radiation, which causes mucosal injury (19). The duration and degree of mucositis induced by radiotherapy are related to the dose, intensity, and cumulative dose of radiotherapy. Therefore, the oral mucosa of patients undergoing radiotherapy, especially when repeated, should be closely observed and early intervention should be given to alleviate the pain of patients. The use of glutamine can reduce the incidence of grade III and IV oral mucositis caused by radiotherapy or chemotherapy (20).

The incidence of oral mucositis in patients who received Nituzumab during radiotherapy was significantly higher than that of non-users, and the greater use of the drug equated with a higher incidence. This may be because the subjects included in this study who received Nituzumab were treated simultaneously with radiotherapy. The first dose was given on the first day of radiotherapy and thereafter once per week of radiotherapy. The longer the duration of radiotherapy, the higher the cumulative radiation dose, and the greater administration of Nituzumab, all equated with a higher the incidence of oral mucositis. Elting *et al.* suggested that the incidence of oral mucositis in tumor patients receiving targeted therapies such as Bevacizumab, Erlotinib, and Sorafenib was significantly increased (21), which is consistent with the results of the present study.

The incidence of oral mucositis in patients with 1–3 cycles or more than 8 cycles of chemotherapy was significantly higher than that in patients not receiving chemotherapy. According to Jones *et al.*, the incidence of oral mucositis in chemotherapy patients is 20–40%, and the incidence in high-dose chemotherapy patients is 90% (22). Chemotherapy-induced mucositis was related to the dose intensity of the chemotherapeutic drugs, which was consistent with the results of our study. The mechanism of chemotherapy-induced oral mucositis involves anti-tumor drugs leading to the release of inflammatory mediators, which weaken the regeneration ability of epithelial cells causing mucosal injury. Oral cryotherapy can effectively prevent and relieve oral mucositis and anorexia caused by chemotherapy (23).

The key measure for the prevention and treatment of

oral mucositis (6) in malignant tumor patients is to maintain the best nutritional support in the process of tumor treatment. If the diet of malignant tumor patients is affected by oral mucositis in the process of treatment, nutritional support programs should be given in time, and analgesic treatment should be given when necessary. At the same time, pay attention to keep your mouth clean. Brush and gargle at least 4 times a day with a soft-bristled toothbrush. When gargling, use non-alcoholic mouthwash with 15 mL mouthwash each time for 1 minute. Avoid eating acrid, coarse, overheated food, lest damage oral mucous membrane.

Risk factors of oral mucositis in patients with malignant tumors

The possible etiology of oral mucositis is caused by drugs, infection and immune deficiency, and the two main causes of oral mucositis in patients with head and neck tumors are high-dose radiotherapy and chemotherapy (6). Mucosal barrier injury can be divided into five stages: initiation, up-regulation of messenger generation, signaling and amplification, inflammatory ulcer formation and final healing (4). In patients receiving radiotherapy, oral mucosal endothelial injury is the early change of mucosal injury, and then due to oxidative stress and reactive oxygen species caused by chemotherapy or radiation therapy, DNA in the upper cortex is damaged, and epithelial cells lose their ability to renew, leading to the death, atrophy and subsequent formation of ulcers of clonal cells (4). Elevated levels of inflammatory factors such as tumor necrosis factor-α (TNF-A) and interleukin-1 and 6 (IL-1 and IL-6) in peripheral blood of patients after chemotherapy may also increase mucosal toxicity (4).

The results of this study showed that oral cleanliness, radiotherapy, and radiotherapy duration were independent risk factors for oral mucositis in patients with malignant tumor. However, there are few studies investigating these factors. Nishii *et al.* suggested that patients with oropharyngeal cancer, male patients, low hemoglobin levels, low white blood cells or lymphocytes, and cisplatin or cetuximab application were prone to severe oral mucositis (24). However, in the present study, low hemoglobin was not found to be a risk factor, which may be related to the small sample size. Mlak *et al.* (25) suggested that high concentrations of TNF-α and CC genotypes of TNF-α in blood of patients with head and neck tumor radiotherapy were associated with increased risk of severe oral mucositis. High plasma TNF-α concentration and CC genotype of TNF-α were independent prognostic factors in patients with radiotherapy for head and neck tumors. Çakmak *et al.* (11) found that advanced age, inappetence and long duration of chemotherapy were risk factors in the study of cancer patients undergoing outpatient chemotherapy. Although Shouval *et al.* found that age, lower body mass index, smoking, antibiotic use, and methotrexate were associated with the development of moderate to severe oral mucositis (10), their work was on allogeneic hematopoietic stem cell transplant recipients. Age, lower body mass index, and smoking were not found to be risk factors in the present study.

In conclusion, oral cleanliness, radiotherapy, and radiotherapy duration are independent risk factors for oral mucositis in patients with malignant tumors. The results provide a basis for the prevention and intervention of oral mucositis and intervention should be carried out according to the above risk factors. Patients with radiotherapy should be given preventive measures during radiotherapy, and intervention to minimize the incidence and degree of oral mucositis.

Limitations

One limitation of this study is its small sample size, and a larger cohort is recommended to verify the results. After that, the occurrence of oral mucositis of the same tumor or different types of tumor can be analyzed in detail. In addition, we only investigated oral cleanliness, tumor location, radiotherapy, radiotherapy duration, chemotherapy cycle, and the frequency of use of nimotuzumab as risk factors for oral mucositis in patients with malignant tumors. There may be other risk factors such as immune function status not included in this study that could be investigated further in the future.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the ethics board at the Affiliated Hospital of Nantong University and informed consent was taken from all the patients. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013)

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