

Original Article

Frequency of chemoradiotherapy-induced mucositis and related risk factors in patients with the head-and-neck cancers: A survey in the North of Iran

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ABSTRACT

Background: In this study, we aimed at evaluating the frequency of chemoradiotherapy-induced mucositis (CIM, RIM) and its related risk factors in patients with the head-and-neck cancers (HNCs).

Materials and Methods: In this cross-sectional prospective descriptive study, we evaluated a total of 54 HNCs patients referred to the Oncology Chemoradiotherapy Department of Razi and Amiralmomenin University Hospitals of Rasht, for site and grade (WHO classification) of CIM/RIM, based on their demographic features and possible risk factors. SPSS software version 18 and statistical tests (i.e., Fisher's exact test) were used, and the level of significance was considered as $P < 0.05$.

Results: Finally, patients enrolled in the study were 34 men and 20 women (40–72-year-old), of which 43 cases (79.6%) showed signs and symptoms of CIM/RIM (mostly aged 60–69-year-old). Grade 2 mucositis was the most frequent type (18 cases: 33.3%) and mouth floor was the most common site of CIM/RIM (15 patients: 34.9%). Age ($P = 0.023$), gender ($P = 0.012$), and the severity of pain ($P = 0.018$) were significantly related to mucositis in patients with HNCs who underwent chemotherapy or radiotherapy.

Conclusion: Mucositis, especially in the oral cavity, is a common complication of chemoradiotherapy in HNCs patients. Age, gender, and the severity of pain are significantly associated with the frequency of CIM/RIM.

Key Words: Chemoradiotherapy, mucositis, neoplasms

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INTRODUCTION

Although it is estimated that the head-and-neck cancers (HNCs) account for about 5% of all human cancers worldwide,^[1,2] various therapeutic approaches, including surgery, radiotherapy, and chemotherapy are still required for treating such patients.^[1-3] Radiotherapy, alone or with surgery, is often considered as the first

choice of treatment for most patients with HNCs.^[1,4-6] According to the medical literature, lethargy, oral mucositis, weakness, dry mouth, mouth sores with pain, taste changes, and sore throats are among the possible complications of chemoradiotherapy.^[1,2,7]

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Mucositis, as an acute debilitating complication of chemoradiotherapy, leads to partial or total mucosal damage in either the exposed mucosal lining areas radiotherapy-induced mucositis (RIM) or more susceptible anatomical/histological regions of the patients chemotherapy-induced mucositis (CIM). Clinical characteristics of RIM or CIM vary from mild erythema to deep mucosal ulcerations based on the degree of mucosal inflammation and epithelial cell loss.^[1,2,6,7] This serious complication is found in almost all patients who undergo radiotherapy, and in about 40% of those receiving chemotherapy following the initial cycle of treatment.^[1,2,6,8] In certain patients, mucositis may hinder the process of therapy as it takes weeks or even months to resolve.^[1,2,7,9] Despite various studies on RIM and CIM and their possible contributing factors, determining the most effective and important risk factors is still a matter of controversy.

In the present study, the objective was to evaluate the frequency of RIM and CIM in the Iranian population with HNCs. Further investigated were the predisposing and associated factors with RIM or CIM among our subjects.

MATERIALS AND METHODS

In this cross-sectional prospective study, which lasted from September 2011 to October 2012, we enrolled 54 patients with HNCs who were referred to the Oncology-Chemoradiotherapy Department of Razi and Amiralmomenin University Hospitals of Rasht. The study protocol was approved by the Ethical and Scientific Review Committee of Guilan University of Medical Sciences with a registration code number of 1682.

The inclusion criteria were as follows: (1) The patient's agreement to take part in the study, and (2) patients with head-and-neck malignancies (i.e., oral cavity, salivary glands, nasopharynx, larynx, and upper cervical region) who were referred for radiotherapy or chemotherapy and had no prior history of chemoradiotherapy in the affected area. The only exclusion criterion was if the patients declined to participate in the study.

All the patients received radiotherapy, but 31.5% of the patients received chemoradiotherapy. All the radiotherapy/chemotherapy protocols were the same in the patients (i.e., three definitive chemoradiotherapy courses using low-energy linear accelerator (Siemens

Company, Germany) with a daily dose of 200 centigray (cGy) and a total dose of 6600–7000 cGy. The chemotherapy protocol was based on weekly cisplatin administration (40–50 mg/m²). The sample size was calculated as 54 cases based on the Hashemipour study,^[10] with an overall mucositis incidence rate of 83.3%.

Mucositis was classified according to the WHO classification on a 0–4 staging system based on the following clinical manifestations: no mucositis (Grade 0), erythema and/or mucosal ulceration in oral cavity, on the hard and soft palates, and oropharynx without pain (Grade 1), erythema or painful ulceration that does not interfere with food consumption (Grade 2), painful ulceration interfering with food consumption (Grade 3), and severe symptoms that necessitate enteral or parenteral feeding support for the patients (Grade 4).^[11] All study variants were recorded before and 1 week following the completion of the treatments. Patients were further evaluated for mucositis regarding the following variables: gender, age, type and location of cancer, therapeutic approaches (surgery, radiotherapy, or chemotherapy), primary site of mucositis, general dental status (denture, partial denture, number of damaged teeth, and ratio of damaged teeth to total teeth), smoking and drinking status, fasting blood sugar levels (mg/dl), blood pressure (mmHg), blood cell counts (white blood cells [WBCs] [cell/mm³], hemoglobin levels [g/dl], and platelets [cells/mm³]), taste sensation status, history of gastric regurgitation, and mucositis-related pain (based on Visual Analog Scale: VAS).^[11] Using standardized laboratory methods, all necessary laboratory samples were obtained at 08:00–09:00 am, after an overnight fasting period. Systolic and diastolic blood pressures were measured at the same hour (08:00–09:00 am) using a mercury sphygmomanometer with a standard covering cuff on the right arm in a seated position following 5 min of rest. Before the study, all patients were examined by an otolaryngologist, an oncologist, and the co-operative dentist of the study.

Diabetes mellitus (DM) and hypertension (HTN) were diagnosed based on the latest American Diabetic Association and American Heart Association guidelines and reliable previous medical histories. One week after the treatment, all patients underwent physical examinations by the same otolaryngologist and oncologist for possible complications (including mucositis, taste dysfunctions, gastric regurgitations,

and VAS pain evaluations); data were then recorded on a checklist and analyzed using SPSS IBM software version 18. The study variables were initially evaluated applying statistical tests for normality, and *t*-tests or nonparametric statistical tests. The level of significance was considered as <0.05 .

RESULTS

As detailed in Table 1, 34 men (63%) and 20 women (37%) aging from 40 to 72-year-old (mean age of 61.33) were enrolled in the present research. The primary sites of HNCs were mainly the salivary glands, nasopharynx, larynx, and oral cavity [Table 2]. Most of the patients with HNCs had received radiotherapy (68.5%), whereas 31.5% had undergone chemoradiotherapy.

Forty-three patients demonstrated the symptoms and signs of oral mucositis (79.6%). Mucositis was more frequent among men (31 out of 34 men, compared with 12 out of 20 women; $P = 0.012$) [Table 1]. The mouth floor was the most common site of mucositis (15 patients; 34.9%). Furthermore, Grade 2 mucositis (based on the WHO classification) had the highest frequency (18 cases; 33.3%).

Out of the 25 HNCs patients with no oral pain, 16 patients (64%) developed mucositis 1 week after the treatment, whereas 100% and 87.5% of those with mild or severe pain developed oral mucositis, respectively ($P = 0.018$). Moreover, 20 patients (83.3%) out of the 24 cases with HNCs who had dentures, developed CIM, RIM. This was more frequent compared with CIM, RIM in HNCs cases without denture (76.6%), though the difference was not statistically significant ($P = 0.736$).

With respect to other risk factors of CIM or RIM, 80.7% of patients had WBC counts $>2000/\text{mm}^3$, whereas 33 patients had platelet levels of $>20,000/\text{mm}^3$. Furthermore, 37 nondrinker and 26 nonsmoker cases, 31 cases without DM, 34 patients without HTN, 28 cases without regurgitation, and 34 patients with normal taste sensation status (79.1%) finally developed CIM or RIM. None of these differences were statistically significant ($P > 0.05$), [Table 1].

All patients receiving chemoradiotherapy for HNCs in the oral cavity or larynx, developed mucositis (7 of 7, for both regions), unlike other studied anatomical areas, including salivary glands, nasopharynx, larynx, or upper cervical region [Table 2].

Table 1: Frequencies of chemotherapy-induced mucositis and radiotherapy-induced mucositis based on study variables

Variable	HNC	Mucositis number (%)	P
Gender			
Male	34	31 (91.1)	0.012
Female	20	12 (60)	
Age (years old)			
40-49	7	5 (71.4)	0.023
50-59	12	7 (58.3)	
60-69	24	23 (95.8)	
70-80	11	8 (72.7)	
Type of treatment			
Radiotherapy	37	29 (78.3)	0.522
Chemo-radiotherapy	17	14 (82.3)	
Severity of pain (VAS)			
No pain	25	16 (64)	0.018
Mild pain	13	13 (100)	
Severe pain	16	14 (87.5)	
Denture status			
Yes	24	20 (83.3)	0.736
No	30	23 (76.6)	
Number of extracted teeth			
$<1/3$ of all teeth	40	31 (80.7)	0.7
$>1/3$ of all teeth	14	12 (85.7)	
WBC count (cells/mm ³)			
2000	2	1 (50)	0.369
>2000	52	42 (80.7)	
Drinking (alcohol) status			
Consumer	6	6 (100)	0.327
Nonconsumer	48	37 (77.1)	
DM			
Yes	16	12 (75)	0.714
No	38	31 (81.5)	
HTN			
Yes	15	9 (60)	0.054
No	39	34 (87.1)	
Regurgitation			
Yes	22	15 (68.1)	0.1
No	32	28 (87.5)	
Smoking status			
Smoker	18	17 (94.4)	0.77
Nonsmoker	36	26 (72.2)	
Platelet count (cells/mm ³)			
200,000	10	10 (100)	0.1
$>200,000$	44	33 (75)	
Hemoglobin count (g/dl)			
10	2	1 (50)	0.369
>10	52	42 (80.7)	
Taste status			
Normal	43	34 (79.1)	0.604
Abnormal	11	9 (81.7)	

HNC: Head and neck cancer; VAS: Visual analogue scale; WBC: White blood cell; DM: Diabetes mellitus; HTN: Hypertension

Among all the studied variables, only age, gender, and the severity of mucositis-induced pain had a significant

Table 2: Frequencies of sites of head and neck cancer treatment, sites of mucositis, and clinical grades of mucositis among 54 patients with head-and-neck cancers in the North of Iran

Sites of HNCs	Mucositis, n (%)	Total
Oral cavity (n=7)	7 (100)	54
Salivary glands (n=12)	10 (83.3)	
Nasopharynx (n=10)	7 (70)	
Larynx (n=7)	7 (100)	
Upper cervical region (n=18)	12 (66.6)	
Site of mucositis		
Anterior tongue	8 (18.6)	54
Lateral tongue	5 (11.6)	
Mouth floor and gingiva	15 (34.9)	
Buccal mucosa	7 (16.3)	
Soft and hard palate mucosa	6 (14)	
Nasal mucosa	2 (4.7)	
Clinical grade of mucositis		
Grade 0	11 (20.4)	54
Grade 1	16 (29.6)	
Grade 2	18 (33.3)	
Grade 3	8 (14.8)	
Grade 4	1 (1.9)	

HNCs: Head-and-neck cancers

association with CIM or RIM frequency ($P < 0.05$) in HNCs patients [Tables 1 and 2].

DISCUSSION

Among various complications of chemoradiotherapy, mucositis is a very serious one, involving soft tissues of the affected oral surfaces, which can have debilitating effects on the quality of life in HNCs patients. Different studies have been conducted to evaluate the frequency and possible risk factors of CIM/RIM.^[1-3,5,7]

In this study, we evaluated 54 cases with HNCs who underwent radiotherapy and/or chemotherapy for mucositis. There were significant relationships between the frequency of mucositis and age and gender among our patients. Mucositis was mostly found among the 60–69-year-old age group, and also among men (72%). Suresh *et al.* (M/F ratio = 3.6/1) and Devaraju *et al.* (M/F ratio = 4/1) reported similar results,^[12,13] whereas Taheri *et al.*^[14] found equal gender ratios (M/F ratio = 1/1). Patussi *et al.*,^[15] on the other hand, studied 16 women and 15 men. The mean and standard deviation (SD) of the ages of patients with mucositis in the studies by Taheri *et al.*, Devaraju *et al.*, and Patussi *et al.* were 45.17 ± 15.8 , 45 ± 14 and 48.8-year-old, respectively.^[13-15] These studies may indicate that patients younger than 50 years old

have higher rates of CIM or RIM. In the study by Vera-Llonch *et al.* in line with the present research, the mean and SD for the ages of patients with mucositis were 61.3 ± 12.3 and 61.33 ± 2.33 -year-old, respectively.^[16] Perhaps, the sample size and the mean age of these studies were different from ours, which may explain the difference in the results. Suresh *et al.* reported even younger population groups with mucositis (34 ± 18 years old).^[12] In this study, a significant relationship was reported among older age groups who had mucositis, which is probably owing to the early diagnosis of HNCs in the study group (the youngest patient was 40 years old).

We did not find any significant relationships between comorbidities (i.e., DM and HTN) and CIM or RIM; however, according to previous studies, these factors are able to influence the frequencies of CIM or RIM, as they can affect the immune system in such patients, particularly the elderly cases.^[1,2]

Frequencies of mucositis have also been assessed in different studies, including those by Taheri *et al.* (100%) and Vera-Llonch *et al.* (83%).^[14,16] All these studies revealed the fact that nearly all (90%–97%) patients who receive radiotherapy in the head-and-neck anatomical zones will develop certain degrees of mucositis. Vera-Llonch *et al.* reported that 83% of patients who underwent radiotherapy developed mucositis, whereas 33% developed severe mucositis.^[16] In this study, this rate was 79.6% (43 patients), of whom 16.7% had severe mucositis (Grade 3 or 4) which interferes with food consumption. Our results are slightly different from the foregoing studies regarding both frequency and in severity, probably because of our newer radiotherapy equipment and protocols, and the fact that our cases had undergone radiotherapy or chemotherapy (78.3% vs. 82.3%, respectively).

Most of the patients with mucositis in the studies by Devaraju *et al.* and Suresh *et al.* had Grade 4 mucositis (36 patients: 40%, and 87 patients: 40%, respectively), whereas Patussi *et al.* reported Grade 1 mucositis in most affected patients (15 patients, 48%).^[12,13,15] In this study, patients developed signs of mucositis mostly consistent with Grade 2 (18 patients, 33.3%). Such various patterns in the grades of mucositis in different studies might be owing to therapeutic-related factors such as radiation dose, or demographic features.^[12,13]

Smoking was evaluated by Suresh *et al.*, Taheri *et al.*, and Devaraju *et al.*, where 75%, 23.3%,

and 45% of the patients had a history of smoking, respectively.^[12-14] Patussi *et al.* suggested that most patients with a history of smoking developed Grade 0 or 1 of mucositis,^[15] which is consistent with the findings of the present study as most of our patients with a history of smoking manifested mucositis [Table 1].

WBCs were evaluated in most former studies, probably due to their significant roles in the treatment of cancers and more importantly, the possible effects of cancer treatment on these cells. WBC counts were $4.12 \pm 1.4 \times 10^9$ L and 5567 ± 1235 cells/mm³ in the work by Devaraju *et al.* and Suresh *et al.*, respectively; in the current research, WBC count was >2000 cells/mm³.^[12,13] According to Devaraju *et al.*, the development of mucositis after chemoradiotherapy is multifactorial. It is also implied that the more advanced the underlying cancer is, the higher the risk of developing mucositis will be; smoking, oral hygiene, and nutritional status are among other possible risk factors. Although the relationships were not statistically significant in this study, it seems that these factors play crucial roles; hence, the necessity of future studies on this subject.^[13]

Other studies have also considered oral hygiene status as a significant independent factor following cancer treatment, playing an important role in the process of inflammation leading to mucositis.^[14,16] This factor itself is influenced by exposure to various microbial species in the oral cavity (i.e., *Candida* species), which either triggers mucositis or deteriorates the grade of primary induced mucositis.^[1,2]

In this study, we considered the number of extracted or caried teeth, history of gastric regurgitation, and possible denture applications (partial or total) as factors indicative of oral health status among the studied patients. Our results showed that most of the patients had relatively acceptable levels of oral hygiene, a factor not significantly associated with mucositis. VAS, to evaluate the severity of the pain (that may be due to inflammatory effects of RT or CRT)^[13,14] reported by the patients with mucositis, revealed that all patients complained of mild pain, and 87.5% developed severe pain around the primary sites of mucositis ($P < 0.05$).

Vera-Llonch *et al.* reported that 24.4% of mucositis cases occurred in the oral cavity region;^[16] in the current study, however, all patients treated for HNCs

manifested mucositis in their oral cavity. This is probably due to the radiotherapy or chemotherapy and in certain cases, the genetic predispositions of the studied patients. Authors such as Stokman *et al.*,^[17] conducted studies for more objective and sensitive approaches to an early diagnosis of RIM, reporting that the oral washings (i.e., the serum with which the patients washed their mouths and gurgled obtained for laboratory analysis) of patients with RIM or CIM could determine the viability of epithelial cells, therefore predicting the changes earlier than the subjective mucosal changes consistent with the WHO scoring system.

CONCLUSION

Mucositis, particularly in the oral cavity, is a common complication of radiotherapy or chemoradiotherapy in HNC patients. Different variables such as age, gender, and the severity of pain are significantly related to the frequency of CIM, RIM. Thus, clinical presumption and proper examinations following chemoradiotherapy in specific age and gender groups and in patients with severe pain may conduce to detecting and treating mucositis properly.

Limitations and recommendations

Although the sample size was based on the number of HNC referrals to our medical centers, the relatively small sample size of the present study is considered as its major limitation. For future studies, we recommend considering multi-centric similar studies with larger sample sizes.

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or nonfinancial in this article.

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