



Mucositis-Induced Pain due to Barrier Dysfunction may have a Direct Effect on Nutritional Status and Quality of Life in Head and Neck Cancer Patients Receiving Radiotherapy

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OBJECTIVE

To maintain the barrier function against mucositis-induced pain and to improve the nutritional status and quality of life in head and neck cancer patients during radiotherapy.

METHODS

All patients (n=30) used oral gel to reduce mucositis-induced pain. Patients were examined weekly for the severity of mucositis, pain and nutritional status. The quality of life parameters was measured at the beginning and at the end of treatment. There was no restriction for pain killers against mucositis.

RESULTS

The only significant factor affecting the severity and frequency of mucositis was the cumulative radiation dose ($p<0.001$). Despite the regular use of oral gel, weight loss was observed in 65% of the patients. There was no difference concerning the severity of mucositis, cumulative radiation doses, or mean dose of oral mucosa between patients with no risk or at risk, according to SGA. However, self-assessment pain scores were significantly better in the well-nourished group ($p=0.05$ vs. 0.015) with better scores for dry mouth ($p=0.043$), social eating ($p=0.006$), swallowing difficulties ($p=0.001$) and communication ($p=0.049$).

CONCLUSION

Supporting the barrier function alone does not help to reduce the severity and frequency of mucositis, nor the oral pain in high doses. Mucositis-induced pain may have a direct effect on malnutrition risk and quality of life in head and neck cancer patients. Powerful strategies are required to manage pain due to mucositis during curative radiotherapy.

Keywords: Head and neck cancer; hyaluronic acid; nutrition; polyvinyl prolidone; quality of life; radiotherapy.

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Introduction

Oral mucositis is one of the most frequent side-effects of head and neck radiotherapy.[1] Mucosal inflamma-

tion and ulceration cause pain and swallowing difficulties during radiotherapy and may have a detrimental effect on treatment, causing prolongation with unintended interruptions.[2,3] Several strategies to reduce

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the severity and frequency of mucositis are described in the literature, but none of them are completely effective or strongly recommended.[4-7] The total radiation dose for oral mucosa is one of the most important factors in mucositis. Therefore, a severe side-effect is inevitable during definitive radiotherapy.[6] Mucositis-induced pain may adversely affect nutritional status, especially the oral health-related quality of life of patients receiving curative treatment.[8,9]

In this prospective single-arm study, we aimed to maintain the barrier function against mucositis-induced pain with an oral gel containing glycyrrhetic acid, hyaluronic acid and polyvinylpyrrolidone in head and neck cancer patients during radiotherapy.[6,10] This oral gel has previously been described as effective in reducing pain during chemotherapy, and in a few radiotherapy studies.[11-13] In this study, our goal is to maintain nutritional status and quality of life by maintaining the mucosal barrier function and reducing oral pain.

Materials and Methods

Ethical Considerations

Ethics approval for this study was obtained from Marmara University School of Medicine Ethical Committee with the number 7037436-050.06.04-140018640. All volunteers signed consent forms after a full explanation of this clinical study.

Patients and Settings

Thirty patients diagnosed with head and neck cancer were included in this study. However, one patient died due to disease progression in the third week of radiotherapy. Thus, 29 volunteers were included in the analysis (loss rate: 3.3%). The characteristics of the study group are summarized in Table 1. All patients were examined by a dentist experienced in head and neck radiotherapy (KBK) for oral hygiene evaluation and periodontal and dental treatment was carried out if necessary, before radiotherapy. None of the volunteers reported any alcohol or tobacco usage during radiotherapy.

Radiotherapy was applied in a linear accelerator with 6 MV photon energy using the volumetric arch technique to patients with curative intent in a median six weeks, with a mean dose of 66 Gy (range, 60 to 70 Gy). Each patient received the treatment with intensity-modulated radiotherapy planning (IMRT). Most of the patients received concurrent weekly cisplatin-based chemotherapy (83.3%). Oral mucosa for each

Table 1 Demographics of the patients and treatments characteristics

Variable	Mean (SD); Min-Max
Gender	
Male	24 (82%)
Female	5 (28%)
Age (years)	56.79 (13.57); 23-87
Location of tumor	
Oral cavity	11
Nasopharynx	7
Larynx	6
Paranasal sinuses	3
Oropharynx	1
Primary unknown neck	1
Chemotherapy	
Neoadjuvant	6 (20%)
Concurrent	25 (83.3%)
Mean dose of radiotherapy	66 Gy (60-70 Gy)
Mean dose of oral mucosa (Gy)	36.84 (23.72); 3.1-62.2
Volume of oral mucosa (cc)	135.11 (28.14); 81.9-201.37
	Median (IQR); Min-Max
V10 (%)	82.33 (30.38); 0-100
V20 (%)	75.22 (32.98); 0-100
V30 (%)	59.92 (31.84); 0-100
V40 (%)	48.25 (32.83); 0-100
V50 (%)	38.02 (34.01); 0-100

SD: Standard deviation; V10-50: Percentage of oral mucositis volume that receive the related doses of radiation in Gray

patient was countered by a radiation oncologist for organs at risk, including the teeth and buccal mucosa. The mean volume of oral mucosa was revealed with a 3D radiotherapy planning system (Eclipse v11.0) and it was 132.69 cc (SD 24.94; range, 81.9 to 201.37 cc). The percentage of the mean volume received radiation dose (in Gy) by oral mucosa (V10 to V50) was 40.19% (SD 23.72%; range, 3.1 to 100%) (Table 1).

Oral mucositis was measured and graded weekly from the beginning to the end of radiotherapy. The prevalence of severe oral mucositis was documented by Common Toxicity Criteria v3.0.[14] A grade of three or higher indicates the prevalence of severe mucositis.

All patients were assessed weekly for other side-effects by a radiation oncologist (BMA), and for oral and dental care (physical changes in mucosa, gingiva and teeth) by a dentist (KBK), and for nutritional status and treatment by a dietitian (BD) using the subjective global assessment test (SGA).[15] The oral gel containing glycyrrhetic acid, hyaluronic acid and polyvinylpyrrolidone (GelClair®) was provided from

Helsinn Pharmaceutical Company without any charge. The oral gel was used to coat the ulcerated oral mucosa surface and to reduce mucositis-induced pain during eating. The application of oral gel was started at the 12 Gy of radiotherapy when the clinical symptoms biologically start.[16] Therefore, patients used oral gel before every meal, at least three times a day. They used oral gel for one minute for each administration and performed self-measurement using a sand timer. Regular usage was checked weekly via patients and/or caregivers' paper-based reports. The self-assessment visual analog score (VAS) was used for assessing oral pain weekly during radiotherapy.[17] Pain scores ranging from 0 to 10 on a continuous scale were measured (0=no pain to 10=very painful). There was no restriction for painkiller usage, and patients did not use any other strategy to reduce the mucositis. Oral health-related quality of life was assessed using the EORTC QoL-HN35 questionnaire at the beginning and at the end of radiotherapy.[18]

Statistical Analysis

For descriptive purposes, numerical variables were summarized using means and standard deviations, or medians and interquartile ranges according to the distribution. The distribution of the continuous variables was investigated using the Shapiro Wilks test, QQ, PP plots, skewness and kurtosis values. Patients' mucositis-related symptoms were measured each week of radiotherapy. Mucositis was classified as being severe (2 and 3) or not severe (0 and 1). This reasoning warranted the decision to dichotomize the outcomes, as well as the choice of threshold. The proportion of severe mucositis was tested using the Cochran-Armitage test for trend. A longitudinal study design, with repeated measures, was used. Changes in VAS scores over time were assessed. Patients' oral mucosa and VAS were assessed at six-time points. Generalized estimating equations (GEE) were used to analyze the predictive factors of VAS scores. Patients were also analyzed after being divided according to malnutrition. Thus, the Wilcoxon

signed-rank test was used to examine the differences in the prevalence of oral mucositis related symptoms (revealed by the EORTC QoLHN35 questionnaire), such as pain, swallowing, speech, social eating, communication and altered taste) within groups across different time-points. It was also of interest, given patients' pain status (no/yes) at the beginning of the therapy, to see whether oral mucositis related symptoms changed concerning time was investigated. The McNemar test was used to detect whether the nutritional assessment test SGA (no risk=SGA A/under risk=SGA B or C) proportion changed between the beginning and the end of this study. Another analysis was also carried out looking at weight loss. The mean percentage of weight loss was 5%, and groups were split by weight loss <5% vs. ≥5%. These statistical tests were performed with R 3.5.3 (R Core Team [2019]; R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna Austria; URL <http://www.R-project.org/>). A p-value of <0.05 was considered statistically significant.

Results

Mucositis and Pain

The prevalence and proportion of severe oral mucositis increased from week one to week five, peaked at week five, then decreased until the end of radiotherapy, as expected. A significant linear increasing trend for severe oral mucositis was found by the Cochran-Armitage linear trend test ($p<0.001$) (Table 2). Meanwhile, oral mucositis-induced pain increased each week from the beginning to the end of radiotherapy ($p<0.001$). The only significant predictor for changes in VAS scores was the cumulative radiation doses of radiotherapy ($p<0.001$) (Table 3).

Nutritional Status and Quality of Life

There was a significant increase in the prevalence of patients' mucositis (64.3%) who become at risk (SGA B or C) at the end of radiotherapy ($p<0.001$) (Table 4).

Table 2 Frequencies and prevalence of the severe oral mucositis concerning weeks of radiotherapy

		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	P value*
None-severe	Count	29	27	19	12	21	13	<0.001
Grade 1-2	Percent	97%	90%	63%	40%	38%	46%	
Severe	Count	1	3	11	18	18	15	<0.001
Grade 3	Percent	3%	10%	37%	60%	62%	54%	

*: Cochran-Armitage linear trend test

Table 3 Predictors for the changes in VAS scores

Variable	Coef.	Std. Err.	Lower (95% CI)	Upper (95% CI)	Z (Wald test)	p
Oral pain at the beginning of radiotherapy (Yes)	-0.462	0.650	-1.735	0.812	0.505	0.477
CCRT (Yes)	0.996	1.139	-1.236	3.227	0.765	0.382
Volume of oral mucosa (135 cc)	0.010	0.0117	-0.013	0.033	0.765	0.382
Mean dose of oral mucosa (36.8 Gy)	0.022	0.020	-0.017	0.061	1.18	0.277
Cumulative radiation dose	0.560	0.117	0.331	0.789	22.94	<0.001

VAS: Visual analogue score; CCRT: Concurrent chemoradiotherapy

Table 4 Changes of the prevalence of malnutrition at the beginning and end of this study according to SGA

Beginning of radiotherapy	End of radiotherapy		p
	No risk (SGA A)	Under risk (SGA B or C)	
No risk	10 (35.7%)	18 (64.3%)	<0.001
Under risk	0 (0%)	1 (100%)	

SGA: Subjective global assessment

The mean percentage of weight loss was 4.95%. There was no difference concerning the severity of mucositis, cumulative radiation doses or mean dose of oral mucosa between patients <5% and ≥5% weight loss or SGA A and SGA B and C. On the other hand, the VAS score was worse in the SGA B and C group of patients (Fig. 1).

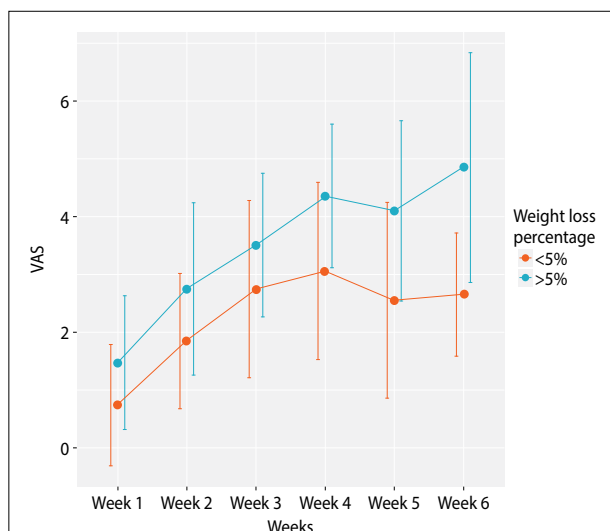


Fig. 1. VAS scores according to the weight-loss proportion in weeks.

Oral health-related quality of life parameters worsened at the end of radiotherapy in all patients. Although analysis showed that pain ($p=0.01$ vs $p=0.02$), mouth pain ($p=0.123$ vs $p=0.07$), talking difficulties ($p=0.06$ vs $p=0.001$), swallowing difficulties ($p=0.09$ vs $p=0.001$), social eating difficulties ($p=0.176$ vs $p=0.006$), communication ($p=0.549$ vs $p=0.049$), taste altering ($p=0.004$ vs $p=0.000$) and dry mouth ($p=0.05$ vs $p=0.04$) were significantly worse in patients with ≥5% weight loss (SGA B or C) (Table 5).

Patients were split according to the mean percentage of weight loss (≥5%). The severity of mucositis was not different between groups according to V40, V50 of the oral mucosa. However, VAS scores were lower in the well-nourished group of patients. Quality of life parameters was also significantly better in this group of patients (Table 6).

Discussion

Mucositis is a dose-limiting and common side-effect of head and neck radiotherapy.[1-3] It is not possible to maintain the integrity of the mucosa before the end of treatment. There are mainly two ways to reduce the effects of mucositis during head and neck radiotherapy. One is to reduce the volume of the high dose area of the mucosa, and another is to use medication, such as protective agents, anti-inflammatory agents and painkillers.[4-6] Due to the primary tumor side and treatment protocols, and despite modern techniques, it is not always possible to reduce the mucosal volume receiving high doses. Moreover, none of the recommendations for the medication fully work for severe mucositis. The Multinational Society for Supportive Care in Cancer (MASCC) recommends benzydamine for high-level treatment of mucositis to reduce and improve radiotherapy related mucositis.[5,6,19] We aimed to use an oral gel that coats the damaged mucosal area to decrease the severity of mucositis and

Table 5 Comparisons of the EORTC QoLHN35 oral health-related parameters between the beginning and the end of the radiotherapy

Variable Individual symptom	Beginning of radiotherapy Median (IQR); Min-Max	End of radiotherapy Median (IQR); Min-Max	p ^a
Mouth pain	8.33 (16.6); 0-50	33.3 (49.97); 0-83.3	<0.001
Talking difficulties	0 (44.4); 0-100	77.8 (58.28); 22.2-100	<0.001
Swallowing difficulties	8.33 (16.62); 0-58.3	33.3 (66.7); 0-100	<0.001
Social eating difficulties	0 (8.33); 0-50	16.6 (26.17); 0-100	0.002
Communication	0 (0); 0-60	0 (23.3); 0-80	0.036
Taste altered	100 (0); 100-100	0 (33.3); 0-100	<0.001

^a: Wilcoxon signed-rank test**Table 6** Severity of mucositis, VAS and oral health-related quality of life parameters changes during treatment split by percentage of weight-loss

	Weight-loss at the end of radiotherapy			
	<5% (n=12)		≥5% (n=17)	
	Z	p	Z	p
V40	-3.059d	0.002	-3.180d	0.001
V50	-3.059	0.002	-3.296d	0.001
Mucositis severity	-3.002c	0.003	-3.464c	0.001
VAS	-1.963c	0.05	-2.429c	0.015
EORTC QoL HN35 parameters				
Pain (Q1-4)	-2.448c	0.014	-2.231c	0.026
Mouth pain	-1.542c	0.123	-1.792c	0.073
Talking difficulties	-1.869c	0.062	-3.366c	0.001
Swallowing difficulties	-1.689c	0.091	-3.208c	0.001
Social eating difficulties	-1.355c	0.176	-2.746	0.006
Communication	-0.535c	0.593	-1.970c	0.049
Taste altered	-2.850d	0.004	-3.700d	0.000
Dry mouth	-1.933c	0.053	-2.028c	0.043

VAS: Visual analogue score

the pain it causes. Oral mucositis becomes worse in the later weeks of radiotherapy. In our study, we observed mucositis severity and frequency as expected in high-dose radiotherapy. The goals of this study are to reduce mucositis-induced pain, to protect against weight-loss and improve quality of life with oral gel. In the literature, there are a couple of randomized control studies to test the barrier function against mucositis. Two prospective trials found no difference in mucositis incidence comparing standard care.[11,20] In their randomized study, Barber et al.[11] found that the barrier function is not more effective than Sucralfate and Mucaïne in relieving the pain associated with radiotherapy-induced oral mucositis. However, Hadjieva et al.[13] found a positive effect of the gel on mucositis

in their randomized study. Our results showed that the coating agent itself could not decrease the frequency and severity of radiation-induced mucositis against a definitive high dose of radiotherapy (≥60 Gy).

It is difficult to assess pain as a symptom due to its subjective nature.[21] Therefore, we used a self-assessment method of VAS to measure pain in our patients. [17] Mucositis-induced pain increased week by week, and the difference between the initial period and the end of radiotherapy was significant (p<0.001). This result may reflect inadequate pain relief. We found that concurrent chemotherapy, the mucosal volume of high doses, oral mucosa volume and oral pain at the beginning of radiotherapy has no impact on VAS scores expect cumulative radiation dose (p<0.001).

There is not a single type of pain in radiotherapy for head and neck cancer patients.[21] Therefore, we asked about previous pain experience before radiotherapy and used the oral health-related QoL parameters of the EORTC HN35 questionnaire.[18] Pain (Q1-Q4), mouth pain, talking difficulties, swallowing difficulties, social eating difficulties, communication, altered taste and dry mouth all got significantly worse at the end of radiotherapy. Furthermore, more than 60% of the patients became at risk of malnutrition. What is interesting is that there was no difference according to the cumulative radiation dose (V40 and V50) of the oral mucosa or mucosal severity between patients according to nutritional status. However, the VAS score was lower in well-nourished patients (Table 6, Fig. 1). All parameters except altered taste were significantly worse in the malnutrition group. Hence, we think that the key point is to reduce mucositis-induced pain to maintain quality of life and nutritional status in head and neck radiotherapy.

In this study, we followed a multidisciplinary approach for the evaluation of mucositis-induced pain by radiation using an oncologist, dentist and dietitian. However, there are some limitations to this study. This had no control group to compare the standard of care, and a lack of long-term follow-up to observe late toxicities.

Conclusion

Severe mucositis incidence and frequency cannot be reduced in high definitive doses of radiotherapy. Mucositis-induced pain may have a direct effect on malnutrition risk and quality of life during radiotherapy. Therefore, it is crucial to find effective solutions against mucositis-induced pain concerning maintaining the nutritional status and quality of life of head neck cancer patients.

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