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Efficacy of Cryotherapy in Comparison to Standard Oral Care to Prevent Oral Mucositis during Concurrent Chemoradiotherapy in Head and Neck Cancer Patients

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Abstract

A quasi-experimental study was conducted at Radiation Oncology Department of National Institute of Cancer Research & Hospital (NICRH), Dhaka, Bangladesh, between November 2020 and October 2021, to determine the efficacy of cryotherapy in comparison to standard oral care to prevent oral mucositis in head and neck cancer patients during receiving CCRT. A total 100 Patients (50 patients in each arm) were included in this study according to inclusion and exclusion criteria by purposive sampling technique. All patients in Arm A and Arm B received total 66 Gray in 33 daily fractions, 1 fraction per day, 5 fractions per week and inj. Cisplatin 40mg/m² was given intravenously 2/3 hours before radiotherapy on 1st day and then weekly. Arm A received cryotherapy and Arm B received standard oral care. Intervention started from the 1st day of CCRT up to the end of CCRT. WHO oral mucositis grading and visual analogue scale (VAS) were employed to determine the effects. All the information was recorded in a pre-tested semi-structured questionnaire. Total 100 patients (50 patients in each arm) were enrolled. Mean age of the patients of Arm A and Arm B was 55.28±7.82 and 55.92±8.33 respectively. Male and female ratio was 6.14:1 in two Arms. Other demographic profile, baseline characteristics were statistically not significant in both arms (P>0.05). The grade-3 mucositis appeared after 5th week in Arm B and after 6th week in Arm A. The incidence of grade-3 mucositis after 5th week during CCRT to 4 weeks after completion of therapy was 6% vs 0%, 14% vs 6%, 22% vs 10%, 14% vs 6%, 8% vs 2%, respectively for arm B and Arm A. (P<0.05). Total number of patients suffering from grade 3 mucositis was 6 (12%) and 12 (24%) for Arm A and Arm B respectively (p value was <0.05). The mean duration of grade-3 or more mucositis between Arm A and Arm B was 2.04±1.78 and 10±1.72 days respectively (P<0.05). The difference of median pain intensity between two arms was not statistically significant for 1st and 2nd week (P>0.05). However, it was significant after 3rd week during CCRT to 4 weeks after completion of CCRT (P<0.05). Cryotherapy during CCRT may be beneficial to prevent oral mucositis and pain than maintaining standard oral care.

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Introduction

Head and neck cancer is one of the major public health problems which constitute approximately 10% of all cancers.[1] GLOBOCAN (2020) showed that in Bangladesh total 156775 patients were diagnosed as cancer. In terms of incidence, lip and oral cavity cancer was the 2nd most common cancer (8.9%) in both sexes, 3rd in male and 5th in female cancer in 2020.[2]

National Institute of Cancer Research & Hospital (NICRH) published Hospital Cancer Registry Report 2015-2017. There it was documented that total 14,044 newly diagnosed cancer patients attended at outpatient department of NICRH in 2017.[3] Among them total head and neck cancer patients were 1,470 (10.5% of total patients). Male patients were 914 (62.17%) and female patients were 556 (37.82%). Among HNC patients the most common site of tumor was the lip and oral cavity-802 (54.56%) followed by hypopharynx-202 (13.74%), oropharynx-188 (12.79%), nasopharynx-39 (2.65%) and larynx-17 (1.16%).[3]

The three main modalities of treatment for managing head and neck cancer are radiation therapy, surgery and chemotherapy. Combined modality therapy is generally recommended for the patients with locally advanced disease at diagnosis according to National Comprehensive Cancer Network NCCN guidelines Version 1.2021.[4] The primary treatments are radiation therapy or surgery or combination of both. Chemotherapy is usually used as an induction therapy or Concurrent chemoradiotherapy (CCRT). CCRT is the treatment of choice for locally advanced HNC. CCRT improves the loco-regional control of advanced stage disease but with increased toxicity.[5]

During the CCRT treatment of head and neck cancer patients the major side effect encountered is oral mucositis.[6] The incidence of oral mucositis is 80% to 100% in patients receiving RT to head and neck region. Its extent and severity depends on total dose, fraction size, volume irradiated, over all treatment time, fractionation regimen (e.g. hyperfractionated or accelerated scheme) and use of concurrent chemotherapy. The risk of oral mucositis is higher in accelerated schedule, smoking and alcohol consumption and concurrent use of chemotherapy. The cumulative point dose is less than 32 Gy for development of oral mucositis.[7] The impact of oral mucositis is usually devastating for patients and challenging for radiation oncologists. It causes oral pain in 69% of patients, dysphagia in 56% of patients, opioid use in 53% of patients, weight loss of 3-7 kg, feeding tube insertion and hospitalization in 15% of patients and treatment modification and interruption in 11-16% of patients.[8,9] The economic impact is also significant. The cost associated with pain management, liquid diet supplements, feeding gastrostomy tube placement, total parenteral nutrition, management of secondary infection produce an economic burden.[9] Therefore prevention and alleviation of symptoms of oral mucositis during CCRT has great role to provide an effective radiation therapy to Head and Neck Cancer patients. Many centers recommended oral rinses using salt-soda, povidone-iodine mouthwash, amifostine etc. However, an ideal method which should be used as an effective preventing agent for oral mucositis during CCRT is yet to be defined.

Cryotherapy is a newer treatment modality based on the application of low temperature usually zero

degree centigrade or less on a body part. The purpose of the treatment is to reduce inflammation, cellular metabolism, pain and cell survival by vasoconstriction. Due to vasoconstriction inflammatory mediators can't reach to that site. So onset of mucositis delays and pain intensity becomes less (Peterson *et al.* 2013).[10]

There is a huge burden of head and neck cancer (HNC) patients in Bangladesh. Our study is to compare efficacy between cryotherapy and maintaining standard oral care to prevent oral mucositis during CCRT in head and neck cancer.

Methods

This Quasi-experimental study was conducted between November 2020 and October 2021 in the Department of Radiation Oncology, National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh. Patients with histopathologically diagnosed head & neck squamous cell carcinoma and selected for concurrent chemoradiotherapy with 2-dimentional technique by LINAC machine at Radiation Oncology Department of NICRH. A total 100 cases were selected by purposive sampling method for two arms. Arm A and B. Each Arm had 50 patients.

Inclusion Criteria

1. Histopathologically proven head and neck squamous cell carcinoma.
2. Stage III and IVA patients.
3. Patients selected for definitive CCRT.
4. COVID-19 negative patients.

Exclusion Criteria

1. Patients who were suffering from oral mucositis due to other causes like previous chemotherapy, pre-existing bacterial or fungal infections
2. Patients suffering from atrophic mucosal change or dry mouth before radiotherapy.
3. Age <18 years or >70 years.
4. ECOG performance status >0 to 2.
5. Patients having severe cold allergy.
6. Carcinoma unknown primary, salivary gland tumor, paranasal sinus malignancy and nasopharyngeal carcinoma.
7. Serious uncontrolled concomitant medical illness including heart disease, diabetes mellitus, hypertension or renal disease etc.
8. Laboratory criteria for exclusion:
    a) Total WBC count >11000 cells/cubic mm with absolute neutrophil count above normal level
    b) SGPT level more than normal level
    c) Serum bilirubin level >1.5 mg/dl
    d) Serum creatinine level >1.4 mg/dl
    e) Creatinine clearance < 60 ml/min

Finally, 100 patients were enrolled for the study. At enrollment, the patients were registered as odd and even number. Every patient carrying odd number was assigned as Arm A and carrying even number were assigned as Arm B. Cryotherapy was advised to Arm A and maintaining standard oral care to Arm B. Informed written consent was taken from each patient before his/her participation in the study in Bangla. Then patient's demographic characteristics including age, sex, height, weight, occupation, socioeconomic condition, educational qualification, smoking status, nutritional status, ECOG performance status, sub sites of cancer, stage of cancer of the patient were listed and documented in questionnaire. The intervention started from the first day of starting radiotherapy up to completion of it. The follow up was conducted in each week during radiotherapy and 2 weekly after completion of radiotherapy up to 4

weeks. Appropriate data were collected by using a pretested semi structured questionnaire. Following introducing and informing the study purpose and objectives, an informed written consent was sought from the patient to take part in this study. Data were collected by face-to-face interview ensuring privacy and confidentiality of the patients. All other required data were collected from available relevant papers. Statistical analysis was done according to the study's objective by using SPSS version 25.0 for windows. A P-value less than 0.05 was considered statistically significant with 95% confidence interval for all. At every step of data collection, processing and analysis suggestions were sought from a statistician and all the procedures were rechecked. The study was approved by the Ethical review Committee of National institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh.

Results

Most of the patients belonged to age group 51-60 years. The mean age was 55.28±7.82 in arm A and 55.92±8.33 in arm B. Minimum age was 40 years in Arm A and 43 years in Arm B. Maximum age was in Arm A 68 years and in Arm B 65 years. The difference was not statistically significant (P>0.05) between two arms (Table-I). Most of the patients used tobacco formerly in any form. 40(80%) patients in Arm A and 38(76%) patients in Arm B. Only 2(4%) patients of Arm A and 4(8%) of Arm B was never tobacco user and 8 (16%) patients of each Arm had smoker in family. However, the difference was not statistically significant (P>0.05) (Table-II). Grade-1 mucositis first appeared after 4th week and grade 3 mucositis after 6th week during CCRT in Arm A whereas grade 1 mucositis developed after 3rd week and Grade-3 mucositis after 5th week during CCRT in Arm B (Fig. 1). After 5th week 3 (6%) patients developed grade-3 mucositis in Arm B and 0 (0%) patients in Arm A (P<0.05). After 6th week it was 3(6%) and 7(14%) patients for Arm A and Arm B respectively (P<0.05). After 7th week 5(10%) patients of Arm A and 11(22%) patients of Arm B experienced grade-3 mucositis (P<0.05). 2 weeks after completion of CCRT at 1st follow up grade 3 mucositis decreased. 3(6%) and 7(14%) patients for Arm A and Arm B respectively (P<0.05). After 4 weeks of CCRT only 1 (2%) patient of Arm A and 4 (8%) patients of arm B was suffering from grade 3 mucositis (P<0.05) (Table-III).

Overall response of mucositis after 4 weeks of CCRT showed that oral mucositis decreased significantly in both Arms, but more in Arm A and the difference was statistically significant (P<0.05) (Fig. 2). 6(12%) patients in Arm A and 12(24%) in Arm B developed Grade 3 oral mucositis. The mean duration of grade 3 oral mucositis in Arm A and in Arm B were 2.04±1.78 and 10±1.72 days respectively. The difference was statistically significant (P<0.05) (Table-IV). The differences of mean pain intensities in two between two arms were not statistically significant on 1st and 2nd week (P>0.05). However, it was significant from 3rd week of CCRT to 4 weeks after completion of radiotherapy (P<0.05) (Table-V).

To control pain analgesics mainly oral NSAIDs were used by all the patients in both Arms (P>0.05). But opioid analgesics were used by 25(50%) patients in Arm B and 10 (20%) patients in Arm A (P<0.05). Arm B patients had more need of oral local antifungal suspension (100%) in comparison with Arm A patients (92%) although the difference was not statistically significant (P>0.05). The occurrence of treatment

interruption in Arm B and Arm A was 10/50 and 5/50 patients respectively (P<0.05) (Table-VI).

Table-I: Age distribution of the patients (n=100)

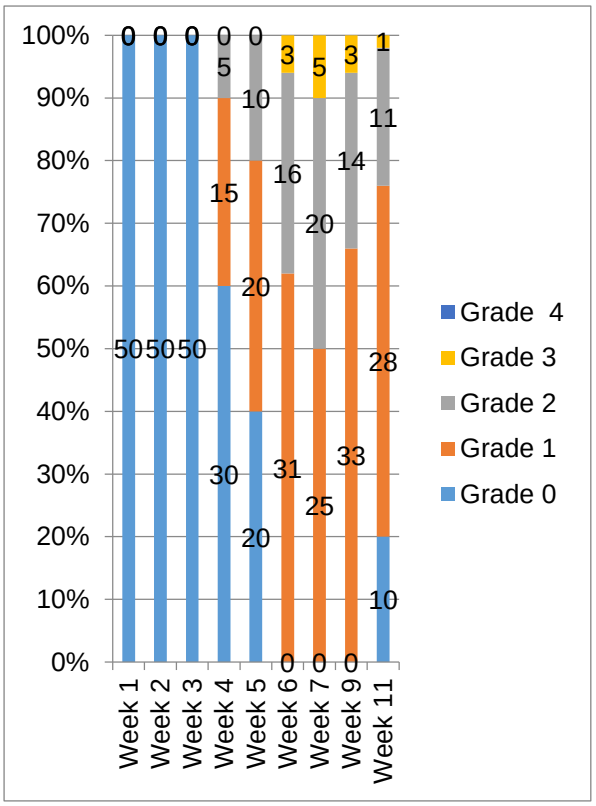
Variable Age (Years)	Arm A	Arm B	P value (Independent 'z' test)
Mean	55.28	55.92	>0.05
(±SD)	7.82	8.33	
Range	40-68	43-65	

Table II: Tobacco using status of the patients of two Arms

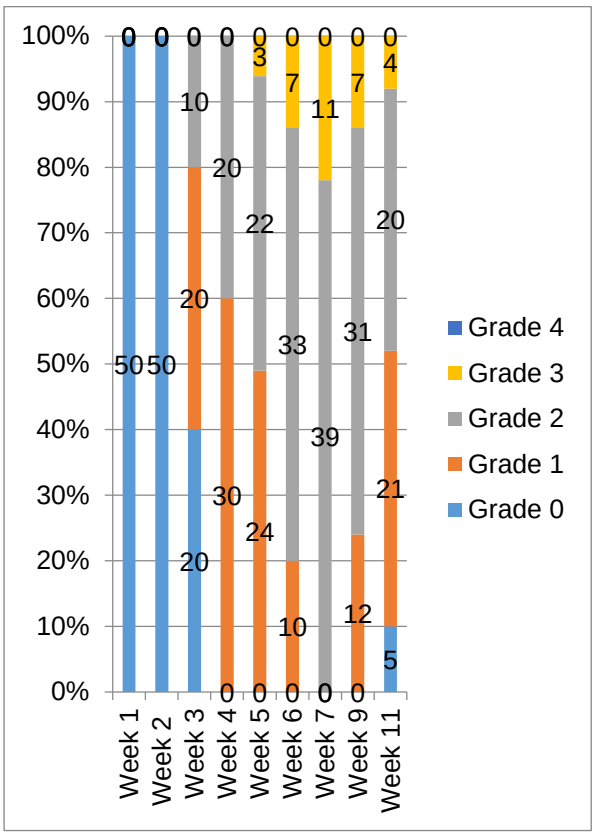
Tobacco users (smoking or smokeless}	Arm A	Arm B	*P* Value (Pearson chi – square test)
	n (%)	n (%)	
Never	2 (4%)	3 (6%)	
Former	28 (56)	26 (52)	>0.05
Smokers in family	8 (16)	8 (16)	
Current Smokeless tobacco user	0 (0) 12 (24)	0 (0) 13 (26)	

Table III: Comparison of WHO grade 3 mucositis between two Arms after 5th week during CCRT to 4 weeks after completion of radiotherapy.

Week	Arm A	Arm B	*P* value (Pearson chi – square test)
	n (%)	n (%)	
Week 5	0 (0%)	3 (6%)	<0.05
Week 6	3 (6)	7 (14)	<0.05
Week 7	5 (10)	11 (22)	<0.05
2 weeks after RT	3 (6)	7 (14)	<0.05
4 weeks after RT	1 (2)	4 (8)	<0.05



Arm A



Arm B

Fig 1: Distribution of mucositis grade in each visit of both Arms A & B.

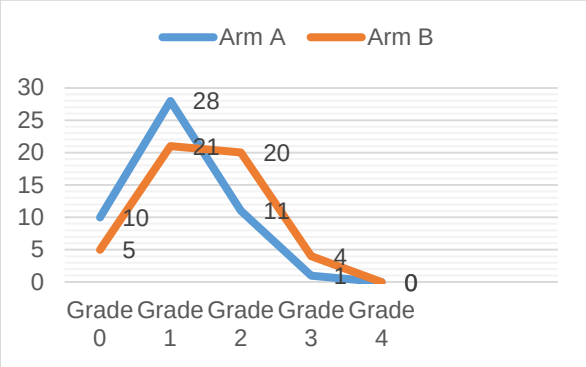


Fig 2: Overall response of mucositis after 4 weeks of CCRT

Table IV: Comparison of duration of WHO Gr-3 mucositis between 2 Arms

Duration of mucositis (in days)	Arm A	Arm B	*p* value (Independent sample z test)
Mean±SD	2.04±1.78	10±1.72	<0.05

Table V: Comparison of pain intensity between 2 groups in weekly and follow-up visits

Variables	Arm A Mean ± SD	Arm B Mean ± SD	*p* value (Independent sample z test)
Week 1	0.04± 0.19	0.84± 0.61	>0.05
Week 2	0.16± 0.46	1.84± 0.93	>0.05
Week 3	0.76± 0.65	2.68± 0.97	<0.05
Week 4	1.08± 0.63	3.48± 1.28	<0.05
Week 5	1.56± 0.86	4.28± 1.41	<0.05
Week 6	2.04± 0.96	5.08± 1.58	<0.05
Week 7	2.58± 1	5.18± 1.78	<0.05
2 weeks after radiotherapy	2.0± 0.90	5.96± 1.79	<0.05
4 weeks after radiotherapy	1.28± 0.83	5.2± 1.69	<0.05

Table VI: Comparison of secondary outcomes between two Arms

Variables	Arm A n (%)	Arm B n (%)	*P* value (Pearson chi-square test)
Use of analgesic	50 (100%)	50 (100%)	>0.05
Use of opioid analgesics	10 (20)	25 (50)	<0.05
Use of antifungal drug	46 (92)	50 (100)	>0.05
Treatment interruption	5 (10)	10 (20)	<0.05

Discussion

Mouthwash is widely used in Bangladesh for prevention and treatment of oral mucositis, the most common toxic effect of chemotherapy and radiation therapy for head and neck cancer but none proven to completely prevent it. Most of the patients in this study belonged to age group 51 to 60 years. The mean age was 55.28n±7.82 years in Arm A and 55.92±8.33 years in Arm B (P>0.05). Dhull *et al.*[11] conducted a retrospective study at regional cancer center, PGIMS, Rohtak, India from 2001 to 2012 on head and neck cancer. There they have found highest number of patients were in 51 to 60 age group (31%).

Multiple risk factors are responsible for head and neck cancers. Smoking and smokeless tobacco use are the leading causes. In this study 40 (80%) in Arm A and 39 (78%) in Arm B patients were smoker or used any form of tobacco like sada pata, gul, jarda etc. 2(4%) patients in arm A and 3 (6%) patients in arm B were never smoker. 8 (16%) patients in each arm had smoker in family. There was no current smoker patient in both arms (p value was >0.05). Dhull *et al.*[11] attributed the association of HNC with smoking and alcohol. Among all the patients 89% were smoker and 59% was alcoholic. Hospital Cancer

Registry Report (2015-2017)[3] from NICRH reported that in 2017 about 74.8% (5587) male cancer patients were ever smoker and only 1.3% (83) female patients were ever smoker. 56.5% males (n=4125) were habituated with chewing tobacco and among female this percentage was 52.5% (n=3455). In Bangladesh betel nut chewing is more common than alcohol intake among the rural people.

Clinically detectable grade-1 mucositis was found after 3rd week during CCRT in Arm B whereas that occurred after 4th week in Arm A. After 1st, 2nd, and 3rd week no patient of Arm A developed any mucositis. After 4th week 30 patients had grade 0 mucositis, 15 patients had grade 1 mucositis, and 5 patients had grade 5 mucositis in Arm A. After 5th week it was found 20 patients of grade 0 mucositis, 20 patients of grade 1 mucositis and 10 patients of grade 2 mucositis. WHO grade 3 mucositis was found in Arm A after 6th week. In Arm B after 3rd week during CCRT 20 patients had grade 0 mucositis, 20 patients had grade 1 mucositis and 10 patients had grade 2 mucositis. It increased in next week. There was no patient found of grade 0 mucositis. 30 patients of grade 1 mucositis and 20 patients of grade 2 mucositis were found. WHO grade 3 mucositis was first found at 5th week in Arm B. This difference demonstrated that cryotherapy along with maintaining standard oral care is more helpful for delaying the onset of mucositis. Naseem *et al.*[12] conducted a study at the department of radiotherapy in post graduate institute of medical education and research, Chandigarh, India to assess the effect of oral ice application in preventing oral mucositis in heads and neck cancer patients. Grade 1 mucositis was noted at 5th day in control arm whereas at 10th day in experimental arm. Grade 3 mucositis was reported only in control arm on 20th day and significantly lower incidence of mucositis was found in experimental arm. This study concluded that oral ice application is useful for delaying mucositis and severity of it. Santos *et al.*[13] conducted a study on mucositis in head and neck cancer patients undergoing radiochemotherapy. In that study, predominance of grade 1 and 2 mucositis was observed (68%) with higher incidence levels in the oropharyngeal region (51%) between the third and sixth week of treatment.

In this study, after 7th week 5 (10%) patients of Arm A and 11 (22%) patients of Arm B experienced grade-3 mucositis. 2 weeks after completion of radiotherapy at 1st follow up grade 3 mucositis decreased in both Arms. 3 (6%) and 7 (14%) patients for Arm A and Arm B respectively. 4 weeks after completion of radiotherapy only 1 (2%) patient of Arm A and 4 (8%) patients of Arm B was suffering from grade 3 mucositis. Soliman *et al.*[14] conducted a study done in Egypt and found that after 1st week of radiotherapy grade 2 mucositis in experimental group was 20% and in control group it was 46.7 % ($p<0.001$). After 2nd week the percentage was 16.7% and 50% respectively for experimental arm and control arm ($P<0.001$). Auletta *et al.*[15] found that the use of ice cubes reduces significantly chemotherapy induced oral mucositis. Wang *et al.*[16] conducted a review study and reported that oral cryotherapy significantly decreased the incidence of severe OM (RR=0.52, 95% CI=0.27 to 0.99) and OM severity (SMD= -2.07, 95% CI= -3.90 to -0.25). In addition, the duration of TPN use and the length of hospitalization were markedly reduced (SMD= -0.56, 95% CI= -0.92 to -0.19 and SMD= -0.44, 95% CI= -0.76 to -0.13 respectively).

El-Tohamy *et al.*[17] conducted a study in Egypt and found that all children of all groups under study had healthy oral cavity at the first day before starting the chemotherapeutic session. While on the 5th day from chemotherapeutic session 47.8% of them had a healthy oral cavity in flavored cryotherapy with honey and basil group compared to 65.2% of them had moderate stomatitis in chlorohexidine group. Similarly, 87% of studied children had a healthy oral cavity in flavored cryotherapy with honey and basil group 21.7% of them had sever stomatitis in chlorhexidine group at 21st day. All these studies reflect the result of this study. Total 6 (12%) patients of Arm A suffered from grade 3 mucositis and 12 (24%) patients of Arm B suffered from grade 3 mucositis (P<0.05). As all the patients of both Arms developed grade 1 or 2 mucositis so incidence was not compared.

The differences of mean pain intensities were not statistically significant between two Arms on 1st and 2nd week (P>0.05). But after 3rd week during CCRT to 28 days after completion of treatment (P<0.05). As in the first 2 weeks mucositis grading was 0 in both Arms so pain intensity was also low. However, on the subsequent weeks incidence of mucositis was increasing more in Arm B. Therefore, pain intensity was also increasing. On the other hand, in Arm A incidence of mucositis was less. Hence, pain intensity was also less. Moreover, due to cryotherapy local numbness was created. In a study done in Iran, Kakoei *et al.*[18] showed efficacy of cryotherapy to prevent oral mucositis during CCRT. After 2 weeks study increase of pain severity in the control group was statistically significant (P<0.001) but the experimental group were not (P=0.155). Assessment of patient judged mucositis grading showed a significant increase of mucositis in the control group (P=0.003) while the increase in the experimental group was not statistically significant (P=0.598). Soliman *et al.*[14] showed in their study that pain incidence at the midst day of RT was 6.7% in study group and 83.3% in control group. At the latest day of RT, it was 10% for study group and 40% for control group. They concluded that there was significant difference observed in mucositis intensity and pain incidence between the study and control group.

Conclusion

Our study results suggest that cryotherapy during CCRT in head and neck cancer patients may be beneficial in terms of onset, incidence and duration of mucositis and pain intensities than maintaining standard oral care. It may be a better option to use cryotherapy during chemoradiotherapy in head-neck cancer patients to prevent oral mucositis. However, further study involving multiple centers with a larger sample size should be carried out to determine the overall survival, long term toxicities and quality of life.

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