Int. J. Oral Maxillofac. Surg. 2019; 48: 857–864
https://doi.org/10.1016/j.ijom.2018.10.010, available online at https://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Randomised Controlled Trial
Head and Neck Oncology

Effectiveness of a comprehensive oral management protocol for the prevention of severe oral mucositis in patients receiving radiotherapy with or without chemotherapy for oral cancer: a multicentre, phase II, randomized controlled trial

Y. Kawashita[1], Y. Koyama[2], H. Kurita[2], M. Otsuru[3], Y. Ota[4], M. Okura[5], A. Horie[6], H. Sekiya[7], M. Umeda[8]

[1]Oral Management Centre, Nagasaki University Hospital, Nagasaki, Japan; [2]Department of Dentistry and Oral Surgery, Shinshu University School of Medicine, Nagano, Japan; [3]Department of Oral and Maxillofacial Surgery, Tokai University Oiso Hospital, Kanagawa, Japan; [4]Department of Oral and Maxillofacial Surgery, Division of Surgery, Tokai University School of Medicine, Kanagawa, Japan; [5]First Department of Oral and Maxillofacial Surgery, Graduate School of Dentistry, Osaka University, Osaka, Japan; [6]Department of Dental and Oral Surgery, Kanto Rosai Hospital, Japan Organization of Occupational Health and Safety, Kanagawa, Japan; [7]Department of Oral Surgery, School of Medicine, Toho University, Tokyo, Japan; [8]Department of Clinical Oral Oncology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Y. Kawashita, Y. Koyama, H. Kurita, M. Otsuru, Y. Ota, M. Okura, A. Horie, H. Sekiya, M. Umeda: Effectiveness of a comprehensive oral management protocol for the prevention of severe oral mucositis in patients receiving radiotherapy with or without chemotherapy for oral cancer: a multicentre, phase II, randomized controlled trial. Int. J. Oral Maxillofac. Surg. 2019; 48: 857–864. © 2018 Published by Elsevier Ltd on behalf of International Association of Oral and Maxillofacial Surgeons.

Abstract. The aim of this phase II, multicentre, randomized controlled trial was to evaluate the effectiveness of a comprehensive oral management protocol for the prevention of severe oral mucositis in patients with oral cancer receiving radiotherapy alone or chemoradiotherapy. In total, 124 patients with oral cancer were enrolled from five institutions. Of these, 37 patients undergoing radiotherapy were randomly divided into an intervention group ($n = 18$) and a control group ($n = 19$). The remaining 87 patients, who were undergoing chemoradiotherapy, were also randomized into an intervention group ($n = 42$) and a control group ($n = 45$). During radiotherapy, patients in the control group received only oral care, while those in the intervention group additionally received spacers to cover the entire dentition, pilocarpine hydrochloride, and topical dexamethasone ointment for oral mucositis. The primary endpoint was the incidence of severe oral mucositis.

0901-5027/070857 + 08

The intervention was significantly associated with a decreased incidence of severe oral mucositis in patients receiving radiotherapy alone ($P = 0.046$), but not in those receiving chemoradiotherapy ($P = 0.815$). These findings suggest that an oral management protocol can prevent severe oral mucositis in patients with oral cancer undergoing radiotherapy without concurrent chemotherapy.

Key words: oral cancer; oral mucositis; radiotherapy.

Accepted for publication 16 October 2018
Available online 2 January 2019

Radiotherapy for head and neck cancer almost always induces oral mucositis. The initial clinical signs of oral mucositis include mucosal erythema and superficial sloughing, which can occur with cumulative radiation doses as low as 10 Gy. At a cumulative radiation dose of 20–30 Gy, the intact mucosa begins to break down, followed by ulceration[1]. Oral mucositis is accompanied by complications such as oral discomfort, pain, poor nutrition, and consequently poor quality of life[2]. However, if radiotherapy is discontinued, head and neck cancer cannot be controlled.

Several interventions for the prevention or amelioration of oral mucositis have been studied[3]. Benzydamine, an anti-inflammatory agent, significantly reduces erythema and ulceration when used as a mouthwash; however, it has little effect in patients receiving a radiotherapy dose of $\geq$50 Gy along with chemotherapy. Prophylactic low-level laser therapy ameliorates severe mucositis and pain in patients with cancer and recipients of hematopoietic stem cell transplantation[4,5]; it has also been shown to prevent oral mucositis in patients with head and neck cancer who are receiving radiotherapy without concomitant chemotherapy[6]. However, the effects of low-level laser therapy on tumour behaviour and the tumour response to treatment remain unclear[7]. A single-blind randomized controlled clinical trial showed that the incidence of intolerable radiation-induced oral mucositis was lower in patients receiving topical honey than in those receiving lignocaine[8]. There is currently no consensus-based protocol for the prophylaxis and treatment of chemoradiotherapy-induced oral mucositis in patients with head and neck cancer[9–12].

It has been shown that oral care alone does not sufficiently lower the incidence of severe oral mucositis in patients with head and neck cancer who are receiving chemoradiotherapy, whereas a systematic and comprehensive oral care protocol may indirectly improve treatment compliance by decreasing the infection risk[13]. Although oral care is essential for radiotherapy-induced oral mucositis, it cannot prevent severe oral mucositis by itself.

At Nagasaki University Hospital, an original protocol is used to manage patients undergoing radiotherapy for head and neck cancer. The aim of this protocol is to prevent osteoradionecrosis of the jaw and facilitate the timely completion of radiotherapy by preventing severe oral mucositis. Therefore, any infected teeth are extracted before the initiation of radiotherapy. In addition, patients are made to wear spacers during radiotherapy in order to prevent scatter radiation. They also take pilocarpine hydrochloride, use a topical steroid (dexamethasone) ointment for oral mucositis, and receive professional oral care at least once a week. In consideration of the fact that xerostomia and rampant dental caries with subsequent osteonecrosis may occur after radiotherapy[14], topical fluoride treatment and routine check-ups in dental offices are recommended after the resolution of oral mucositis. In a pilot study, it was found that the use of spacers, pilocarpine hydrochloride, and topical steroid therapy in addition to professional oral care prevented severe radiation-induced oral mucositis in patients with oral or oropharyngeal cancer[15]. Accordingly, this multicentre randomized controlled trial was conducted to evaluate the effectiveness of this oral management protocol for the prevention of severe oral mucositis in patients with oral cancer receiving radiotherapy with or without chemotherapy.

Materials and methods

This open-label, phase II, randomized controlled trial was conducted in the oral surgery departments of five university hospitals: Nagasaki University, Shinshu University, Tokai University, Osaka University, and Toho University Omori Medical Centre. The study group comprised patients with oral carcinoma scheduled to undergo radiation therapy with or without chemotherapy between September 2013 and December 2016. Patients were excluded if they had previously received radiotherapy to the head and neck region. The institutional review boards at each participating hospital approved the study protocol and amendments. The study complied with the Declaration of Helsinki and was conducted in accordance with good clinical practice guidelines. All patients included in the trial provided written informed consent.

The sample size was calculated on the basis of a previous report and the pilot study. It was assumed that the incidence of grade 3 or higher oral mucositis in the control group would be 40%, and that intervention could reduce this value to 20%. A moderate sample size was determined for the screening trial of the experimental treatment against a control group[16]. Power and Sample Size Calculation software (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize; Department of Biostatistics, Vanderbilt University, Nashville, TN, USA), a two-tailed significance level of $\alpha = 0.2$, and a power of 0.8 were used to determine that at least 46 patients were needed in each group. Allowing for dropout, the recruitment target was a total of 120 patients.

At the commencement of the study, it was verified that none of the participants had oral mucositis. The patients were randomly allocated in a 1:1 ratio to a control group or an intervention group using a stratified randomization method adjusted for the treating institution and the use of radiotherapy alone or in combination with chemotherapy (block size = 2). One of the researchers supervised the randomization procedure.

Patients in the control group received professional oral care from a dental hygienist or dentist at least once a week until the end of radiotherapy. Oral care involved the removal of dental plaque using mechanical tooth cleaning methods and the gentle removal of mucosal debris with a water-drenched sponge to keep the oral cavity as clean as possible. Moreover, patients were advised to gargle with azulene and use a commercial saliva substitute four times a day, after meals and before bedtime.

Patients in the intervention group received spacers, pilocarpine hydrochloride, and a 0.1% dexamethasone ointment for oral mucositis in addition to the oral care received by the control group patients. The dexamethasone ointment was softened

with olive oil and applied over areas with redness or pseudomembrane formation four times a day, after meals and before bedtime. The spacers measured 3–5 mm in thickness and were used to prevent scatter radiation caused by metallic restorations and enamel surfaces in contact with the oral mucosa. Pilocarpine hydrochloride was administered at a dose of 5 mg three times daily from the first day of radiotherapy; it was continued at least until the end of radiotherapy. If side effects such as sweating or nausea occurred, patients were administered a dose of 2.5 mg four times daily. This low-dose treatment with pilocarpine hydrochloride has been shown to significantly decrease the sensation of oral dryness, with the amount of secreted saliva remaining unchanged[17]. Regardless of whether patients were allocated to the intervention group, those who were edentulous did not receive spacers. Furthermore, pilocarpine hydrochloride was not administered to patients with obstructive pulmonary disease, severe ischemic heart disease, stricture of the gastrointestinal tract or the bladder neck, Parkinson's disease, or iritis, as these conditions are considered contraindications to its use''. All randomized patients were included in the intention-to-treat (ITT) analysis.

The primary outcome was the incidence of severe oral mucositis classified as grade 3 or higher according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI-CTCAE v4.0)[18]. Oral mucositis was scored as follows: grade 1, asymptomatic or mild symptoms, intervention not indicated; grade 2, moderate pain not interfering with oral intake or a modified diet; grade 3, severe pain interfering with oral intake; grade 4, life-threatening consequences, urgent intervention indicated; and grade 5, death. The researchers at each of the five hospitals received lectures on these criteria prior to study initiation, and they assigned the grades on the basis of the visual features of oral mucositis, pain intensity, type of nutrition, and analgesic agent used. The highest grade observed during radiotherapy was recorded for each patient. All researchers evaluating the severity of oral mucositis were aware of the patient group.

The incidence of oral mucositis and various clinical factors were investigated prospectively. The following variables were examined: demographic factors including age, sex, and the presence of diabetes mellitus; tumour stage; radiotherapy technique and dose; neutrophil counts and albumin level; oral intake status; use of opioids; oral dryness before radiotherapy. Oral moisture levels were measured using an oral moisture-checking device (Mucus; Life Corporation, Saitama, Japan) at the lingual or buccal mucosa[19]. The oral wetness value was the median of three measurements obtained from the same site at the start of radiotherapy.

All statistical analyses were conducted using IBM SPSS software (version 22; IBM Japan, Tokyo, Japan). Quantitative variables are expressed as numbers or the mean and standard deviation, while qualitative variables are expressed as numbers and percentages. The incidence of grade 3 or higher oral mucositis was compared between subgroups using the χ^2 test or Fisher's exact test. A P-value of <0.05 was considered statistically significant. Furthermore, univariate and multivariate logistic regression analyses based on forward stepwise inclusion were performed.

This trial has been registered with the UMIN Clinical Trials Registry (UMIN 000011254).

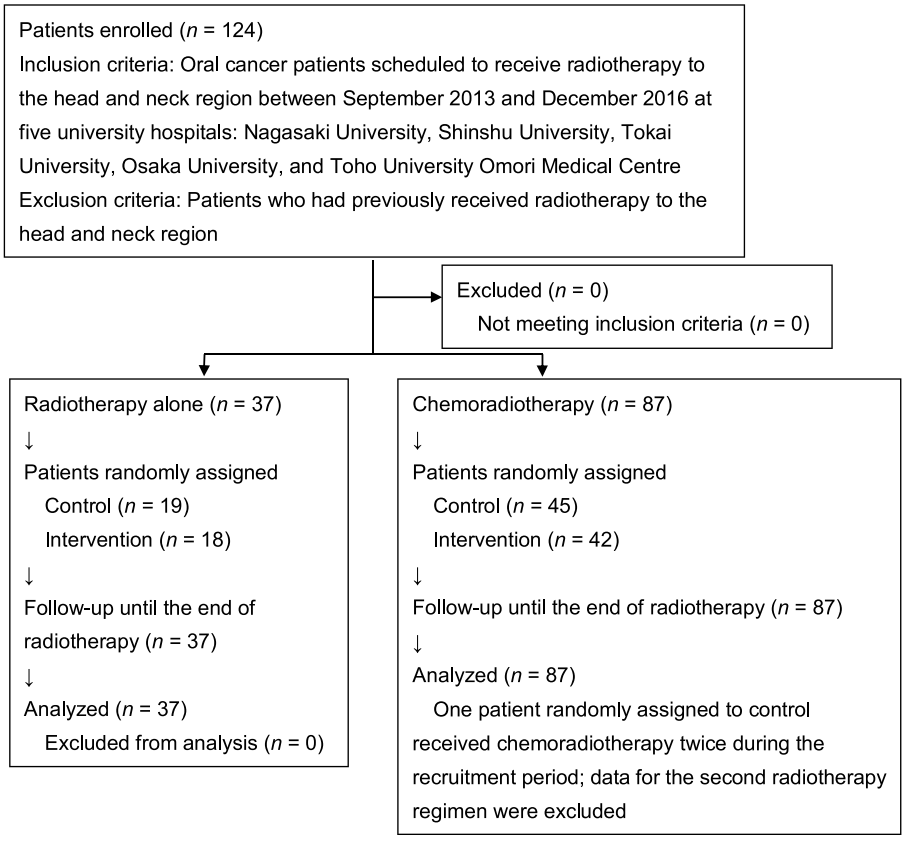

Fig. 1. Flow diagram showing the enrolment of patients with oral cancer who received radiotherapy alone or chemoradiotherapy.

Results

Figure 1 presents a flow diagram showing the patient enrolment procedure. In total, 124 patients were enrolled between September 2013 and December 2016. One patient received chemoradiotherapy twice during the recruitment period, and data for the second radiotherapy regimen were excluded. The final study group comprised 124 patients, including 37 undergoing radiotherapy alone (18 in the intervention group and 19 in the control group) and 87 receiving radiotherapy with concomitant chemotherapy (42 in the intervention group and 45 in the control group).

The patients' characteristics at baseline did not differ significantly between the two groups (Table 1). Numerous chemotherapeutic regimens were used with radiotherapy in addition to the standard cisplatin or cetuximab regimen (Table 2). In both the radiotherapy alone and chemoradiotherapy groups, the median radiotherapy dose was 63 Gy (interquartile range, 60–66 Gy).

Table 2. Chemotherapy regimens used along with radiotherapy for patients with oral cancer.

Regimen	Number
CDDP (CBDCA)	43
CDDP + S-1	2
CDDP intra-arterial injection	1
CBDCA intra-arterial injection + CET	1
CDDP intra-arterial injection → DTX	1
CET	21
CET + CBDCA + PTX	1
CET → CDDP	1
CET → S-1	1
S-1	14
S-1 + CDDP + CET	1
Total	87

CDDP, cisplatin; CBDCA, carboplatin; CET, cetuximab; DTX, docetaxel; PTX, paclitaxel; S-1, tegafur–gimeracil–oteracil potassium.

The effects of treatment exposure were assessed for each group. Grade 3 oral mucositis occurred in 35 of the 124 patients (28%); no grade 4 or grade 5 oral mucositis was observed. In the intervention group, grade 3 oral mucositis occurred in 15 patients receiving chemoradiotherapy and none of the patients receiving radiotherapy alone (Table 3). Thus, the oral management protocol prevented severe oral mucositis in patients receiving only radiotherapy ($P = 0.046$), but not in those receiving chemoradiotherapy ($P = 0.815$. The occurrence of severe oral mucositis was significantly associated with the use of opioids in patients undergoing radiotherapy ($P = 0.012$), as well as those undergo-

Table 1. Baseline characteristics of patients with oral cancer receiving radiotherapy alone or concurrent chemoradiotherapy.

Radiotherapy alone		Control	Intervention	
Factor	Category	n = 19 (%)	n = 18 (%)	*P*-value
Sex	Male	13 (52)	12 (48)	1.000 a
	Female	6 (50)	6 (50)	
Age	< 70 years	4 (33)	8 (67)	0.170 a
	≥ 70 years	15 (60)	10 (40)	
Diabetes mellitus	Present	5 (71)	2 (29)	0.405 a
	Not present	14 (47)	16 (53)	
Type of radiotherapy	Postoperative radiotherapy	17 (50)	17 (50)	1.000 a
	Definitive radiotherapy	2 (67)	1 (33)	
Stage	I and II	3 (43)	4 (57)	0.693 a
	III and IV	16 (53)	14 (47)	
Oral wetness measured using with Mucus® at the beginning of radiotherapy	Mean ± SD	27.7 ± 3.6	26.9 ± 3.9	0.534 b
Chemoradiotherapy		Control	Intervention	
Factor	Category	n = 45 (%)	n = 42 (%)	*P*-value
Sex	Male	26 (47)	29 (53)	0.276 c
	Female	19 (59)	13 (41)	
Age	< 70 years	28 (58)	20 (42)	0.171 c
	≥ 70 years	17 (44)	22 (56)	
Diabetes mellitus	Present	5 (63)	3 (37)	0.715 a
	Not present	40 (51)	39 (49)	
Type of radiotherapy	Postoperative radiotherapy	40 (53)	36 (47)	0.753 a
	Definitive radiotherapy	5 (45)	6 (55)	
Stage	I and II	9 (64)	5 (36)	0.387 a
	III and IV	36 (49)	37 (51)	
Oral wetness measured using with Mucus® at the beginning of radiotherapy	Mean ± SD	26.4 ± 6.2	27.7 ± 4.2	0.269 c

SD, standard deviation. Control group: patients who received only oral care during radiotherapy. Intervention group: patients who received spacers, took pilocarpine, and used a topical steroid in addition to receiving oral care during radiotherapy.
[a]Fisher's exact test.
[b]Student *t*-test.
[c]χ^2 test.

Table 3. Events observed during radiotherapy or chemoradiotherapy for oral cancer.

Radiotherapy alone		Control	Intervention	
Factor	Category	n = 19 (%)	n = 18 (%)	*P*-value
Oral mucositis	Grade 1, 2	14 (44)	18 (56)	0.046 a
	Grade 3	5 (100)	0 (0)	
Completion of radiotherapy	Completion	16 (48)	17 (52)	0.604 a
	Discontinuation	3 (75)	1 (25)	
Total radiotherapy dose	< 63 Gy	7 (44)	9 (56)	0.515 a
	≥ 63 Gy	12 (57)	9 (43)	
Type of nutrition	Oral ingestion	12 (44)	15 (56)	
	Combination oral ingestion and tube feeding	2 (50)	2 (50)	0.226 b
	Tube feeding or intravenous infusion	5 (83)	1 (17)	
Opioids	Yes	14 (44)	18 (56)	0.046 a
	No	5 (100)	0 (0)	
Antifungal agent	Yes	1 (20)	4 (80)	0.180 a
	No	18 (56)	14 (44)	
Minimum leukocyte count during radiotherapy (cell/μl)	Mean ± SD	4205 ± 2541	4022 ± 1811	0.812 c
Minimum albumin level during radiotherapy (g/dl)	Mean ± SD	3.3 ± 0.4	3.4 ± 0.4	0.401 c
Chemoradiotherapy		Control	Intervention	
Factor	Category	n = 45 (%)	n = 42 (%)	*P*-value
Oral mucositis	Grade 1, 2	30 (53)	27 (47)	0.815 b
	Grade 3	15 (50)	15 (50)	
Completion of radiotherapy	Completion	36 (50)	36 (50)	
	Discontinuation	4 (50)	4 (50)	0.553 b
	Stopping	5 (71)	2 (29)	
Total radiotherapy dose	< 63 Gy	21 (53)	19 (47)	0.894 b
	≥ 63 Gy	24 (51)	23 (49)	
Type of nutrition	Oral ingestion	30 (55)	25 (45)	
	Combination oral ingestion and tube feeding	12 (57)	9 (43)	0.217 b
	Tube feeding or intravenous infusion	3 (27)	8 (73)	
Opioids	Yes	7 (41)	10 (59)	0.420 a
	No	38 (54)	32 (46)	
Antifungal agent	Yes	8 (47)	9 (53)	0.789 a
	No	37 (53)	33 (47)	
Minimum leukocyte count during radiotherapy (cell/μl)	Mean ± SD	3128 ± 1577	3265 ± 1663	0.705 c
Minimum albumin level during radiotherapy (g/dl)	Mean ± SD	3.2 ± 0.5	3.2 ± 0.4	0.783 c

SD, standard deviation. Control group: patients who received only oral care during radiotherapy. Intervention group: patients who received spacers, took pilocarpine, and used a topical steroid in addition to receiving oral care during radiotherapy.
[a]Fisher's exact test.
[b]χ^2 test.
[c]Student *t*-test.

ing chemoradiotherapy ($P < 0.001$) (data not shown).

In the intervention group, the administration of pilocarpine hydrochloride did not differ between the radiotherapy alone group and the chemoradiotherapy group. Sixty-seven percent of patients were administered the standard dose and 5% of patients were not administered pilocarpine hydrochloride because of contraindicated diseases. Low-dose pilocarpine hydrochloride was administered to 28% of patients because of side effects, such as sweating or nausea (Table 4).

Univariate analysis showed that chemotherapy and the minimum serum albumin level during radiotherapy were significantly associated with the incidence of grade 3 oral mucositis (Table 5). Multivariate logistic models also showed that chemotherapy (odds ratio (OR) 5.87, 95% confidence interval (CI) 1.22–28.21) and the minimum serum albumin level during radiotherapy (OR 0.14, 95% CI 0.04–0.57) were significantly associated with the incidence of grade 3 oral mucositis.

Discussion

In this open-label, phase II trial, it was found that the use of spacers, pilocarpine hydrochloride, and topical dexamethasone ointment for oral mucositis in addition to oral care during radiotherapy significantly lowered the incidence of grade 3 oral mucositis in patients with head and neck cancer receiving radiotherapy alone, but not in those receiving chemoradiotherapy. The lack of effectiveness in patients receiving chemoradiotherapy could be attributed to the numerous chemotherapy

regimens employed during radiotherapy (Table 2) and their decreased effectiveness. In the intervention group, the administration of pilocarpine hydrochloride did not differ between the radiotherapy alone group and the chemoradiotherapy group (Table 4), and patients received spacers, except for edentulous patients. Therefore, topical dexamethasone ointment is considered to have very weak effects in patients with severe chemoradiotherapy-induced oral mucositis.

The incidence of oral mucositis varies significantly with the use of different treatment regimens[20]. While taxane- and platinum-based regimens are associated with similar incidences of grade 3 mucositis, radiotherapy for the head and neck is associated with an increased incidence of grade 3–4 oral mucositis, which often occurs in >50% of patients. The administration of a 5-fluorouracil-based regimen with radiotherapy may increase the risk of grade 3–4 oral mucositis to >30%. The Bonner trial showed that the addition of cetuximab to radiotherapy does not exacerbate oral mucositis associated with head and neck irradiation[21]. However, another study showed that the incidence of grade 3 or higher oral mucositis was significantly greater with cetuximab and radiotherapy than with cisplatin and radiotherapy for patients with locally advanced head and neck squamous cell carcinoma ($P = 0.014$)[22].

Rugo et al. reported the effects of topical steroid therapy on oral mucositis[23]. They showed that the prophylactic use of oral dexamethasone solution substantially lowered the incidence and severity of stomatitis in patients receiving everolimus and exemestane and could lead to a new standard of oral care. Moreover, topical steroid therapy is used to treat oral chronic graft-versus-host disease (cGVHD) and lichen planus[24]. Noce et al. reported that clobetasol was significantly more effective than dexamethasone in ameliorating the symptoms and clinical signs of oral lesions in patients with cGVHD[25]. Topical steroid therapy stronger than dexamethasone may be needed to

Table 4. Administration of pilocarpine hydrochloride in the intervention group.

	Radiotherapy alone	Chemoradiotherapy	
Pilocarpine hydrochloride	n = 18 (%)	n = 42 (%)	*P*-value
Standard dose	12 (67)	28 (67)	0.993 [a]
Low dose	2 (11)	4 (9)	
Discontinuation	3 (17)	8 (19)	
Withholding	1 (5)	2 (5)	

[a]χ^2 test.

Table 5. Risk factors for radiotherapy-induced severe oral mucositis determined by univariate and multivariate logistic regression analysis based on forward stepwise inclusion.

		Univariate analyses		
		Grade 1, 2	Grade 3	
Risk factor	Category	n = 89 (%)	n = 35 (%)	*P*-value
Sex	Male	60 (75)	20 (25)	0.282 [a]
	Female	29 (66)	15 (34)	
Age	< 70 years	44 (73)	16 (27)	0.709 [a]
	≥ 70years	45 (70)	19 (30)	
Diabetes mellitus	Not present	77 (71)	32 (29)	0.553 [b]
	Present	12 (80)	3 (20)	
Type of radiotherapy	Postoperative radiotherapy	82 (75)	28 (25)	0.065 [b]
	Definitive radiotherapy	7 (50)	7 (50)	
Combination of chemotherapy	Radiotherapy alone	32 (86)	5 (14)	0.018 [b]
	Chemoradiotherapy	57 (66)	30 (34)	
Treatment	Control	44 (69)	20 (39)	0.440 [a]
	Intervention	45 (75)	15 (25)	
Total radiotherapy dose	< 63 Gy	37 (66)	19 (34)	0.200 [a]
	≥ 63 Gy	52 (76)	16 (24)	
Minimum leukocyte count during radiotherapy (cell/μl)	Mean ± SD	3518 ± 1953	3314 ± 1487	0.591 [c]
Minimum albumin level during radiotherapy (g/dl)	Mean ± SD	3.3 ± 0.4	3.0 ± 0.4	<0.001 [c]
Oral wetness measured using Mucus® at the beginning of radiotherapy	Mean ± SD	27.7 ± 4.3	25.7 ± 5.8	0.055 [c]

		Multivariate logistic regression analysis		
Risk factor	Category (reference)	Odd's ratio	95.0% CI	p-value
Combination of chemotherapy	Chemoradiotherapy (Radiotherapy alone)	5.87	1.220-28.205	0.027
Minimum albumin level during radiotherapy (g/dl)		0.14	0.037-0.570	0.006

CI, confidence interval; OR, odds ratio; SD, standard deviation. Control group: patients who received only oral care during radiotherapy. Intervention group: patients who received spacers, took pilocarpine, and used a topical steroid in addition to receiving oral care during radiotherapy.

[a]χ^2 test.

[b]Fisher's exact test.

[c]Student *t*-test.

prevent severe chemoradiotherapy-induced oral mucositis.

Topical steroid therapy is frequently used to treat radiation-induced oral mucositis, although it is thought to be associated with oral candidiasis. In the present study, the use of topical steroid therapy was not significantly associated with the occurrence of oral candidiasis (Table 3). Thus, topical steroid therapy for oral mucositis may not be associated with the occurrence of oral candidiasis, which is probably dependent on the oral condition or immunocompetence of the host.

Radiotherapy-emergent adverse events include dry mouth and oral mucositis. The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) Head and Neck Cancers[26] provide principles for dental management that are necessary for the timely completion of radiotherapy. The NCCN recommends the use of silicone guards to minimize radiation backscatter in patients with metal restorations and the use of cholinergic agonists (pilocarpine, cevimeline) for salivary stimulation. In the present study, all dentate patients in the intervention group received silicone spacers, took pilocarpine, and used topical dexamethasone in addition to receiving oral care. The results showed that a combination of adequate oral moisturization, maximum oral cleanliness and hygiene, and topical dexamethasone therapy prevented severe oral mucositis caused by radiotherapy alone, but not that caused by chemoradiotherapy. This suggests that therapy with strong or very strong topical steroids may prevent severe oral mucositis caused by chemoradiotherapy.

In addition to oral management, the serum albumin level has been suggested as an important factor in the prevention of severe oral mucositis. An increased frequency of mucositis grade 3 associated with a greater reduction in serum albumin has been reported in patients receiving chemoradiotherapy for head and neck cancer[27]. In another study, Elental was a significant factor associated with the degree of oral mucositis in patients with oral squamous cell carcinoma receiving radiotherapy alone. However, there was no significant difference between the Elental group and the control group in terms of the mean change in serum albumin levels before and after radiation[28].

The present study has some limitations. First, it was an open-label, multicentre trial. Dentists from each centre managed patients and assigned the oral mucositis grades. Nevertheless, to minimize variations among dentists, a meeting was held concerning the oral mucositis grading procedure based on NCI-CTCAE v4.0 before study initiation. Second, the number of patients with the same regimen was small as a result of the use of numerous regimens. Even though the study period was prolonged, the sample size may not have been sufficient, one reason being the use of new regimens for the treatment of head and neck cancer.

This study also has strengths. First, it was a randomized clinical trial analyzing the grade of oral mucositis in patients undergoing radiotherapy alone and those undergoing chemoradiotherapy. Potential bias was minimized by the randomized controlled trial design and the analysis of multiple datasets for oral mucositis.

In conclusion, the findings of this study suggest that a comprehensive oral management protocol involving the use of spacers, pilocarpine, and a topical steroid ointment in addition to oral care can prevent severe oral mucositis in patients with oral cancer undergoing radiotherapy alone, but not in those undergoing concurrent chemoradiotherapy. Therapy with strong or very strong topical steroids and nutritional control might prevent severe oral mucositis caused by chemoradiotherapy.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Competing interests

The authors declare that they have no conflicts of interest.

Ethical approval

Reference number: 13072241.

Patient consent

Not required.

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Address:
Yumiko Kawashita
Oral Management Centre
Nagasaki University Hospital
1-7-1 Sakamoto
Nagasaki 852-8102
Japan
Tel.: +81 95 819 7663
Fax: +81 95 819 7665
E-mail: yumiko-t@nagasaki-u.ac.jp