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ORIGINAL ARTICLE

Factors associated with severe oral mucositis and candidiasis in patients undergoing radiotherapy for oral and oropharyngeal carcinomas: a retrospective multicenter study of 326 patients

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Abstract

Purpose The present retrospective multicenter study intended to investigate the factors associated with severe oral mucositis and candidiasis in patients undergoing radiotherapy for oral and oropharyngeal carcinomas.

Methods A total of 326 patients who underwent radiotherapy for oral and oropharyngeal cancers were enrolled in the study. The patients' age, sex, body mass index, primary site, diabetes, serum albumin, creatinine, hemoglobin, leukocyte and lymphocyte, concurrent cisplatin or cetuximab, method of radiation, total radiation dose, feeding route, use of spacers, pilocarpine hydrochloride, and corticosteroid ointment were examined, and the associations of each variable with oral mucositis and candidiasis were analyzed by multivariate Cox regression analysis.

Results Grade 3 oral mucositis occurred in 136 (41.7%) patients. Male sex, oropharyngeal cancer, low hemoglobin levels, low leukocytes or lymphocytes, concurrent cisplatin or cetuximab, and oral feeding were found to be significantly associated with a higher incidence of severe oral mucositis. Oral candidiasis occurred in 101 (31.0%) patients. Oropharyngeal cancer, low leukocyte count, and oral mucositis of grade 2 or higher were found to be significantly associated with a higher incidence of oral candidiasis. The use of a topical steroid ointment was not found to be a risk factor for oral candidiasis.

Conclusions The present retrospective study demonstrated that certain factors may predispose patients with oral and oropharyngeal cancers receiving radiotherapy to develop severe oral mucositis and oral candidiasis. A preventive strategy for severe oral mucositis needs to be established in the future for high-risk cases.

Keywords Oral mucositis · Oral candidiasis · Radiotherapy · Head and neck cancer · Risk factors

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Introduction

Patients with oral and oropharyngeal cancers frequently receive radiotherapy (RT) treatments, with various adverse effects including, oral mucositis, xerostomia, taste disturbances, oral candidiasis, and osteoradionecrosis of the jaw. Oral mucositis, in particular, causes difficulties in feeding by mouth owing to severe pain, which decreases patients' quality of life (QoL). Oral mucositis also hinders the continuation of RT. Despite the difficulties caused by oral mucositis during RT, preventive strategies and treatment measures have not been established [1–4]. The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) clinical practice guidelines provide recommendations on the management of oral mucositis resulting from RT for head and neck cancer. The guidelines recommend the use of mouthwashes containing benzydamine,

2% morphine, or 0.5% doxepin; the use of low-level laser therapy and systemic zinc supplements has also been advocated [5]. However, evidence on the efficacy of these treatments is not strong. In Japan, these treatments are not commonly employed as they are not covered by public health insurance.

Oral mucositis is caused by the direct cytotoxic effect of radiation [6]. The presence of infective pathogenic microorganisms in the oral cavity increases the severity of mucositis. The prevention of severe stomatitis, therefore, requires a reduction in the bacterial load in the oral cavity, which may be achieved with the use of disinfectant mouthwashes, such as povidone iodine or chlorhexidine. In addition, application of a steroid ointment after the development of oral stomatitis has a clinically evident anti-inflammatory effect. However, the topical administration of a steroid ointment for oral mucositis during RT is not encouraged owing to concerns regarding the development of oral candidiasis.

This retrospective, multicenter, observational study intended to investigate the factors related to severe oral mucositis. The present study also investigated whether the administration of topical steroids had any impact on the development of oral candidiasis in patients who underwent RT, with or without chemotherapy.

Patients and methods

Patients

The study cohort comprised of 326 patients with oral and oropharyngeal cancer, who underwent RT of more than 50 Gy at the Kobe University Hospital, Nagasaki University Hospital, and Kansai Medical University Hospital, between 2011 and 2017. All patients underwent dental evaluation including panoramic radiographs, and infected teeth were extracted prior to initiation of RT. In addition, during RT, all patients received standard oral care under the supervision of dentists and dental hygienists.

Variables

The data on the factors investigated were retrieved from the medical records and the panoramic radiographs. The selected variables included age, sex, body mass index (BMI), primary site (oral cavity or oropharynx), presence of diabetes, levels of serum albumin, serum creatinine, and hemoglobin, and total leukocyte and lymphocyte counts. Treatment modality was also assessed, which included RT alone, concurrent cisplatin (CDDP) (CRT), and concurrent cetuximab (BRT). The types of radiotherapy treatment, including the three-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT), were also investigated. Additionally, the total radiation dose, feeding route at initiation of RT (oral feeding or tube feeding through gastric fistula), use of spacers, and administration of pilocarpine hydrochloride (Salagen®, Kissei Pharmaceutical, Co., Ltd., Nagano, Japan) and corticosteroid ointment (Dexaltin Oral Ointment®, Nihon Kayaku, Co., Ltd., Tokyo, Japan) were individually recorded. Panoramic radiograph findings including the number of teeth, number of metal restored teeth, and alveolar bone loss of the residual teeth ($< 1/2$ or $\geq 1/2$) were recorded. Parameters of periodontal disease also include pocket depth and hemorrhage during probing; only alveolar bone loss by panoramic X-ray was examined for retrospective investigation. The incidence of oral stomatitis and oral candidiasis were noted individually. Oral stomatitis was categorized according to the Common Terminology Criteria for Adverse Events (CTCAE) criteria v 5.0 [7]. According to these criteria, grade 3 oral stomatitis is defined as the inability to feed orally or the presence of severe pain due to severe stomatitis. For the purposes of the study, pain necessitating systemic administration of opioids was considered to be severe. Oral mucositis and oral candidiasis were observed for up to 90 days from the initiation of RT.

Oral care

Oral care by dentist and dental hygienist was started from the time the decision for RT was made and performed once or twice a week. It concluded extraction of teeth with severe periodontal disease or periapical lesion at least 1 week before RT, oral health instruction, removal of dental calculus (scaling), professional mechanical tooth cleaning (PMTC), removal of tongue coating with a toothbrush, and cleaning denture. In some cases, spacer to minimize radiation backscatter when patients had metal restorations, administration of pilocarpine to treat dry mouth, and use of mouthwash containing local anesthetic were performed by cancer treatment doctors.

Statistical analysis

All statistical analyses were performed by using SPSS software (version 24.0; Japan IBM Co., Tokyo, Japan). Grade 2 mucositis promotes important clinical repercussions, but it occurred in most patients and it is difficult to prevent grade 2 mucositis. Therefore, the outcome of this study was set to prevent grade 3 mucositis. Correlation between each variable and grade 3 oral mucositis was analyzed by univariate and multivariate Cox regression. Kaplan-Meier curves were analyzed for the categorical data that significantly correlated with oral mucositis. The variables related to the development of oral candidiasis were also analyzed by univariate and multivariate Cox regression; Kaplan-Meier curves were analyzed for selected categorical data. During multivariate analysis, all variables were input into the Cox regression model using stepwise selection. In all analyses, two-tailed p values < 0.05 were considered statistically significant.

Results

Demographic factors of the patients

The patient characteristics of the cohort are shown in Table 1. The cohort had 326 patients comprising 247 males and 79 females, with a median age of 65 years. A total of 182 and 144 patients had oral and oropharyngeal cancers, respectively. RT alone, CRT, and BRT had been delivered to 95, 200, and 31 patients, respectively. Overall, 240 and 86 patients underwent 3D-CRT and IMRT, respectively. Radiation therapy was performed with a standard fractionation of 2 Gy/day. The median dose of RT was 66 Gy, with doses in the range of 60 to 70 Gy between the 25th and 75th percentile. Spacers were used in some patients, while others received pilocarpine hydrochloride from the start of RT. These were administered at the physician's discretion. Topical steroid ointments were also prescribed at the physician's discretion; there was a tendency to administer them when oral mucositis became more severe.

Factors related to development of grade 3 oral mucositis during RT

Oral mucositis occurred in 323 (99.1%) of 326 patients. The mucositis was of grades 1, 2, and 3 in 19 (5.8%), 168 (51.5%), and 136 (41.7%) patients, respectively.

Seven variables were found to be independent factors significantly correlated with the development of grade 3 severe oral mucositis (Table 2). Males developed severe oral mucositis more frequently. Stomatitis was more severe in patients who received RT for oropharyngeal cancer than those receiving RT for oral cancer. Patients with lower leukocyte or

Table 1 Demographic factors of the 326 patients

Variable		Number of patients or median (25–75% tile)
Age		65 (59–73)
Gender	Male	247
	Female	79
Body mass index (BMI)		20.6 (18.5–23.0)
Primary site	Oral cavity	182
	Oropharynx	144
Diabetes	(−)	271
	(+)	55
Albumin (g/dL)		3.6(3.3–3.9)
Creatinine (mg/dL)		0.75(0.64–0.91)
Hemoglobin (mg/dL)		11.7 (10.6–12.7)
Leukocyte (/μL)		2800 (2100–3800)
Lymphocyte (/μL)		320 (200–484)
Combination chemotherapy	RT alone	95
	CRT	200
	BRT	31
Radiation method	3D-CRT	240
	IMRT	86
Total dose (Gy)		66 (60–70)
Feeding method	Oral feeding	295
	Tube feeding	31
Spacer	(−)	242
	(+)	84
Pilocarpine hydrochloride	(−)	284
	(+)	42
Corticosteroid ointment	(−)	212
	(+)	114
Number of teeth		18.5 (7–24)
Number of metal teeth		5.0(1–9.25)
Alveolar bone loss	< 1/2	262
	≥ 1/2	64

Table 2 Variable related to severe oral mucositis (multivariate analysis)

Variable		*p* value	HR	95% CI
Age		0.257		
Gender	Male vs. female	*0.009	1.886	1.168–3.043
Body mass index (BMI)		0.572		
Primary site	Oropharynx vs. oral cavity	*0.005	1.600	1.107–2.314
Diabetes	(+) vs. (−)	0.629		
Albumin (g/dL)		0.853		
Creatinine (mg/dL)		0.131		
Hemoglobin (mg/dL)		*0.005	0.881	0.805–0.963
Leukocyte (/μL)		*0.020	1.000	1.000–1.000
Lymphocyte (/μL)		*0.004	0.999	0.998–1.000
Combination chemotherapy	BRT vs. CRT vs. RT alone	*< 0.001	1.965	1.470–2.627
Radiation method	IMRT vs. 3D-CRT	0.191		
Total dose (Gy)		0.394		
Feeding method	Tube feeding vs. oral feeding	*0.003	0.282	0.123–0.649
Spacer	(+) vs. (−)	0.436		
Pilocarpine hydrochloride	(+) vs. (−)	0.308		
Corticosteroid ointment	(+) vs. (−)	0.403		
Number of teeth		0.126		
Number of metal teeth		0.745		
Alveolar bone loss	≥ 1/2 vs. < 1/2	0.223		

Cox regression (stepwise selection)

*$p < 0.05$

lymphocyte counts and those with lower hemoglobin levels demonstrated a significantly higher incidence of severe mucositis. RT alone carried the lowest risk of severe stomatitis; CRT was associated with high risk, while BRT had the highest risk (Fig. 1). Patients receiving tube feeding had a significantly lower risk of grade 3 stomatitis.

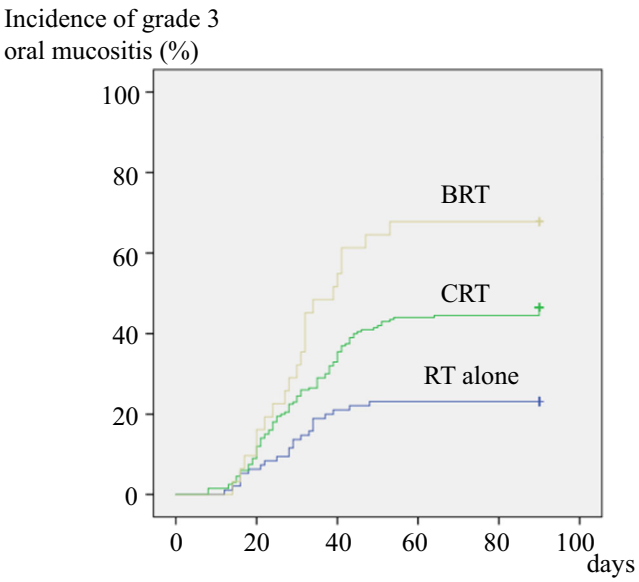

Fig. 1 Relationship between concurrent chemotherapy and incidence of grade 3 oral mucositis

Factors related to development of oral candidiasis during RT

Oral candidiasis developed in 101 of 326 (31.0%) patients. Three variables were found to be significantly correlated with the development of oral candidiasis (Table 3). Patients with oropharyngeal cancers developed oral candidiasis more frequently than those with oral cancer. Lower leukocyte count was significantly associated with a higher risk for the development of oral candidiasis (Fig. 2). Patients with oral mucositis of grade 2 or higher exhibited a higher incidence of oral candidiasis than those with grades 0–1 mucositis. The use of a topical steroid ointment, however, was not a risk factor for developing oral candidiasis (Fig. 3).

Discussion

RT is a standard treatment modality in head and neck cancer. It is employed either as an initial treatment or in the postoperative setting, with or without CDDP. In recent years, RT has also been used in combination with cetuximab for locally advanced cases. However, there are few known effective measures to prevent the adverse effects of RT, which include oral mucositis, xerostomia, taste disturbances, or osteoradionecrosis.

Table 3 Variable related to development or oral candidiasis (multivariate analysis)

Variable		*p* value	HR	95% CI
Age		0.150		
Gender	Male vs. female	0.664		
Body mass index (BMI)		0.829		
Primary site	Oropharynx vs. oral cavity	*0.005	1.781	1.195–2.654
Diabetes	(+) vs. (−)	0.885		
Albumin (g/dL)		0.567		
Creatinine (mg/dL)		0.781		
Hemoglobin (mg/dL)		0.508		
Leukocyte (/μL)		*0.041	1.000	1.000–1.000
Lymphocyte (/μL)		0.339		
Combination chemotherapy	BRT vs. CRT vs. RT alone	0.418		
Radiation method	IMRT vs. 3D-CRT	0.489		
Total dose (Gy)		0.774		
Neck dissection	(+) vs. (−)	0.874		
Feeding method	Oral feeding vs. tube feeding	0.110		
Spacer	(+) vs. (−)	0.460		
Pilocarpine hydrochloride	(+) vs. (−)	0.224		
Corticosteroid ointment	(+) vs. (−)	0.384		
Number of teeth		0.752		
Number of metal teeth		0.457		
Alveolar bone loss	≥ 1/2 vs. < 1/2	0.829		
Oral mucositis	Grade 0–1 vs. grade 2–3	*0.045	7.517	1.047–53.975

Cox regression (stepwise selection)

*$p < 0.05$

In 2016, Moslemi et al. [1] published a review of the literature on the management of chemo/radiation-induced oral mucositis in patients with head and neck cancer. However, no suggestions were made regarding the effective preventive measures for severe oral mucositis. The MASCC/ISOO guidelines provide recommendations for the management of oral mucositis

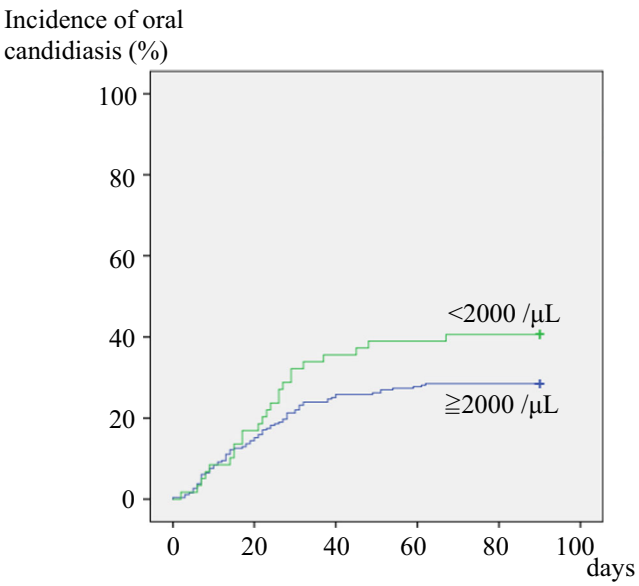

Fig. 2 Relationship between leucocyte count and incidence of oral candidiasis

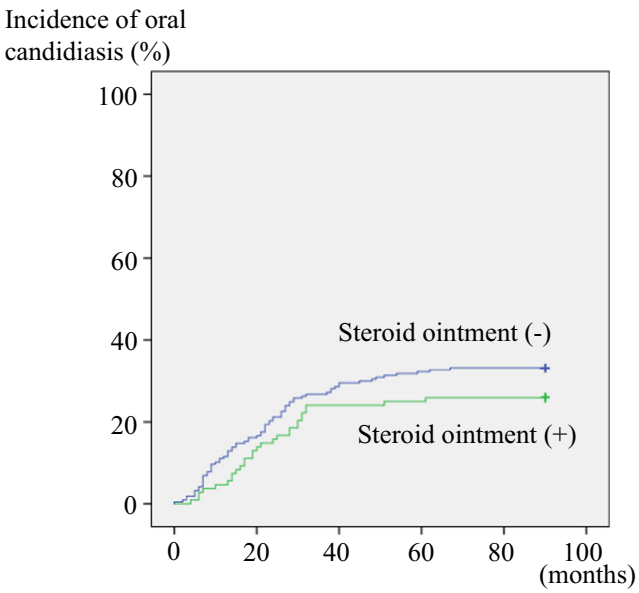

Fig. 3 Relationship between use of steroid ointment and incidence of oral candidiasis

resulting from RT for head and neck cancer [1]. In Japan, however, these recommendations are not accepted, owing to low levels of evidence. In addition, some of the recommended preventive medicines are not approved in Japan. The National Comprehensive Cancer Network (NCCN) guidelines [6], which are widely followed by oncologists globally, have enumerated the principles of dental evaluation and management in patients with head and neck cancer who undergo RT. The recommendations are intended to prevent osteoradionecrosis, xerostomia, corticosteroid ointment-related trismus, and radiation-induced dental caries. However, no recommendations have been made regarding the prevention and treatment of oral stomatitis during RT. Kawashita et al. [8] recommended a prophylactic routine for radiation-induced adverse events in patients with oral and oropharyngeal cancers. The routine consisted of extraction of infected teeth prior to initiation of RT, use of spacers to minimize radiation backscatter in patients with metallic dental restorations, oral care, administration of pilocarpine hydrochloride, topical administration of corticosteroid ointments, skin management, and topical application of fluoride. The efficacy of these procedures in preventing severe oral mucositis was also demonstrated in a phase II study. Furthermore, they conducted a multicenter, randomized clinical trial to investigate the impact of topical steroid administration, spacers, and pilocarpine hydrochloride on the prevention of severe oral mucositis. They reported that patients in the intervention group showed a significantly lower incidence of grade 3 oral mucositis when they received RT alone. However, in those undergoing CRT, the chemotherapy regimen varied, and the efficacy of the routine was not demonstrated [9]. As described above, there is no established management for oral mucositis occurring during RT.

A few published reports have studied the prevention of severe oral mucositis during head and neck RT; the associated risk factors have also been investigated. In the current study, oral stomatitis was found to be more severe in males, patients with oropharyngeal cancer, those with lower levels of hemoglobin, low leukocyte and lymphocyte counts, and in those who received RT at higher doses in combination with CDDP or cetuximab. These findings suggest the need for investigating effective preventive measures in this group of patients.

Topically administered corticosteroids have been widely used for the treatment of oral mucositis resulting from various causes. Rugo et al. have recently reported that the prophylactic use of dexamethasone oral solutions substantially reduced the incidence and severity of stomatitis in patients receiving everolimus and exemestane in their study, and that this could be a new standard of oral care in these patients [10]. However, steroid ointments are not generally administered for oral stomatitis during head and neck RT, probably owing to concerns regarding steroid-induced oral candidiasis. Oral candidiasis is an opportunistic infection, developing due to a decline in systemic and local immunity. In theory, the long-term administration of topical steroids may promote candidiasis. However, there is no clinical evidence on the impact of topical steroids on candidiasis during head and neck RT. In the present study, decreased leukocyte counts and oral mucositis of grade 2 or higher significantly increased the risk of developing oral candidiasis. Stomatitis of grade 2 creates an epithelial defect, lowering the defense of the local barrier, while leukopenia leads to a decline in systemic immunity. In the present study, the use of a steroid ointment did not increase the risk of developing oral candidiasis. Since the topical administration of steroid ointments prevent oral mucositis, it is probable that it also reduces the incidence of oral candidiasis during head and neck RT. However, no conclusions may be drawn from the results of the current study, owing to the likelihood of bias associated with retrospective research.

The scope of the present study is limited, as it is a retrospective investigation, and generalization of the results may therefore be inaccurate. However, to the best of our knowledge, this is the first report investigating risk factors for severe oral mucositis and oral candidiasis in a large number of patients with cancers of the oral cavity or oropharynx, who underwent RT. Furthermore, a prospective trial has been planned to investigate the impact of topical steroid ointments on the prevention of severe oral stomatitis and oral candidiasis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval and informed consent This study was performed in accordance with the 1964 Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Boards (IRB) of Kobe University Hospital (No. 180250), Nagasaki University Hospital (No. 18091008), and Kansai University Hospital (2018164). As this was a retrospective study, the research plan was published on the homepage of the participating hospitals according to the instructions of the IRB in accordance with the guaranteed opt-out opportunity.

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