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ORIGINAL RESEARCH–HEAD AND NECK SURGERY

Oral candidiasis in patients receiving radiation therapy for head and neck cancer

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ABSTRACT

OBJECTIVE: To investigate oral candidiasis in patients with head and neck cancer before, during, and after radiation therapy, and to explore its association with clinical oropharyngeal symptoms.
STUDY DESIGN: A cohort study.
SETTING: University hospital.
SUBJECTS AND METHODS: Subjects who received radiation therapy (RT) for the treatment of head and neck cancer were divided into two groups: an oral cavity irradiated group (OIRR group, n = 29) and an oral cavity nonirradiated group (ONIRR group, n = 17). A control group consisted of 18 healthy subjects. Patients were examined for signs of oral candidiasis before, during, immediately after, and one month after RT. Mouth and throat soreness (MTS), dysphagia, and xerostomia were evaluated by self-reported questionnaires, and associations between oral candidiasis and these symptoms were analyzed.
RESULTS: The incidence of oral candidiasis during RT was significantly higher in the OIRR group (55.2%) than in the ONIRR group (11.8%). Similarly, the occurrence of xerostomia during RT was significantly higher in the OIRR group (86.2%) than in the ONIRR group (52.9%). In the OIRR group, the mean MTS score at the 20th fraction of RT was significantly higher in patients with candidiasis (mean ± SD, 5.8 ± 2.1) than in those with RT-induced mucositis without candidiasis (3.7 ± 2.0). In the OIRR group, 65.2 percent of patients who experienced dysphagia developed oral candidiasis, compared with only 10 percent in the ONIRR group.
CONCLUSION: Oral candidiasis concurrent with oral mucositis due to RT may increase oropharyngeal discomfort during RT.

Radiation therapy (RT) is an important treatment for malignant tumors of the head and neck. However, RT to these regions can result in acute and chronic complications arising from tissue toxicity, change in vascular supply, fibrosis in connective tissue and muscle, and change in the cellularity of tissues.[1] Oral candidiasis is observed as an adverse effect in irradiated patients, and the rate of oral candidiasis in patients with head and neck carcinoma who receive RT is estimated to range widely, from 27 to 77 percent.[2-4] *Candida* colonization, the quantitative count of fungi, and oral symptoms related to *Candida* infection usually increase during RT in such patients.[5,6] Reduced salivary secretion due to RT is thought to be a major predisposing factor leading to *Candida* infection[7] since, in healthy subjects, human saliva helps to regulate the oral environment by moisturizing, lubricating, buffering, and performing various antimicrobial activities.[8]

The field for RT depends on the location and stage of the primary tumor. The oral cavity is usually irradiated in patients with pharyngeal carcinoma, maxillary sinus carcinoma, or oral cavity carcinoma, but the oral cavity is outside the field in the treatment of other head and neck malignancies, such as early laryngeal carcinoma.[9] Patients who receive RT to the oral cavity commonly complain of upper aerodigestive tract symptoms, including sore throat or dysphagia. Previous studies have suggested that such symptoms are related to RT-induced oral mucositis. Severe oral mucositis may necessitate breaks in RT or placement of a gastric tube for nutrition, and may also result in weight loss.[10-12] Patients with RT-induced oral mucositis sometimes present with concomitant oral candidiasis. The aim of the present study was to determine whether oral candidiasis is associated with the symptoms of RT-induced oral mucositis, such as sore throat, xerostomia, and dysphagia, and whether it increases patient discomfort.

Subjects and Methods

Between 2008 and 2009, 46 patients who received external-beam radiotherapy for the treatment of head and neck cancer were enrolled in this prospective study, and were divided into an oral cavity irradiated (OIRR) group and an oral cavity nonirradiated (ONIRR) group (i.e., irradiated outside the field of the oral cavity). Exclusion criteria for this study were total radiation dosage of 40 Gy or lower, the presence of oral mucositis or candidiasis before RT, a history of an immuno-

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logical-deficiency disease, and lack of cooperation in the study. In addition, 18 healthy subjects without oral symptoms (10 men, 8 women; mean age 55.2 years; range 20-82 years) participated in the study as a control group. The study protocol was approved in advance by the Human Institutional Review Board of University of the Ryukyus. After the participants were provided with a full explanation of the study protocol, they provided written informed consent, according to the guidelines of the Ethics Committee of the Faculty of Medicine, University of the Ryukyus. This study conformed to the principles of the Declaration of Helsinki.

Patients were examined for oral candidiasis at the following treatment stages: before RT (stage 1, baseline), at the 10th fraction of RT (stage 2, approximately 20 Gy total dose), at the 20th fraction of RT (stage 3, approximately 40 Gy total dose), immediately after RT (stage 4), and one month after RT (stage 5). *Candida* infection was defined as the presence of white plaques in the oral cavity due to *Candida* species as confirmed by 10 percent potassium hydroxide preparation and/or positive culture.[2] Cultures for fungi were obtained by firmly rubbing a sterile, nontoxic, cotton swab on all oral mucosal sites.[5] A specimen from each patient was inoculated in CHROMagar Candida (CHROMagar B.D., Franklin Lakes, NJ) and Sabouraud dextrose agar with 50 mg/mL chloramphenicol, and incubated at 37°C for up to one week for isolation and presumptive identification of *Candida* species. Fungal growth was quantified by counting colony-forming units (CFUs) on the primary plate. A CFU count under 500 was defined as light growth, and a CFU count of more than 500 as heavy growth.[13] The isolates were identified through the germinative tube test or carbohydrate assimilations (VITEK 2 Compact; bioMérieux, Marcy l'Etoile, France).

Associations between oral candidiasis and the clinical oropharyngeal symptoms of mouth and throat soreness (MTS), dysphagia, and xerostomia were investigated with self-reported questionnaires completed at each treatment stage. MTS was expressed by using a visual analog scale from 0 to 10, with 10 reflecting the worst discomfort possible. The patients answered questions about whether dysphagia and xerostomia were "present" or "absent." Additionally, the grade of dysphagia was assessed with the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. Briefly, grade 0 indicates no symptoms; grade 1, mild dysphagia, but the ability to eat regular food; grade 2, dysphagia requiring predominantly a pureed, soft, or liquid diet; grade 3, dysphagia requiring a feeding tube, intravenous hydration, or hyperalimentation; and grade 4, complete obstruction.

The grade of mucositis was also classified from 0 to 4 on the basis of the NCI-CTC. Briefly, grade 0 indicates no effects on mucosa; grade 1, erythema of mucosa; grade 2, patchy pseudomembranous reaction; grade 3, a confluent pseudomembranous reaction; and grade 4, necrosis or deep ulceration.

None of the participants in the present study were treated with antifungal drugs, regardless of detection of *Candida* species. Every patient with MTS received a mix of polaprezinc and alginate sodium for protection of oral mucosa.

A two-tailed Pearson's χ^2 test or Fisher's exact test was carried out to determine differences between the incidence of oral candidiasis in the OIRR group and ONIRR group, the association between oral mucositis and dysphagia, and the association between oral candidiasis and dysphagia. The percentage of patients with a CFU count over 500 at each stage was statistically evaluated by a one-tailed exact Wilcoxon rank sum test. Relative risks (RRs) with 95 percent confidence intervals (CIs) and two-tailed P values were calculated. An unpaired Student t test was used to determine differences in the incidence of MTS between patients with mucositis concomitant with candidiasis and patients with mucositis but no candidiasis. All analyses were performed with the SPSS statistical package (SPSS for Windows version 12.0; SPSS Inc., Chicago, IL). Statistical significance was established at the $P < 0.05$ level.

Results

Patients' Characteristics

The clinical features of both groups are summarized in Table 1. The OIRR group consisted of 28 men and one woman (mean age 63.9 years; range 41-78 years) who received entire or partial oral cavity irradiation. The primary sites were the oropharynx (n = 9), hypopharynx (n = 9), nasopharynx (n = 4), oral cavity (n = 4), maxillary sinus (n = 2), and larynx (n = 1). All patients in this group received RT once daily for five days per week in fractions of 1.8 to 2 Gy, for a mean cumulative dose of 70.0 Gy (range 45-76 Gy). Three patients with hypopharyngeal cancer and one with oral cavity cancer were irradiated postoperatively at doses ranging from 45 to 54 Gy. The ONIRR group consisted of 16 men and one woman (mean age 64.5 years; range 30-85 years) whose oral cavities were outside the radiation field. The primary sites were the larynx (n = 16) and external canal (n = 1). The patients received the same regimen of RT as the OIRR group, with a mean cumulative dose of 66.0 Gy (range 50-70 Gy). All subjects were primarily treated with radiation, except for one with cancer of the external ear canal. Concomitant chemotherapy consisting of nedaplatin and 5-fluorouracil was administered to 23 of 29 patients (79.3%) in the OIRR group and 11 of 17 patients (64.7%) in the ONIRR group. Demographic and clinical features including gender, age, radiation dosage, and concomitant chemotherapy did not differ between the two groups ($P = 1.000$, $P = 0.872$, $P = 0.940$, and $P = 0.314$, respectively, χ^2 test).

Candida Colonization

Candida colonization was observed before RT (stage 1) in 14 of 29 patients (48.3%) in the OIRR group and 11 of 17 patients (64.7%) in the ONIRR group, indicating no significant difference between the groups. In addition, the incidence of *Candida* colonization did not differ significantly

Table 1
Clinical features of patients in the OIRR and ONIRR groups

Clinical feature	OIRR	ONIRR	*P* value
Gender (n)			
Male	28	16	1.000
Female	1	1	
Age (yrs)			
Mean	63.9 ± 10.7	64.5 ± 14.7	0.872
Range	41-78	30-85	
Dose of radiation (Gy)			
Median	70.0	66.0	0.940
Range	45-76	50-70	
Concomitant chemotherapy	23	11	0.314
Diabetes mellitus (n)	5	3	1.000
Denture wearer (n)	11	8	0.544
Tumor type (n)			
Nasopharyngeal SCC	4		
Oropharyngeal SCC	9		
Hypopharyngeal SCC	9		
Oral cavity SCC	4		
Maxillary sinus SCC	2		
Laryngeal SCC	1	16	
External ear canal SCC		1	
T stages (n)			
T1	5	3	
T2	14	11	
T3	6	2	
T4	4	1	
N stages (n)			
N0	7	15	
N1	5		
N2	14	2	
N3	2		
NX	1		

OIRR, oral cavity irradiated group; *ONIRR,* oral cavity nonirradiated group; *SCC,* squamous cell carcinoma.

between the control group (55.6%) and the OIRR (48.3%) or ONIRR group (64.7%). There was also no significant difference in *Candida* colonization between the OIRR group and the ONIRR group at each treatment stage.

Heavy *Candida* growth in the OIRR group was observed in only 6.9 percent of patients (n = 2) at the beginning of RT, but this frequency rose to 31.0 percent at stage 2, 27.6 percent at stage 3, 33.3 percent at stage 4, and 39.1 percent at stage 5. The percentages of heavy *Candida* growth in stages 2, 3, 4, and 5 were each significantly higher than that at stage 1 ($P < 0.05$). In contrast, in the ONIRR group, heavy *Candida* growth was observed in 0 percent of patients at stages 1 and 2, 5.6 percent at stage 3, 11.8 percent at stage 4, and 0 percent at stage 5, indicating no significant change in frequency among treatment stages (Fig 1).

Oral Candidiasis, Mucositis, and Xerostomia

The incidences of mucositis were 79.3 percent (23 of 29) in the OIRR group and 52.9 percent (9 of 17) in the ONIRR group. The incidences of severe mucositis (grade 3 or 4) were 41.4 percent (12 of 29) in the OIRR group and 11.8 percent (2 of 17) in the ONIRR group. During RT, the incidences of oral candidiasis with mucositis were 55.2 percent (16 of 29) in the OIRR group and 11.8 percent (2 of 17) in the ONIRR group. The incidence of developing oral candidiasis was significantly higher in the OIRR group than in the ONIRR group ($P = 0.004$; RR 4.690; 95% CI 1.225-17.955) (Table 2).

In the OIRR group, three, eight, and five patients developed oral candidiasis at the 10th fraction, 20th fraction, and completion of RT, respectively. All patients with oral candidiasis in the OIRR group except one received concurrent chemotherapy with RT. In seven of 16 patients who developed oral candidiasis in the OIRR group, the oral candidiasis persisted until at least one month after RT. A detailed examination of the detected fungi revealed that 14 of 16 patients (87.5%) carried *Candida albicans*, and the remaining two patients carried a non-*albicans* species. In the ONIRR group, oral candidiasis was observed in only two patients at treatment stage 3. Concurrent chemotherapy with RT was performed in one of these patients. The oral candidiasis in both patients had disappeared at treatment stage 5 (1 month later).

During RT, oral mucositis without candidiasis was diagnosed in nine of 29 (31.0%) patients in the OIRR group and in seven of 17 (41.2%) patients in the ONIRR group, indicating no significant difference between the two groups (χ^2 test, $P = 0.486$). During RT, xerostomia was reported by 25 of 29 patients (86.2%) in the OIRR group and nine of 17 (52.9%) in the ONIRR group. The incidence of xerostomia in the OIRR group was significantly higher than that in the ONIRR group ($P = 0.033$; RR 1.628; 95% CI 1.016-2.609) (Table 2).

Difference in Clinical Symptoms of Oral Mucositis with or without Candidiasis

The respective mean MTS scores in 16 patients with oral candidiasis in the OIRR group were 4.1 ± 2.6, 5.8 ± 2.1, and 6.3 ± 2.7 at the 10th fraction, the 20th fraction, and completion of RT, respectively. The comparative mean

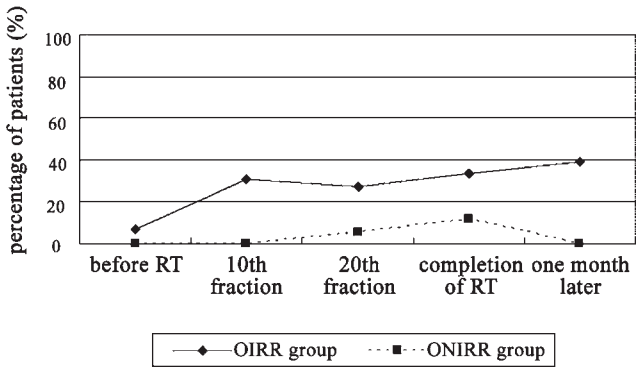

Figure 1 Percentage of patients with heavy *Candida* growth in the OIRR and ONIRR groups. *OIRR,* oral cavity irradiated group; *ONIRR,* oral cavity nonirradiated group.

Table 2
Incidence of oral candidiasis and xerostomia in the OIRR and ONIRR groups

	Oral candidiasis		Xerostomia	
	(+)	(–)	(+)	(–)
OIRR group	16 (55.2%)	13 (44.8%)	25 (86.2%)	4 (13.8%)
ONIRR group	2 (11.8%)	15 (88.2%)	9 (52.9%)	8 (47.1%)
P value	0.004		0.033	
RR (95% CI)	4.690 (1.225-17.955)		1.628 (1.016-2.609)	

OIRR, oral cavity irradiated group; *ONIRR,* oral cavity nonirradiated group; *RR (95% CI),* relative risk (95% confidence interval).

MTS scores in nine patients with oral mucositis without candidiasis in this OIRR group were 3.8 ± 2.0, 3.7 ± 2.0, and 4.7 ± 3.2 at the 10th fraction, the 20th fraction, and completion of RT, respectively. In the OIRR group, MTS was significantly higher in patients with oral candidiasis than in those with oral mucositis without candidiasis at the 20th fraction ($P = 0.030$), but not at the 10th fraction ($P = 0.7869$) or completion of RT ($P = 0.184$) (Fig 2).

In the OIRR group, of the 23 patients who developed dysphagia of varying degrees during RT, 22 (95.7%) had oral mucositis and 15 (65.2%) had oral candidiasis. Fourteen patients required placement of a gastric tube during RT, and all such patients experienced severe mucositis; nine of these patients had concomitant oral candidiasis. Oral mucositis correlated significantly with the development of dysphagia ($P = 0.020$) (Fig 3), but no significant correlation was observed between oral candidiasis and dysphagia ($P = 0.064$) (Fig 4).

In the ONIRR group, statistical analysis of the MTS score could not be performed because of the small number of the patients with oral candidiasis (n = 2). Of 10 patients in the ONIRR group with dysphagia, eight had oral mucositis and only one had oral candidiasis. Dysphagia in this group was strongly associated with oral mucositis ($P = 0.015$) (Fig 3), but not with oral candidiasis ($P = 1.000$) (Fig 4). Those patients who developed oral candidiasis required gastric tube placement during RT.

Discussion

Candida colonization and infection in the oral cavity are common in patients who receive RT for head and neck cancer. Previous studies have shown that the frequency of *Candida* colonization increases from the beginning to the completion of RT.[3,5] In the present study, although the rates of *Candida*-positive culture in the OIRR and ONIRR groups at the beginning of RT were not significantly different from that in the control group, the frequency of *Candida* colonization increased during RT. The percentage of heavy *Candida* counts also increased significantly at 20 Gy or higher in the OIRR group and at 40 Gy in the ONIRR group, compared with those before RT. These results are approximately in accordance with previous studies concerning oral candidiasis during RT. In a retrospective study by Jham et al,[14] oral candidiasis was observed in 45.8 percent of the 131 patients during the RT course, with a mean time of onset at the 16th fraction. Belazi et al[4] reported an incidence of fungal infections of 77 percent in their study group

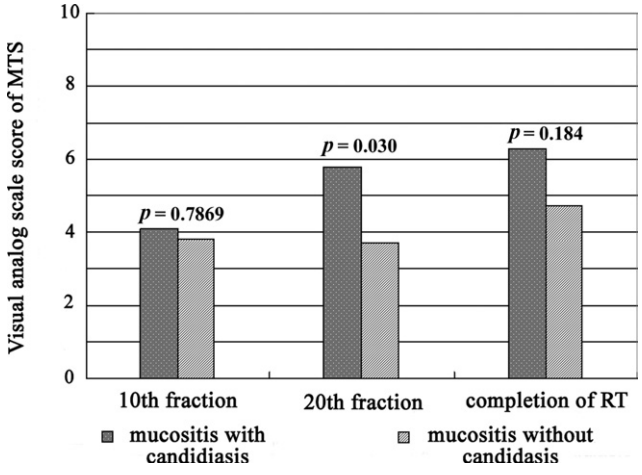

Figure 2 Mean mouth and throat soreness (MTS) in the OIRR group during radiation therapy (RT).

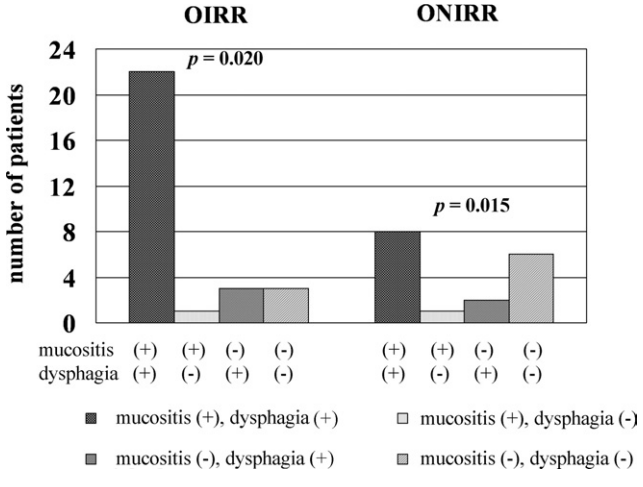

Figure 3 Correlation between oral mucositis and dysphagia. A significant number of patients with oral mucositis developed dysphagia in the OIRR and OINRR groups. *OIRR,* oral cavity irradiated group; *ONIRR,* oral cavity nonirradiated group.

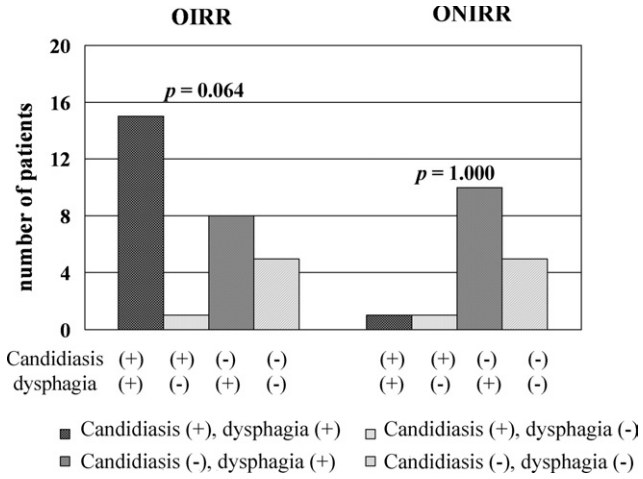

Figure 4 Correlation between oral candidiasis and dysphagia. No significant correlation was observed between oral candidiasis and dysphagia in the OIRR and ONIRR groups. *OIRR,* oral cavity irradiated group; *ONIRR,* oral cavity nonirradiated group.

during RT. In general, however, the influence of radiation dosage on oral candidiasis has not been clearly documented.

The present report is the first to compare *Candida* infection in patients with irradiation to the oral cavity to that in patients without such irradiation. We detected oral candidiasis during RT in 55.2 percent of the patients in the OIRR group and in only 11.8 percent in the ONIRR group. These results suggest that RT to the oral cavity increases the vulnerability of patients with head and neck cancer to *Candida* infection. The incidence of patients with xerostomia in the OIRR group was significantly higher than in the ONIRR group. The reduction of salivary secretion may influence the development of oral candidiasis and heavy *Candida* growth. Indeed, a previous study demonstrated that reduced salivary secretion subsequent to destruction of glandular tissue was probably a major factor leading to *Candida* infection.[8] In our study, 30.4 percent of patients in the OIRR group still had oral candidiasis one month after completion of RT, which falls within the range of 21 to 42 percent of patients reported to have candidiasis after RT.[14,15] Taking all findings together, we suggest that irradiation to the oral cavity increases the likelihood of oral candidiasis through worsening of the oral environment, for example, by inducing oral mucositis and decreasing salivary secretion.

Although *C. albicans* was predominant in those RT patients with *Candida* species, 12.5 percent of the *Candida* species detected in the OIRR group and 50 percent in the ONIRR group were non-*albicans* species. A recent study reported that non-*albicans* species are gradually being recognized as playing an important role in oropharyngeal candidiasis.[2,15] Our results indicate that non-*albicans* infection should not be neglected in antifungal treatment.

At each stage during RT, MTS scores reported by the patients with mucositis and oral candidiasis were consistently higher than those reported by the patients with mucositis but without oral candidiasis in the OIRR group, and these scores differed significantly at the 20th fraction of RT. Osaki et al[16] reported that candidiasis may induce glossodynia without objective abnormalities through hyposalivation. Terai and Shimahara[17] suggested that oral candidiasis plays an important role in functional tongue pain. The high MTS scores observed in our mucositis patients with candidiasis might be related to the *Candida* infection. Previous studies reported that RT-induced candidiasis developed at a mean time of the 14th to 16th fraction.[3,14] Similarly, in the present study, of the 16 patients with candidiasis in the OIRR group, eight (50.0%) developed oral candidiasis at the 20th fraction. This suggests that oral candidiasis, which developed most commonly midway through the RT regime, may increase patient discomfort during RT.

A number of studies have found a significant association between oral mucositis and dysphagia among patients who received RT with or without concomitant chemotherapy for head and neck cancer. Vera-Llonch et al[10] documented that 17 percent of patients with head and neck cancer who suffered from moderate or severe oral mucositis required feeding-tube placement. Elting et al[18] reported that 56 percent of individuals who received chemoradiotherapy required gastric tube placement during RT.[18] Although RT-induced oral mucositis concomitant with oral candidiasis has been reported, the association between oral candidiasis and dysphagia remains obscure. In accordance with the findings of previous studies, we found that dysphagia was significantly associated with oral mucositis in both groups of patients. However, we observed no correlation between oral candidiasis and dysphagia or gastric tube placement ($P = 0.064$). Since nine of the 16 patients with oral candidiasis in the OIRR group required gastric tube placement, examination of a larger number of patients will be needed to clarify the absence or presence of a correlation between oral candidiasis and dysphagia. Future studies should also seek to elucidate the effect of antimycotic drugs in patients with oral candidiasis.

Conclusions

The present study demonstrated that irradiation of the oral cavity in patients with head and neck cancer was associated with the development of oral mucositis and the subsequent development of oral candidiasis. RT-induced oral candidiasis may cause severe MTS and dysphagia. Measures to prevent oral candidiasis should help reduce the incidence of uncomfortable oropharyngeal symptoms that frequently interrupt treatment.

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Zeyi Deng, acquisition and analysis of data, writing of article; **Asanori Kiyuna,** acquisition of data; **Masahiro Hasegawa,** acquisition of data; **Isamu Nakasone,** interpretation of data; **Atsushi Hosokawa,** interpretation of data; **Mikio Suzuki,** design of study, revision of article.

Disclosures

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