Sequential Changes in Oral Dryness Evaluated by a Moisture-Checking Device in Patients with Oropharyngeal Cancer during Chemoradiotherapy: A Pilot Study

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Abstract

Purpose: Although oral dryness is a predictor for oral mucositis caused by Chemoradiotherapy (CRT) for head and neck cancer, there have been few reports evaluating the sequential changes in oral dryness during therapy. Studies have determined the reliability and usefulness of a moisture-checking device for the evaluation of dry mouth. This study aimed to evaluate the oral moisture level in patients with Oropharyngeal Cancer (OPC) during CRT using a moisture-checking device.

Methods: Oral moisture level was measured with an oral moisture-checking device (Moisture Checker Mucus®) at the lingual and buccal mucosa before, at the midpoint, and at the end of CRT in patients with OPC. Sequential changes in oral dryness were evaluated.

Results: A significant decrease in oral moisture level at the lingual mucosa was found when comparing values before and at the end of CRT (P=0.017). Decreases in oral moisture level at the buccal mucosa were not significant.

Conclusions: A moisture-checking device is considered a useful tool for determining the sequential changes in oral dryness during CRT for head and neck cancer. Our findings provide a basis for future larger long-term studies of oral moisture levels in OPC patients receiving CRT.

Key words: Oral dryness, Moisture-checking device, Oral mucositis, Chemoradiotherapy, Oropharyngeal cancer

Introduction

Head and neck cancer is the sixth most common cancer worldwide, accounting for 2.8% of all malignancies [1]. The incidence of Oropharyngeal Cancer (OPC), in particular, appears to be rising, and impressive increases have been reported in some countries [2]. The strongest risk factors for head and neck cancer were thought to be tobacco and alcohol use. However, despite declines in tobacco use in most developed countries, the rising incidence of OPC in these populations is thought to be largely due to an increase in Human Papillomavirus (HPV)-related OPC [3]. HPV-positive OPC is considered distinct from HPV-negative head and neck cancers. Although HPV-positive OPC is associated with increased p16 expression, HPV-negative tumors are more likely to have higher epidermal growth factor receptor expression [4]. The prognosis for patients with HPV-positive OPC is significantly better than that of patients with HPV-negative tumors [5]. Retrospective studies have confirmed a better prognosis in patients with HPV (and *p16* expression)-positive tumors in analyses of chemoradiation trials [6,7]. Currently, radiotherapy is the most commonly used single modality in patients with early-stage OPC, and the optimal treatment of patients with locally advanced OPC involves any given combination and sequence of surgery, radiotherapy, and chemotherapy [5].

Oral mucositis in patients with head and neck cancer is one of the most common troublesome side effects of Chemoradiotherapy (CRT), with a strong impact on Quality-of-Life (QoL). Oral mucositis is associated with pain, dysphagia, infections, food intake impairment, and weight loss, and may require prolonged feeding tube placement and hospitalization [8]. Xerostomia is another prominent complication in patients with head and neck cancer because radiation-induced damage to salivary glands alters the volume, consistency, and pH of secreted saliva [1]. Oral dryness creates a predisposition to mucosal fissures and ulcerations [9].

Previous clinical experiments confirmed the reliability and usefulness of a moisture-checking device for the evaluation of dry mouth [10,11]. This device, which was developed based on the capacitance method and is modified from a moisture-checking device for skin, can easily measure the moisture of the submucosal layer [10]. Water content and its dielectric constant have a positive correlation and because the dielectric constant of water is much higher than other substances, measurement of the skin's dielectric constant reveals the water content ratio [12]. The accuracy of this device was previously confirmed [11]. Previous studies have shown that the moisture value evaluated with a moisture-checking device had a significant negative correlation with the dose of radiation and a positive correlation with the period after radiation [13]. However, few reports have evaluated the sequential changes in oral dryness during CRT. This study aimed to evaluate the oral moisture level in patients with OPC during CRT using a moisture-checking device.

Patients and Methods

We enrolled 18 patients receiving treatment for OPC at the Department of Otolaryngology-Head and Neck Surgery in our institution from January 2009 through December 2010. Patients were referred to the Department of Oral and Maxillofacial Surgery for pretherapeutic screening for odontogenic foci and periodic oral care during CRT. The purpose of the study was explained to the subjects and measurements with an oral moisture-checking device were performed only in patients who approved.

Oral dryness was evaluated with an oral moisture-checking

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device (Moisture Checker Mucus®; Life Co., Japan). The oral moisture level was measured at the lingual mucosa (on the surface of the tongue 10 mm from the apex linguae) and the buccal mucosa (10 mm from the angle of the mouth), as previously described [13]. The oral moisture level was determined by the weight of the water content, expressed as a percentage. All moisture measurements as the amount of unstimulated saliva were performed a few hours after a meal under non-stressful circumstances and three times for each mucosa. The mean value of each measurement was calculated. The oral moisture level was measured at periodic oral care appointments before, at the midpoint, and at the end of CRT.

Epidemiological data were retrospectively gathered from the medical charts as follows: age, sex, histological diagnosis, TNM classification, concurrent neck dissection, the method of nutrition, and opioid use during CRT. The severity of oral mucositis in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 is categorized as follows: grade 1 - asymptomatic or mild symptoms and intervention not indicated; grade 2 - moderate pain but not interfering with oral intake or modified diet indicated; grade 3 - severe pain and interfering with oral intake; grade 4 - life-threatening consequences and urgent intervention indicated; and grade 5 - death related to toxicity; the condition was evaluated before, at the midpoint, and at the end of CRT.

For the statistical analysis, the Mann-Whitney's *U*-test and Fisher's exact test were used. Statistical significance was accepted for *P*-values of <0.05, and all calculations were performed using SPSS ver. 15.0 (SPSS Inc., Chicago, IL).

Results

Subject characteristics are summarized in *Table 1*. At the time of CRT for OPC, the mean age of the 18 patients was 57.7 years (range, 41-70 years). All patients were men. The histological diagnosis was squamous cell carcinoma in all patients. Clinical T-stages were as follows: T1 (n=2), T2 (n=11), and T3 (n=5); N-stages: N0 (n=3), N1 (n=1), N2a (n=5), N2b (n=8), and N2c (n=1); M-stage: M0 (n=18). All patients received concurrent CRT and the dose of radiation was 70 Gy in all patients. Concurrent neck dissection was performed in two patients and chemotherapy consisted of two or three cycles of cisplatin 60-80 mg/m^2 on a three-weekly cycle in 17 patients. One patient received three cycles of carboplatin 80 mg/m^2 on a three-weekly cycle. Opioids were administrated for pain relief during CRT in 13 patients. Although Percutaneous Endoscopic Gastrostomy (PEG) was used for nutritional support in 13 patients (72.2%), five patients (27.8%) completed CRT with oral intake, alone. Therefore, the worst NCI-CTCAE v4.0 grade during CRT was grade 3 in 13 patients (72.2%).

The sequential changes in the NCI-CTCAE v4.0 grade before, at the midpoint, and at the end of CRT are shown in *Figure 1*. Before CRT, all patients were diagnosed as grade 1. Two patients (11.1%) were diagnosed with severe oral mucositis (grade=3) at the midpoint of CRT, and six patients (33.3%) at the end of CRT.

The mean value of the oral moisture level before CRT was 27.1 ± 1.4% at the lingual mucosa and 28.6 ± 1.9% at the buccal mucosa; 26.2 ± 1.3% at the lingual mucosa and 28.2 ± 1.5% at the buccal mucosa at the midpoint of CRT; and 24.8 ± 2.4% at the lingual mucosa and 27.9 ± 2.0% at the buccal mucosa within one week of the end of CRT. A significant decrease in the oral moisture level at the lingual mucosa was found when comparing the values before and at the end of CRT (*P*=0.017), but not when comparing values before and at the midpoint (*P*=0.419), or when comparing values at the midpoint and the end of CRT (*P*=0.347) (*Figure 2*). Decreased oral moisture level at the buccal mucosa was not significant

Table 1. *Subject characteristics.*

No	Gender	Age (yr)	Dose of RT (Gy)	CR regimen	ND	Opioid use
1	M	41	70	Cisplatin 80 mg/m^2 3 cycles	-	-
2	M	58	70	Cisplatin 80 mg/m^2 3 cycles	-	-
3	M	56	70	Cisplatin 80mg/m^2 3 cycles	-	+
4	M	62	70	Cisplatin 80 mg/m^2 2 cycles	-	+
5	M	70	70	Cisplatin 80 mg/m^2 3 cycles	-	+
6	M	52	70	Cisplatin 80 mg/m^2 1 cycle Cisplatin 64 mg/m^2 2 cycles	-	+
7	M	70	70	Cisplatin 80 mg/m^2 1 cycle Cisplatin 60 mg/m^2 2 cycles	-	-
8	M	64	70	Cisplatin 80 mg/m^2 1 cycle Cisplatin 64 mg/m^2 1 cycle	-	+
9	M	64	70	Cisplatin 80 mg/m^2 3 cycles	+	+
10	M	68	70	Cisplatin80mg/m^2 1 cycle Cisplatin 60 mg/m^2 2 cycles	-	+
11	M	45	70	Cisplatin 80 mg/m^2 2 cycles	+	+
12	M	49	70	Cisplatin 80 mg/m^2 3 cycles	-	-
13	M	50	70	Cisplatin 80 mg/m^2 3 cycles	-	+
14	M	63	70	Cisplatin 80 mg/m^2 1 cycle Cisplatin 70 mg/m^2 1 cycle	-	+
15	M	64	70	Cisplatin 80 mg/m^2 3 cycles	-	+
16	M	43	70	Cisplatin 80 mg/m^2 3 cycles	-	+
17	M	63	70	Cisplatin 80 mg/m^2 3 cycles	-	+
18	M	57	70	Cisplatin 80 mg/m^2 2 cycles	-	-

RT: Radiation therapy; CR: Chemotherapy; ND: Neck dissection

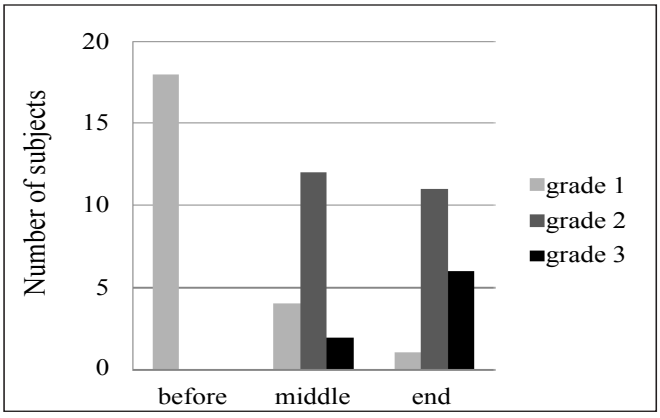

Figure 1. *Sequential changes in CTCAE v4.0 oral mucositis grade during chemoradiotherapy.*

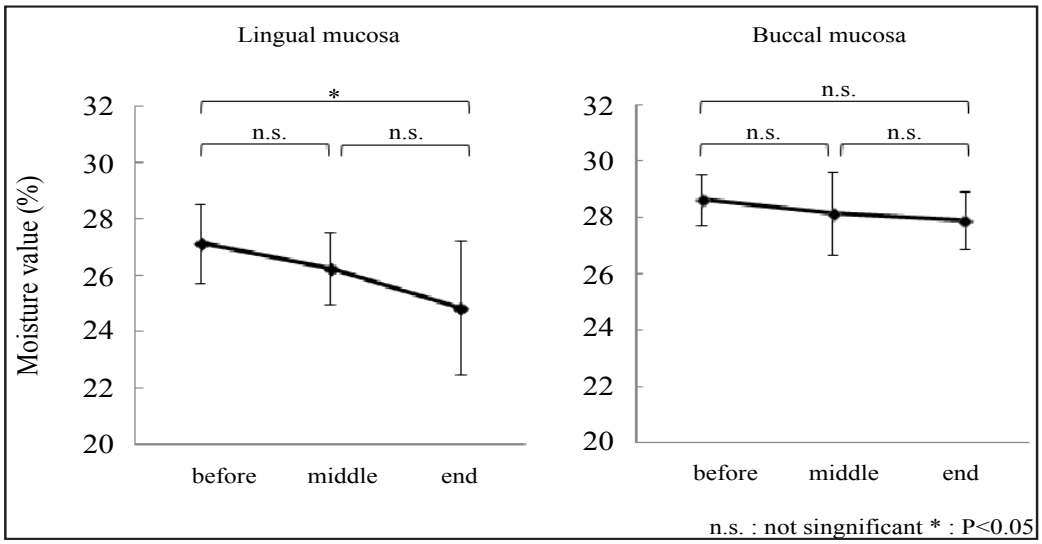

Figure 2. *Sequential changes in oral moisture level at the lingual and buccal mucosa evaluated with a moisture-checking device during chemoradiotherapy.*

Table 2. *Number of subjects with oral mucositis (CTCAE v4.0 grade 3) and sequential decrease in the oral moisture level evaluated with a moisture-checking device.*

Percentage decrease in oral moisture level comparing values before and at the end of CRT (%)	No. of subjects (CTCAE v4.0 grade 3)
≥1	15 (5)
1>	3 (1)
≥2	10 (3)
2>	8 (3)
Not significant	

(*Figure 2*).

The oral moisture level decreased more than 1% in 15 patients (83.3%), and more than 2% in 10 patients (55.6%). The incidence of severe mucositis (grade=3) was not significantly high in patients with obvious decreases in oral moisture level evaluated with the moisture-checking device, as shown in *Table 2*.

Discussion

As the data in this study has shown, the oral moisture level of the lingual mucosa but not the buccal mucosa evaluated with a moisture-checking device in patients with OPC during CRT decreased sequentially. Although one clinical experiment previously reported that oral moisture correlated significantly with the dose of radiation [13], there have been no reports discussing the sequential changes in oral dryness during CRT, to our knowledge.

Conventional methods, such as the spitting method and the cotton method, have been used to measure the amount of unstimulated saliva at rest [14-16]. These methods are thought to be useful for assessment of dry mouth; however, examination of xerostomia in patients with severe oral mucositis caused by CRT should be done simply. A moisture-checking device has been recognized as reliable and useful in both animal [11] and clinical experiments [10,13,17]. Also, assessment with this device took only a few seconds for one site, such as lingual, buccal, or labial mucosa [10]. This study confirmed the simplicity of this device, because measurements were completed in all patients with OPC during CRT without difficulty or complications.

We applied the device to two sites, lingual and buccal mucosa, to measure the oral moisture level, as previously described [10,13], and found a significant decrease in the moisture level only at the lingual mucosa (*Figure 2*). A previous control study between healthy adults and patients with subjective oral dryness reported that the average moisture values at the lingual mucosa and buccal mucosa (30.0 ± 0.5% and 30.3 ± 0.2%, respectively) in the healthy adults group were significantly higher than those (28.6 ± 1.1% and 29.6 ± 0.7%, respectively) in the oral dryness group [18]. A value of 29% for moisture level has been previously used as a reference value [13,17]. Another study reported that the moisture levels evaluated with a moisture-checking device at the lingual mucosa (30.6 ± 0.3%) was approximately 0.3–0.4% lower than those at the buccal mucosa (30.9 ± 0.3%) [19]. The same study concluded that the measurement errors of this device were within 1% using proper measuring pressure [19]. Ishimoto applied the device to the lingual mucosa in an animal experiment and confirmed the reliability of this device because the measured moisture value at the tongue decreased significantly in animals with sialoadenectomy [11]. The manufacturer's instructions recommend taking the measurement at the surface of the tongue 10 mm from the apex linguae, and mentioned that evaluating the value at the buccal mucosa does not adequately assess oral dryness because there is often no difference between normal values and xerostomia, likely due to the fact that wetness of the buccal mucosa tends to be affected by the parotid papilla. Our results confirm a sequential decrease in oral moisture due to CRT when measuring the moisture at the lingual mucosa; therefore, measurements at the lingual mucosa are considered to be more appropriate than those at the buccal mucosa.

A recent large prospective QoL assessment study after CRT for OPC reported that QoL-scores deteriorated during treatment, reaching the worst scores near the end of treatment [20]. Whereas all scores started to improve within 4-12 weeks; and returned to almost baseline levels at 18 months;

dry mouth and sticky saliva scales statistically significantly and clinically deteriorated. Radiotherapy for OPC appears to have a substantial effect on the adjacent organs at risk, especially salivary glands and swallowing muscles, leading to a significant increase in patient-reported xerostomia and dysphagia. Chemotherapy is a predictor for QoL changes over time, mainly for dry mouth, swallowing, and opening mouth scales [20]. In our study, 13 patients (72.2%) required PEG for nutrition near the end of CRT; therefore, these patients were diagnosed as NCI-CTCAE v4.0 grade 3. On the other hand, five patients (27.8%) completed CRT with only oral intake, even though all patients received high-dose concurrent CRT. The percentage of patients diagnosed as NCI-CTCAE v4.0 grade 3 was not significantly high in the group that included patients with sequential deterioration of oral dryness evaluated with the moisture checking device (*Table 2*). This can be explained as follows: the sample size of this study was small; oral dryness was one of the factors that affected patients' oral intake ability and induced oral mucositis and dysphagia, resulting in a need for supplemental nutrition via PEG; other factors included age, numbers of remaining teeth, pain threshold of each patient, and adequate pain management with non-steroidal anti-inflammatory drugs or opioids.

Appropriate oral and dental care for patients with head and neck cancer is also a factor that can improve QoL and reduce morbidity and healthcare costs [21]. In our hospital, experienced oral surgeons screen the odontogenic foci and determine when to extract unpreservable teeth to prevent osteoradionecrosis of the jaw in head and neck patients before beginning CRT, and experienced dental hygienists provide periodic oral and dental care for these patients to reduce oral complications, including oral mucositis, odontogenic infection, pain, and oral dryness during and following CRT. A moisture-checking device can provide objective data on oral dryness for clinicians and patients quickly at chair-side. Moisture measurement is considered to be meaningful to understand the severity of oral dryness and its management for both clinicians and patients.

In conclusion, oral moisture level at the lingual mucosa evaluated with a moisture-checking device decreased in patients during CRT. A moisture-checking device is considered to be a useful tool for understanding the sequential changes in oral dryness during CRT. A long-term follow-up study after the end of CRT using this device should be conducted in the future, because dry mouth caused by CRT persists long-term.

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