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Description	

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Image processing analysis of oral cancer, oral potentially malignant disorders, and other oral diseases using optical instruments

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Abstract. Oral cancer screening is important for early detection and early treatment, which help improve survival rates. Biopsy is invasive and painful, while fluorescence visualization using optical instruments is non-invasive, convenient, and provides results in real time, and examinations can be repeated. The purpose of this study was to determine the usefulness of optical instruments in oral screening. A total of 314 patients who were examined using optical instruments at Tokyo Dental College between 2014 and 2018 were enrolled in this study. Fluorescence visualization images were analyzed using subjective and objective evaluations. Subjective evaluation for detecting oral cancer offered 98.0% sensitivity and 43.2% specificity. Regarding the objective evaluations for detecting oral cancer, sensitivity and specificity were 61.9% and 62.7% for mean luminance, 90.3% and 55.7% for luminance ratio, 56.5% and 67.7% for standard deviation of luminance, and 72.5% and 85.4% for coefficient of variation of luminance. Fluorescence visualization with subjective and objective evaluation using optical instruments is useful for oral cancer screening.

Oral and pharyngeal cancers represent a global health challenge, with recently estimated incidence of over 657,000 newly diagnosed cases and 330,000 fatal cases each year[1]. In Japan, in particular, there has been a tendency of increasing mortality[2]. More than 90% of oral cancers are oral squamous cell carcinoma (SCC)[3]. Delayed diagnosis accounts for poor quality of life and a high mortality rate, and nearly half of SCC cases are at an advanced stage at the time of initial diagnosis[3]. Early detection and early treatment are crucial to help improve the survival rate of patients with SCC[4].

Oral screening plays a vital role in making the correct decision about lesions, and such screening is thus crucial in avoiding unnecessary or delayed referrals and considerably reducing the mortality of SCC[5]. SCC may develop from an oral potentially malignant disorder, such as leukoplakia or oral lichen planus (OLP). It has been reported that the early detection and management of oral epithelial dysplasia (OED) in oral potentially malignant disorder cases is an important preventive step against malignant transformation[6]. During visual inspection and palpation, a major limitation is the difficulty in differentiating between benign and high-risk lesions, as early-stage SCC and OED may not present with typical features. Furthermore, a wide variety of oral mucosal diseases can present in various ways in the oral cavity[7].

Although surgical biopsy is regarded as the gold standard for oral cancer diagnosis, this process is invasive, time-consuming, and painful[8]. Various other methods for diagnosing SCC have emerged[7]. Screening for SCC can involve cytology[9], vital staining[10], and fluorescence visualization (FV)[11]. FV is a non-invasive, convenient, and real-time screening method using optical instruments, and the examinations can be repeated[11,12]. FV uses blue light (400–460 nm) to illuminate collagen cross-links or flavin adenine dinucleotide (FAD) and nicotinamide adenine dinucleotide (NADH)[12]. A selective filter allows the viewer to directly visualize the apple-green autofluorescence given off by normal tissue (fluorescence visualization retention, FVR). On the other hand, abnormal tissues such as those seen in SCC, OED, and inflammatory diseases exhibit decreased autofluorescence and appear as dark-brown areas in comparison with the green surrounding normal tissue. Such dark-brown areas are referred to as FV loss (FVL)[13]. FVL is caused by absorption of a specific wavelength of blue light due to the breakdown of collagen cross-links and decreases in FAD and NADH, and angiogenesis.

The evaluation of FV in studies performed previously has been visual and subjective. Therefore, definitive results are lacking[11]. The purpose of this study was to clarify the utility of subjective and objective evaluations using optical instruments for oral screening.

Materials and methods

A total of 314 patients attending the Department of Oral and Maxillofacial Surgery of Tokyo Dental College from January 2014 to December 2018 were enrolled in this study. Of the 314 participants, 162 were male and 152 were female, and their mean age was 68.3 years (range 35–88 years). The inclusion criteria were (1) patient examined using optical instruments before treatment, (2) patient provided informed consent to participate in the study, and (3) a confirmed diagnosis was obtained by biopsy, except for stomatitis. All patients with SCC were re-staged using the eighth edition of the TNM Classification of Malignant Tumours of the Union for International Cancer Control (UICC)[6]. The study was approved by the institutional review board and performed in accordance with the requirements of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013).

The optical instrument used in the examination protocol for each patient in this study was either ORALOOK (Hits Plan Inc., Tokyo, Japan) or IllumiScan (Shofu Inc., Kyoto, Japan). These optical instruments allow FV images to be taken and saved to the camera as digital data. FV images of the lesion can be observed in real time because the optical instruments have their own monitor. These lightweight instruments can be used with one hand. FV images were taken in a darkened room as
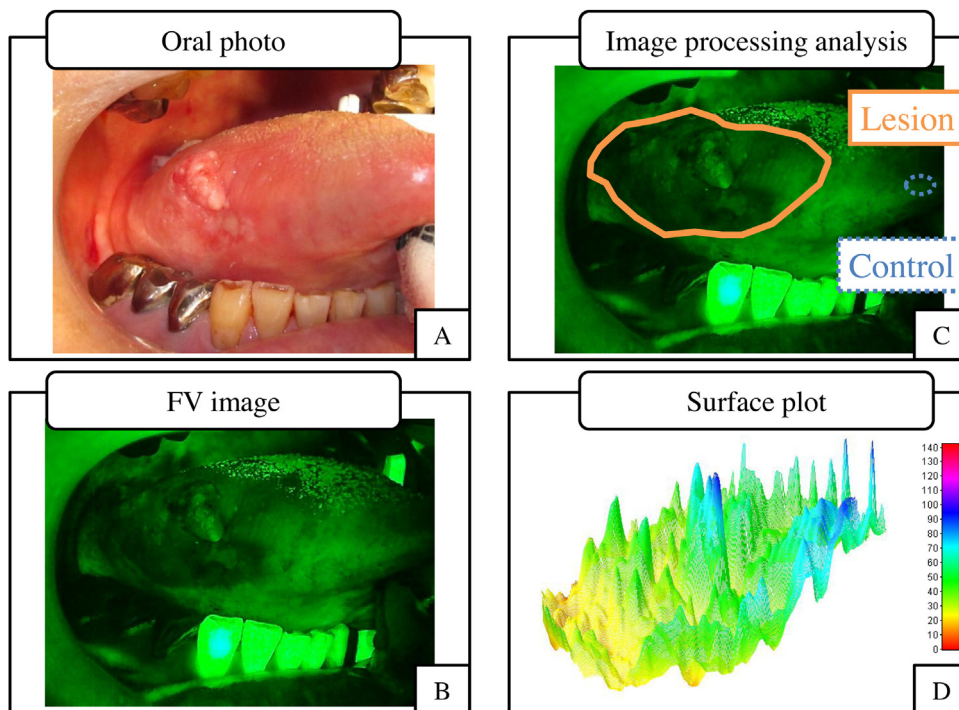
Fig. 1. Methods of subjective and objective evaluation. In the subjective evaluation, oral photographs and FV images were compared (A, B), to evaluate FVR or FVL in the lesions. The ROI of the lesion was defined as the area of FVL. The control ROI was set as a sub-site without FVL in the same oral cavity, in the normal mucosa in front of the lesion (C). The state of the lesion ROI was expressed in a surface plot (D). (FV, fluorescence visualization; FVR, fluorescence visualization retention; FVL, fluorescence visualization loss; ROI, region of interest.)

much as possible, with a distance between the lesion and optical instrument of about 10 cm. The irradiating light was set perpendicular to the lesion and the irradiation range was set to approximately 10 cm[14].

In the subjective evaluations, oral photographs and FV images were compared to evaluate the FVR or FVL in the lesions (Fig. 1A, B). FV images were analyzed using ImageJ software version 1.5 (National Institutes of Health, Bethesda, MD, USA). Regions of interest (ROI) for the lesion and a control area were established in the FV images[14].

The ROI of the lesion was defined as the area of FVL. The control ROI was set at a distance from and in front of the ROI of the lesion, in the same sub-site of the oral cavity, in normal mucosa; there was no FVL or oral mucosal lesion at this site (Fig. 1C). The state of the lesion ROI was expressed in a surface plot. In addition, colour mapping was performed for the surface plot of the lesion ROI (Fig. 1D). The surface plot was used as a reference for subjective evaluation[14].

In the subjective evaluation, positive cases were defined as those with FVL and negative case as those with only FVR; two or more examiners performed this evaluation. The FVL rate was then calculated. Sensitivity and specificity were calculated as follows: sensitivity = (FVL positive cases with SCC/all cases with SCC) × 100%; specificity = (FVL negative cases without SCC/all cases without SCC) × 100%.

In the objective evaluation, the mean area of the ROI (measured in pixels), mean luminance (in candela per square metre, cd/m^2), standard deviation (SD) of luminance, coefficient of variation of luminance, and luminance ratio were calculated. The coefficient of variation of luminance was defined as the ratio of the SD of luminance to the mean luminance. The luminance ratio was defined as the ratio of the luminance of the lesion ROI to the luminance of the control ROI; i. e. luminance ratio = (ROI of lesion/ROI of control) ×100% [14].

For the differential diagnosis of oral mucosal diseases, the χ^2 test, Mann–Whitney *U*-test, and Fisher's exact test were used as statistical analyses. Cut-off values were set using a receiver operating characteristic (ROC) curve for detecting SCC. The area under the curve (AUC), sensitivity, and specificity were calculated by ROC curve analysis. All statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM, Tokyo, Japan). Values of $P < 0.05$ were deemed statistically significant.

Table 1. Patient characteristics.

	Stomatitis $n = 24$	Benign tumour $n = 18$	OLP $n = 98$	Leukoplakia $n = 73$	SCC $n = 101$
Sex, male/female	10/14	10/8	38/60	49/24	55/46
Age, mean years	62.9	58.4	63.8	68.8	65.2
Site, *n*					
Tongue	10	10	20	53	71
Buccal mucosa	3	8	56	8	9
Gingiva	2	0	18	2	13
Other	9	0	4	10	8
Control site, mean					
Area (pixels)	893	839	857	846	862
Luminance (cd/m^2)	80.0	81.2	81.7	82.7	80.8
Standard deviation	3.2	2.8	3.4	2.9	3.1
Coefficient of variation	0.042	0.040	0.043	0.041	0.045
Lesion site, mean					
FVL rate, (%)	95.8%	0.0%	88.8%	15.1%	98.0%
Area (pixels)	34,884	71,742	113,267	109,873	160,731
Luminance (cd/m^2)	62.2	76.7	67.3	85.2	54.5
Standard deviation	8.3	9.1	8.9	9.4	11.9
Coefficient of variation	0.13	0.12	0.13	0.13	0.22
Luminance ratio (%)	83.6%	99.0%	80.5%	109.0%	67.8%

OLP, oral lichen planus; SCC, squamous cell carcinoma; FVL, fluorescence visualization loss.

Results

Patient characteristics are shown in Table 1. Of the 314 patients, 24 had stomatitis, 18 had benign tumours, 98 had OLP, 73 had leukoplakia, and 101 had SCC. With regard to sex, the male/female ratio was 10/14, 10/8, 38/60, 49/24, and 55/46, respectively. Mean age was 62.9, 58.4, 63.8, 68.8, and 65.2 years, respectively. The most common site for stomatitis, benign tumour, leukoplakia, and SCC was the tongue, while the most common site for OLP was the buccal mucosa.

On histopathological diagnosis of the stomatitis cases, 20 were found to have catarrhal stomatitis and four to have viral stomatitis. Patients with stomatitis did not have any symptomatic disease, such as Behçet disease, pemphigus, or pemphigoid. Sixteen of the patients with benign tumours had fibroma, while two had lipoma. With regard to the OLP patients, all had chronic inflammation. Of the 73 patients with leukoplakia, hyperkeratosis was seen in 62 patients and low-grade OED in 11 patients. SCC grade 1 was seen in 82 patients, while grade 2 was seen in 12 patients and grade 3 in seven patients.

Typical cases of each disease are shown in Fig. 2. In stomatitis cases, a narrow and uniform FVL was observed around fibrin, and the boundaries of FVL were clear in the FV images. In benign tumour cases, no FVL was observed. For OLP, uniform FVL was seen in the area of erythema, the boundaries of FVL were clear, and FV acceleration was observed in areas of leukoderma like lace. With leukoplakia, no FVL was observed, but FV acceleration was apparent. In the case of SCC, non-uniform FVL was observed, and the boundaries of FVL were unclear.

In the subjective evaluation, FVL/FVR was 23/1 in stomatitis, 0/18 in benign tumours, 87/11 in OLP, 11/62 in leukoplakia, and 99/2 in SCC. Therefore, the FVL rate was 95.8% for stomatitis, 0.0% for benign tumour, 88.8% for OLP, 15.1% for leukoplakia, and 98.0% for SCC. All leukoplakia with low-grade OED showed FVL. SCC showed the highest FVL rate. Subjective evaluation for detecting SCC provided 98.0% sensitivity and 43.2% specificity.

In the objective evaluation of the control sites, the mean area was within the range of 839–893 pixels ($P = 0.982$), mean luminance was 80.0–82.7 cd/m^2 ($P = 0.954$), SD of luminance was 2.8–3.4 ($P = 0.964$), and mean coefficient of variation of luminance was 0.040–0.045 ($P = 0.995$). No significant differences were observed in any items at the control site.

In the objective evaluation of the lesion site, the mean area was 34,884 pixels in stomatitis cases, 71,742 pixels in benign tumour cases, 113,267 pixels in OLP cases, 109,873 pixels in leukoplakia cases, and 160,731 pixels in SCC cases. Mean luminance was 62.2 cd/m^2 for stomatitis, 76.7 cd/m^2 for benign tumours, 67.3 cd/m^2 for OLP, 85.2 cd/m^2 for leukoplakia, and 54.5 cd/m^2 for SCC (Fig. 3). Mean luminance was significantly higher in leukoplakia than in stomatitis or OLP ($P = 0.032$ and 0.021, respectively). Mean luminance in SCC was significantly lower
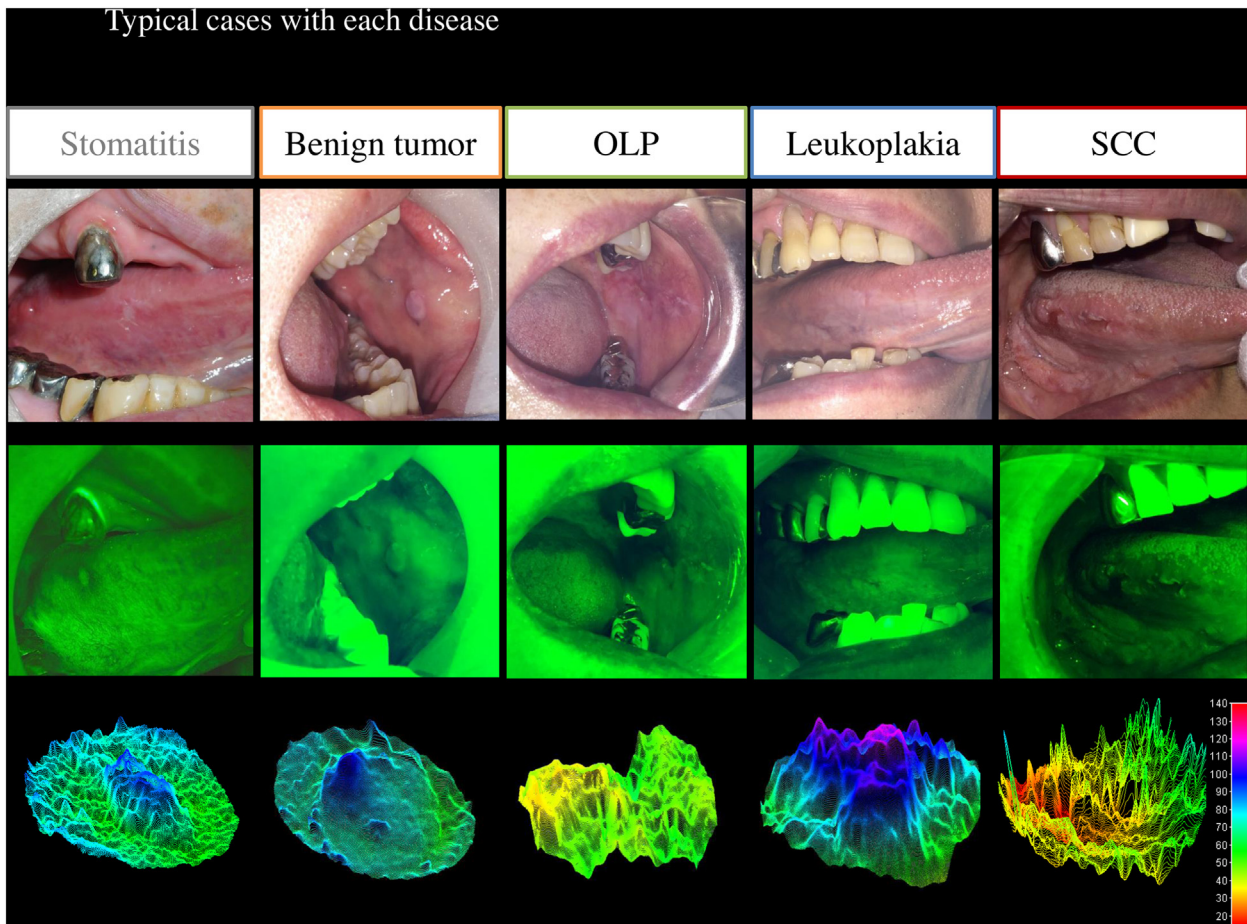
Fig. 2. Typical cases of each disease. The representative case of stomatitis with ulceration of the right tongue had a histopathological diagnosis of catarrhal stomatitis. In the FV images, a narrow, uniform FVL is observed around fibrin, and the boundaries of FVL are clear. In the case of benign tumour with fibroma of the left buccal mucosa, FVL is not evident. The case of OLP with a reticular lesion of the left buccal mucosa had a histopathological diagnosis of OLP. In the FV images, uniform FVL is observed in the erythematous area, and the boundaries of FVL are clear. FV acceleration is observed in areas of leukoderma. The case with leukoplakia with uniform leukoderma of the right tongue had a histopathological diagnosis of hyperkeratosis. In the FV images, no FVL is apparent, although FV acceleration is present. The representative case of SCC with an erosive lesion on the right tongue had a histopathological diagnosis of SCC grade 1. In the FV images, non-uniform FVL is observed, and the boundaries of FVL are unclear. (FV, fluorescence visualization; FVL, fluorescence visualization loss; OLP, oral lichen planus; SCC, squamous cell carcinoma.)

than in the other diseases (all $P < 0.05$). SD of luminance was 8.3 for stomatitis, 9.1 for benign tumours, 8.9 for OLP, 9.4 for leukoplakia, and 11.9 for SCC (Fig. 4). The SD of luminance was significantly higher in SCC than in OLP or leukoplakia ($P = 0.008$ and 0.007, respectively), and it was significantly higher in benign tumours than in OLP ($P = 0.04$). The coefficient of variation of luminance was 0.13 for stomatitis, 0.12 for benign tumours, 0.13 for OLP, 0.13 for leukoplakia, and 0.22 for SCC, again showing a significantly higher value for SCC than for the other diseases ($P < 0.001$, Fig. 4). The luminance ratio was 83.6% for stomatitis, 99.0% for benign tumours, 80.5% for OLP, 109.0% for leukoplakia, and 67.8% for SCC, showing

significant differences between all of the diseases ($P < 0.001$, each, Fig. 3).

The objective evaluation for the detection of SCC by ROC curve analysis is shown in Fig. 5. The AUC was 0.674 for mean luminance, 0.828 for luminance ratio, 0.616 for SD of luminance, and 0.843 for coefficient of variation of luminance. Cut-off values were set at 60 cd/m^2 for mean luminance, 86.8% for luminance ratio, 9.1 for SD of luminance, and 0.18 for coefficient of variation of luminance. Sensitivity and specificity were 61.9% and 62.7% for mean luminance, 90.3% and 55.7% for luminance ratio, 56.5% and 67.7% for SD of luminance, and 72.5% and 85.4% for coefficient of variation of luminance.

Discussion

Early diagnosis by general dentists is considered likely to improve the outcomes of SCC. Screening should be minimally invasive, repeatable, and inexpensive. Cytology[9], vital staining[10], and FV[11,14] are simple and effective methods of screening for SCC.

Oral brush cytology is a well-tolerated, mildly invasive, safe approach for harvesting cells from the oral mucosa[9]. However, it takes several days for the results of oral brush cytology to become available, and the method offers 60–100% sensitivity and 23.5–100% specificity[9]. Also, it is difficult to detect hyperkeratotic lesions with oral brush cytology[9]. Vital staining with iodine solution in the oral cavity

Mean luminance and luminance ratio as objective evaluations

Mean luminance

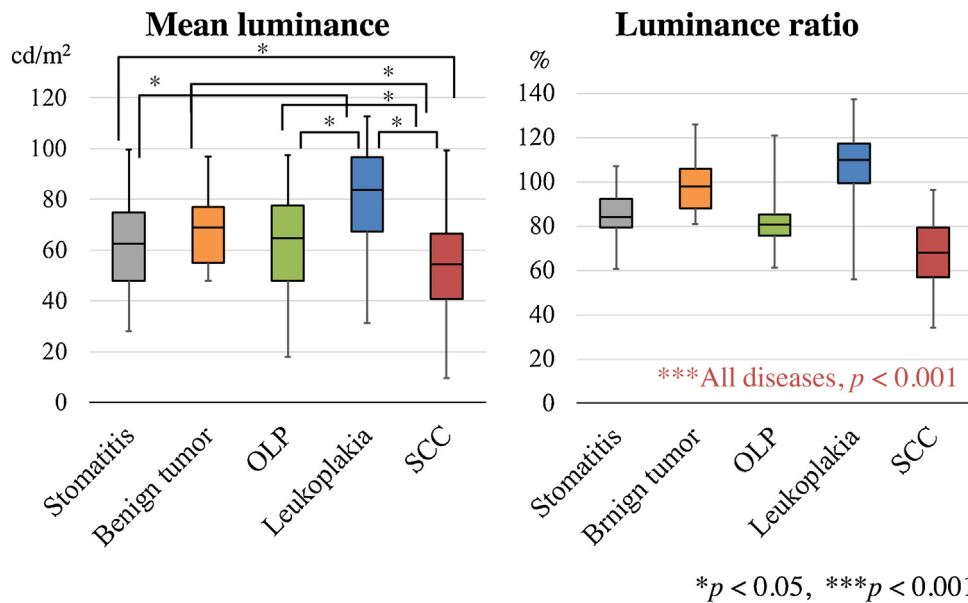cd/m²

Luminance ratio

%

*p < 0.05, ***p < 0.001*

Fig. 3. Mean luminance and luminance ratio as objective evaluations. Leukoplakia showed significantly higher mean luminance than stomatitis and OLP. SCC showed significantly lower mean luminance than the other diseases. All diseases showed significant differences in luminance ratio. (OLP, oral lichen planus; SCC, squamous cell carcinoma.)

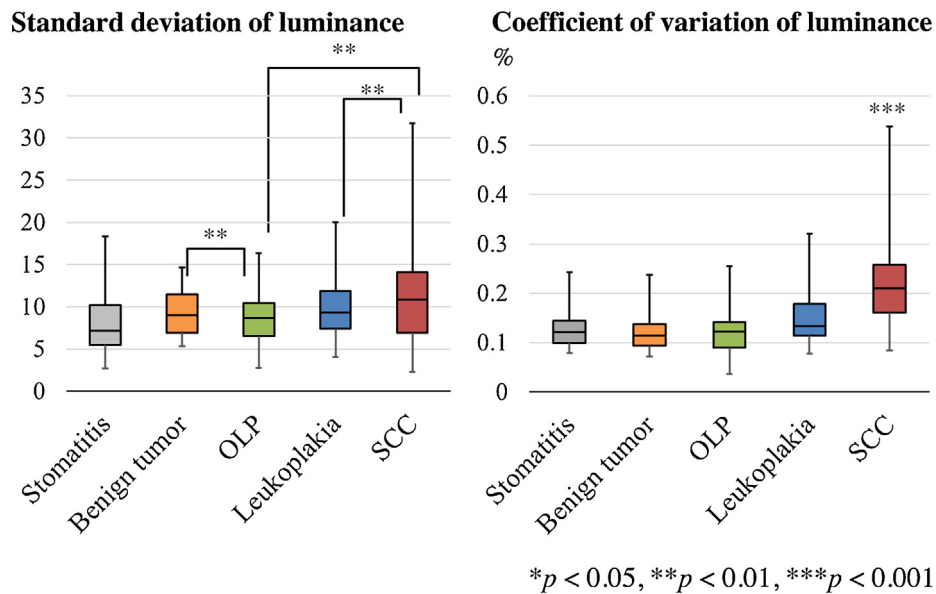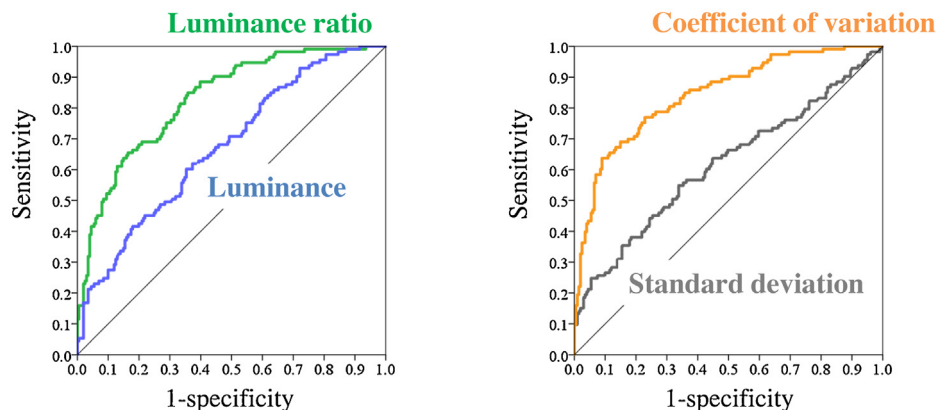Standard deviation of luminance and coefficient of variation of luminance as objective evaluations

Standard deviation of luminance

Coefficient of variation of luminance

%

*p < 0.05, **p < 0.01, ***p < 0.001*

Fig. 4. Standard deviation of luminance and coefficient of variation of luminance as objective evaluations. SCC showed a significantly higher standard deviation of luminance than OLP and leukoplakia. The coefficient of variation of luminance was 0.13 for stomatitis, 0.12 for benign tumour, 0.13 for OLP, 0.13 for leukoplakia, and 0.22 for SCC, showing a significantly higher value for SCC than for the other diseases. (OLP, oral lichen planus; SCC, squamous cell carcinoma.)

allows easy observation of the results in real time. In cases of SCC and in low- and high-grade OED, little glycogen is present in the granule cell layer, resulting in a relative lack of iodine staining. However, iodine solution cannot be used for patients with an iodine allergy, and the technique is mildly invasive[10]. Iodine solution is useful for movable mucosa such as the tongue,

Objective evaluation from ROC analysis

	AUC	*p* value	Cut-off	Sensitivity	Specificity
Luminance	0.674	< 0.001*	60	61.9	62.7
Luminance ratio	0.828	< 0.001*	86.8	90.3	55.7
Standard deviation	0.616	0.001*	9.1	56.5	67.7
Coefficient of variation	0.843	< 0.001*	0.18	72.5	85.4

Fig. 5. Objective evaluation from ROC curve analysis. In terms of AUC, the coefficient of variation of luminance showed the highest value, followed by the luminance ratio. The sensitivity and specificity are 61.9% and 62.7% for mean luminance, 90.3% and 55.7% for the luminance ratio, 56.5% and 67.7% for the standard deviation of luminance, and 72.5% and 85.4% for the coefficient of variation of luminance. (ROC, receiver operating characteristic; AUC, area under the curve.)

oral floor, buccal mucosa, and soft palate, but is difficult to use on keratinized mucosa such as the gingiva and hard palate[10]. Iodine solution offers 71–87.5% sensitivity and 84.2% specificity[10,15,16].

FV with optical instruments is non-invasive, convenient, provides results in real time, and examinations can be repeated[11,12]. This technique can be adapted for use anywhere in the oral cavity. ORA-LOOK is a lightweight and simple instrument with a built-in filter. It captures both FV images and oral photographs. This optical instrument irradiates the target with blue light at an excitation wavelength of about 410 nm and detects only apple-green fluorescence via the filter (520–560 nm). IllumiScan is also a lightweight and simple instrument with a built-in filter. However, it captures only FV images. This optical instrument irradiates the target with blue light at an excitation wavelength of about 425 nm, while it detects only apple-green fluorescence via the filter (470–580 nm). These optical instruments were selected for this study because they detect a single green fluorescence colour and image processing analysis is simple.

The evaluation of FV in previous studies was subjective, varying depending on the report[11]. In the present study, subjective evaluation for the detection of SCC showed high sensitivity (98.0%) and low specificity (43.2%). These factors include FVL in inflammatory diseases[17]. Thus, it was considered that a new evaluation method was necessary in order to obtain an objective evaluation.

In terms of discriminating between various oral mucosal diseases, mean luminance was significantly lower in SCC than in the other diseases; however, all diseases were difficult to distinguish by mean luminance as an objective evaluation. Although the protocol was kept constant in this study, some degree of influence from environmental factors cannot be ruled out[14]. Using the luminance ratio, the influence of environmental factors is reduced; in this way it was possible to discriminate the individual oral diseases from each other. SCC has been reported to show intratumoural heterogeneity[18]. The SD of luminance and coefficient of variation of luminance were significantly higher in SCC cases than in benign lesions[14]. Each objective evaluation showed significant results, suggesting their effectiveness. Semi-quantitative methods can eliminate differences between institutions and can facilitate more uniform medical treatment.

The Oral Cancer Navigation System (Navi-System) was introduced into the Department of Oral and Maxillofacial Surgery of Tokyo Dental College, Japan in 2012. The Navi-System allows medical cooperation via the Internet[19]. Also, in recent years, many reports have described the potential application of artificial intelligence (AI) across the medical fields[20]. We are considering next-generation oral cancer screening with medical AI by accumulating cases and using objective evaluations in the future.

This study revealed the utility of subjective and objective evaluations in oral cancer screening using an optical instrument. Oral cancer screening using an optical instrument can effectively facilitate the early detection of SCC and OED. By adding an optical instrument to the Navi-System, we believe that high-quality medical AI can be established for an oral cancer screening system.

Funding

Competing interests

Ethical approval

This study was approved by the Ethics Committee of Tokyo Dental College (authorization number 740).

Patient consent

Consent was obtained from all participants in this study.

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