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Small form factor, flexible, dual-modality handheld probe for smartphone-based, point-of-care oral and oropharyngeal cancer screening

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Abstract. Oral cancer is a growing health issue in low- and middle-income countries due to betel quid, tobacco, and alcohol use and in younger populations of middle- and high-income communities due to the prevalence of human papillomavirus. The described point-of-care, smartphone-based intraoral probe enables autofluorescence imaging and polarized white light imaging in a compact geometry through the use of a USB-connected camera module. The small size and flexible imaging head improves on previous intraoral probe designs and allows imaging the cheek pockets, tonsils, and base of tongue, the areas of greatest risk for both causes of oral cancer. Cloud-based remote specialist and convolutional neural network clinical diagnosis allow for both remote community and home use. The device is characterized and preliminary field-testing data are shared. © The Authors. Published by SPIE under a Creative Commons Attribution 4.0 Unported License. Distribution or reproduction of this work in whole or in part requires full attribution of the original publication, including its DOI. [DOI: 10.1117/1.JBO.24.10.106003]

Keywords: autofluorescence imaging; mobile health; oral cancer screening; biomedical imaging.

1 Introduction

Oral cancer incidence and death rates are an ongoing concern in low- and middle-income countries (LMICs). LMICs suffer the majority of worldwide new cancer cases and deaths along with <50% five-year survival rates in some locations. The major risk factor for oral squamous cell carcinoma and oral submucous fibrosis in many LMICs is betel quid chewing, with or without the inclusion of tobacco. Furthermore, oral and oropharyngeal cancers are increasing in younger populations (especially men) in middle- to high-income communities (MHICs) due to the spread of human papillomavirus (HPV), mostly affecting the tonsils and base of the tongue (BOT).

Conventional oral examinations (COEs) provide a high specificity for visible lesions. However, lesions can be at an advanced stage before they are visible. Additionally, with higher incidence rates deep in the oral cavity and in oropharyngeal regions, accessibility can be an issue for a COE. Autofluorescence imaging (AFI) has the potential to be an important tool in the detection of oral and oropharyngeal cancer. Auto-fluorescence imaging and polarized white light imaging (PWLI) handheld probe utilizing a commercially available camera module (OV5648, Omnivision, Santa Clara, California), connected by USB to an LG G4 smartphone (LG, Seoul, South Korea) for low-cost, point-of-care oral, and oropharyngeal cancer screening (Fig. 1).

The 3D-printed probe housing of VeroBlackPlus (Stratasys, Eden Prairie, Minnesota) provides mounting for the camera, camera printed circuit board (PCB), illumination LEDs, filters, polarizers, and wiring while also integrating a 25-mm-diameter handle and flexible section near the imaging head. The 135.5-mm usable probe length allows access to the BOT and oropharynx while the 14.4 mm × 8.4 mm probe cross-section maintains patient comfort during imaging tasks. Significantly, the 24-mm flexible silicone (Mold Star 20T and Black Silc Pig, Smooth-On, Macungie, Pennsylvania) section provides up to 470% elongation before break, bending up to 45 deg in either direction (Fig. 1) to better access all areas of the oral cavity. A 250-µm thick, 11-mm wide piece of aluminum sheet metal embedded in the flexible section is a ductile core to the silicone elastomer, maintaining the probe head angle after bending to the desired position. The aluminum sheet keeps the two sections of the probe cross-section maintains patient comfort during imaging tasks.
probes attached with notches to capture the screws joining the two halves of the probe head clamshell while also serving as a thermal sink for the illumination LEDs. To ensure the elastomer stretches with the probe as it is bent and does not pull away from the seams of the 3D-printed plastic/silicone interface (keeping the electronics from being exposed), the silicone overlaps the 3D-printed plastic a minimum of 5 mm and maximum of 11 mm on each end, and 750-μm vertical capture features in the plastic embed into the silicone. The interface is further reinforced with Dow Corning 700 (DowDuPont, Midland, Michigan) silicone adhesive. Creating the silicone section is the last assembly step; the 3D-printed mold is clamped around the two probe halves and the silicone injected through the vents. Opposing vents in the mold reduce air pockets in the final cured silicone shape. The various features and components of the aluminum stiffener, flexible section, and silicone mold are shown in Fig. 2.

Illumination for PWLI and AFI is accomplished with two white (4000 K) and four violet (400 nm) LEDs (Lumileds, Amsterdam, Netherlands), respectively. The LEDs are mounted on an annulus of flexible, polyimide PCB, surrounding the camera module in a plane-symmetric pattern to maximize illumination uniformity without the use of additional optical components. The PCB is filled with large copper planes to increase heat transfer while the backside copper is exposed and attached to the aluminum stiffener with an electrically insulating, thermally conductive epoxy (DP240, 3M, St. Paul, Minnesota). To enable AFI, a 425-nm shortpass excitation filter (Asahi Spectra, Tokyo, Japan) is installed in front of the violet LEDs and a complementary 470-nm longpass emission filter (Asahi Spectra) is installed in front of the camera module.

The fixed emission filter in the imaging channel distorts the color space during WLI and is corrected by applying the transformation matrix calculated using a standard 24-color color checker (X-Rite, Grand Rapids, Michigan).

\[
A = \begin{bmatrix}
0.6198 & 0.0568 & -0.0957 \\
-0.0872 & 0.9391 & -0.1073 \\
0.0692 & 0.3618 & 0.0699
\end{bmatrix}
\]  

(1)

The stray light aperture prevents unfiltered scatter from the edges of the excitation filter to reach the tissue plane. Orthogonal linear polarizers (Edmund Optics, Barrington, New Jersey) in front of the white LEDs and the camera module enable PWLI. The thermally sensitive film polarizer is positioned at a distance from the LED emission surface by a 1-mm-thick PMMA window.

The USB-connected camera module integrates an image sensor (5 MP, 3673.6 μm × 2738.4 μm), a 1.1 mm focal length imaging lens, and control circuitry on a rigid-flex PCB with the image sensor and lens mounted on the end of the 30-mm-long
flexible cable. The long flex PCB cable is embedded in the silicone section of the probe, with the rigid portion of the PCB containing driving and readout circuitry in the nonmoving section. The vendor-supplied lens focal length is calculated from the maximum chief ray angle (29 deg) and the sensor diagonal (4.6 mm) provided in the sensor module datasheet. The lens is installed in a threaded barrel and the position adjusted to provide a working distance of 20 mm, providing a cropped field of view (FOV) of 15 mm × 20 mm.

The probe is compatible with the previously reported 3D-printed structure for mounting of the smartphone, LED driving electronics, and whole-cavity imaging module. Additionally, the system maintains the custom Android application for image capture, processing algorithms, cloud server data upload, convolutional neural network (CNN) classification, and web browser remote diagnosis features of the previously reported system.9,11

During patient testing, the probe is covered with a hygienic sleeve (TIDI Products, Neenah, Wisconsin).

3 Methods

To characterize the imaging system performance, the FOV and cutoff frequency were measured by imaging a 1951 USAF resolution test chart, and a slanted edge test12,13 was used to compare the actual on-axis modulation transfer function (MTF) to the theoretical calculated from the image sensor pixel pitch and lens magnification.

Uniformity and leakage were evaluated to benchmark the illumination system. Illumination uniformity was quantified using the coefficient of variation

\[
\text{uniformity} = 1 - c_x = 1 - \frac{\sigma}{\bar{x}}, \quad (2)
\]

where \(\sigma\) is the standard deviation and \(\bar{x}\) is the mean of the gray-scale pixel values when imaging a 50% neutral value matte card (Munsell, Grand Rapids, Michigan). Illumination leakage was measured by imaging a mirror under violet illumination and measuring the returned signal on each color channel relative to the maximum possible signal for the channel

\[
\text{leakage} = \frac{\sum_{i=0}^{N-1} x_i}{255N}, \quad (3)
\]

where \(x_i\) is the pixel value and \(N\) is the number of pixel in the channel.

The maximum permissible exposure (MPE) of the AFI and PWLI illumination was calculated according to the International Electrotechnical Commission 60825-1:2014.14 Since the AFI LED bandwidth has power in two wavelength regions (315 to 400 nm and 400 to 700 nm), the most stringent limit is applied. With an exposure time of 0.8 s, MPE is calculated as

\[
\text{MPE} = C_1 \text{ J m}^{-2} = 5.6 \times 10^{3} f^{0.25} \text{ J m}^{-2} = 5296 \text{ J m}^{-2}. \quad (4)
\]

With the following assumptions (a) LED power run at 90% of maximum 675 mW, (b) emission area of 1 mm², (c) emission duration of 800 ms, (d) Lambertian emission, (e) the closest tissues could be to the emission plane is 1.5 mm, and (f) skin aperture diameter is 3.5 mm. The flux transfer from an LED to tissue given the correct configuration factor is15

\[
\Phi_{\text{tissue}} = \Phi_{\text{LED}} F = \Phi_{\text{LED}} \frac{1}{2} \left[ X - \left( X^2 - 4 \frac{R_1^2}{R_2^2} \right)^{1/2} \right] \]

\[
= 0.0065 \text{ W}, \quad (5)
\]

where \(R_1 = r_1/d\), the radius of the emitter divided by the distance between the two planes; \(R_2 = r_2/d\), the radius of the tissue plane divided by the distance between the two planes; and \(X = 1 + (1 + R_2^2)/R_1^2\), corresponding to an exposure of 541 J m⁻², safely below the MPE. The white LEDs output is also below the MPE as they have a similar exposure to the violet LEDs but are run at 10% of maximum power and have a higher limit due to the wavelength band.

A pilot human subjects study is currently being performed to demonstrate the capability of the hardware to reach oral and oropharyngeal sites and the feasibility of using CNN classification algorithms. This study is institutional review board approved by Mazumdar Shaw Cancer Centre (NNH/MEC-CL-2016-394), University of California, Irvine (HS#2002-2805), and Rowssell Park Comprehensive Cancer Centre (I 49117). For this study, all subjects provided informed written and oral consent before testing. The workflow for testing the handheld probe was reported previously.9 The patients first have a conventional oral exam, and then the smartphone-based exam is administered. WLI and PWLI are collected with the whole cavity module9 and with the handheld probe. With the probe, both the lesion area and the normal contralateral area are imaged to provide additional data for the CNN. After testing, the images are uploaded either to an internal electronic health record system or to the cloud for remote specialist review and classification by the CNN.

To provide further visual information to the diagnosing specialist, additional images are created from the AFI. Fluorescence loss can be visualized from a luminance map where the green channel mean is subtracted from the green channel

\[
f = I_G - \bar{I}_G, \quad (6)
\]

and a red/green ratio map16,17

\[
f = \frac{I_R}{I_G} \quad (7)
\]

can signal additional areas of concern. The CNN uses both the relative green luminance information and the red/green ratio in its analysis.

4 Results

Figure 3 shows the FOV of the system and a zoomed view to show group 4–3 of the resolution target is resolvable, a spatial frequency of 20.16 lp/mm. This result matches the calculated MTF from the slanted edge test in Fig. 3, where the estimated cutoff frequency of 25 lp/mm results in a calculated image space numerical aperture of NA = 0.007. The resulting depth of field is18

\[
\frac{L_o f D}{f D - L_o B} - \frac{L_o f D}{f D + L_o B} \approx 12.5 \text{ mm}, \quad (8)
\]

where \(L_o\) is the nominal object plane (≈20 mm), \(f\) is the focal length of the lens (4.1 mm), \(D\) is the entrance pupil diameter (0.073 mm), and \(B\) is the blur diameter chosen to be three pixels (4.2 μm).

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Illumination uniformity was measured to be 83.80% for white light illumination and 89.84% for violet light illumination. Leakage was measured as 14.01%, 13.00%, and 28.97% for the red, green, and blue channels, respectively.

Oral and oropharyngeal images demonstrating the ability of the handheld probe to capture AFI and PWLI at the BOT and oropharynx with the maps created from Eqs. (6) and (7) are shown in Figs. 4 and 5. Figure 4 shows AFI and PWLI along with the maps created from Eqs. (6) and (7) for normal and OSCC clinical diagnoses. Figure 5 demonstrates the ability to capture AFI and PWLI at the BOT and oropharynx, areas of increased cancer risk from HPV. For these sets of images, the upper limit of the dynamic range of the fluorescence loss images of column c in Figs. 4 and 5 has been deliberately limited for better visualization of low fluorescence (low luminance) regions. Regions of high luminance in the red-to-green ratio images of column d indicate possible cancerous conditions. The pixelated regions in the corners of some of the red-to-green ratio images are artifacts of small number division.

5 Discussion

AFI with excitation at $\approx 405 \text{ nm}$ along with PWLI is a promising modality for low-cost, low-complexity devices to increase detection rates and provide earlier detection of oral and oropharyngeal cancer. Here, decreased fluorescence signal at $\approx 500 \text{ nm}$ indicates increasing dysplasia while increased signal at $\approx 635 \text{ nm}$ can serve as an additional indicator. The necessary excitation wavelengths now have readily available LED sources.
at increasingly lower cost and the resulting autofluorescence emission spectrum peaks are easily detectable by a smartphone camera.

This new intraoral probe provides marked improvements in geometry to increase access to the significant oral and oropharyngeal cancer sites compared to other AFI devices. Table 1 highlights the differences in form-factor, features, and capabilities between this intraoral probe, our previous device,9 and two commercially available AFI devices, the VELscope™22 (Apteryx Imaging, Akron, Ohio) and the Identifi®23 (StarDental, Lancaster, Pennsylvania).

The new probe has increased its usable intraoral length by ≃20 mm over our previous device while decreasing the maximum cross-sectional area by over 80%. Removing the requirement to use the smartphone camera for imaging enables a smaller and lighter system by eliminating the design constraints, bulk, and cost of a long-track-length, well-aligned optical system. These geometry differences are visualized in Fig. 6. The drastic reduction in cross-sectional area along with the flexible joint enables better accommodation of the oral cavity’s and oropharynx’s contours, leading to the consistent ability to image the BOT and tonsils. The previous device’s length and size were insufficient to reach the BOT, and its inflexible imaging head was unable to orient for imaging the tonsils. While the VELscope™ is not an intraoral device, its geometry and long working distance does allow for imaging some oropharyngeal

Table 1  Comparison of AFI device features and specifications.

| Parameter                                    | This work | Uthoff 20189 | VELscope™ | Identifi® |
|----------------------------------------------|-----------|--------------|-----------|-----------|
| Usable intraoral length                      | 135.5 mm  | 116.6 mm     | Not intraoral | Similar to this work |
| Minimum intraoral cross-sectional area       | 113.1 mm² | 369.5 mm²    | Not intraoral | Similar to this work |
| Maximum intraoral cross-sectional area       | 116.5 mm² | 594.0 mm²    | Not intraoral | Similar to this work |
| Working distance                             | 20 mm     | 10 mm        | 80 mm      | No camera |
| Depth of field                               | 12.5 mm   | 0.6 mm       | >20 mm     | No camera |
| FOV area                                     | 300 mm²   | 247 mm²      | 1257 mm²   | No camera |
| Flexible joint                               | Yes       | No           | Not intraoral | Mirror |
| Accesses BOT                                 | Yes       | No           | No         | Maybe    |
| Accesses tonsils and posterior pharynx       | Yes       | No           | Yes        | Maybe    |
| Native image capture, processing, transmission | Yes     | Yes         | W/peripheral | No       |
| AFI                                          | Yes       | Yes         | Yes        | Yes      |
| PWLI                                         | Yes       | WLI         | No         | WLI      |
| Green-amber imaging                          | No        | No          | No         | Yes      |
its greatly reduced intraoral dimensions. From images, the size of the Identifi® is estimated to be similar to this work’s probe.

The illumination uniformity is decreased compared to the previous probe due to fewer LED sources but still maintains a high uniformity approaching 90%. Leakage data were only available for the current device measuring under 15% for both the red and green channels, the channels of interest (the blue channel is discarded), an area for improvement.

The new probe integrates a full feature set of AFI, PWLI and native image capture, processing, and transmission, giving it a high size-to-feature ratio compared to the other devices. Additionally, the new form-factor is derived from commercially successful intraoral imaging devices, such as the CS1500 (Carestream Dental, Atlanta, Georgia) and Claris i5HD (SOTA Imaging, Orange, California), suggesting improved ergonomics for both the clinician and patient.

Future improvements should include decreasing leakage from the AFI illumination. Additional improvements could include a custom designed lens system to increase the FOV and optimization of the working distance based on doctor use and patient comfort feedback. A sample optical design meeting these criteria is shown in Fig. 7 with the optical prescription provided in Table 2. Here, the angular full FOV has been increased to 120 deg along the diagonal, resulting in a spatial FOV of 45.3 mm × 33.7 mm with increased optical performance as measured by MTF compared to the USB camera lens. The increased FOV would allow remote specialists to more easily orient themselves when analyzing images outside of the clinical setting. The design utilizes a single achromat with an object space NA = 0.0035, image space NA = 0.023, providing a 9.4-mm depth of field where the focal length f = 1.875 mm and the entrance pupil diameter D = 0.165 mm. This large depth of field is critical for reducing the number of out-of-focus images from hand movement during image capture.

The sag of the aspheric surfaces is defined by

$$z = \frac{cr^2}{1 + \sqrt{1 - (1 + k)c^2r^2}} + \alpha_2r^4,$$

where r is the radial distance from the optical axis, c is the surface curvature (1/R), k is the conic constant, and \(\alpha_2\) defines the polynomial coefficients. Specifying plastic lenses (OKP4HT, Osaka Gas Chemicals, Osaka, Japan; E48R, Zeon, Tokyo, Japan) allows for molding technologies to achieve low-cost parts even with aspheric surfaces.

![Fig. 6 Comparison of mechanical outlines for (a) the probe proposed in this paper and (b) the previously published probe demonstrating its greatly reduced intraoral dimensions.](image)

![Fig. 7 Optical design for a 120-deg full FOV, image space NA = 0.023 lens with increased MTF performance compared to Fig. 3. (a) The layout of the optical design with dimensions; (b) provides the theoretical MTF performance.](image)
With the small camera modules, there is opportunity to include two camera modules in the head, one camera with a wide FOV, low NA lens and the other with a high NA lens and narrow FOV, providing wide FOV imaging and high-resolution imaging at the same time. For high-resolution imaging, a camera module with autofocus capability would be preferred. Alternatively, the same lens could be used for both cameras to enable 3-D spectroscopic imaging.

Additionally, the ability to 3D-print the flexible area along with the plastic would greatly decrease assembly time. This was attempted with Stratasy's Tango material along with VeroBlackPlus but the Tango’s elongation at break of only \( \approx 200\% \) was not sufficient as the interface tore after only a few bending cycles. New 3D-printing materials could enable this change in the future.

Lastly, with an exposure time of 250 ms, motion of the probe during image capture affects quality. Usability could be improved by the addition of a camera control button on the probe handle so the clinician could prompt image capture from the probe, as well as the smartphone. In addition, since the LEDs are run at 10% of the emission limit, an increase in LED power and a corresponding decrease in camera exposure time would further limit blur in the images.

6 Conclusion

We have demonstrated a compact, dual-modality imaging device with a flexible head to enable good quality AFI and PWLI in oral (cheek pockets) and oropharyngeal (tonsils and BOT) areas with high cancer incidence rates from betel quid chewing and HPV but more difficult to access with conventional aided or unaided visual examinations, leading to earlier detection and diagnosis of precancerous or cancerous conditions. Advances in high-power, low-cost light sources, 3D-printing, and low-cost smartphones are instrumental to the creation of simple AFI and PWLI prototype devices for oral and oropharyngeal cancer screening in LMICs and MICs. USB-connected cameras remove design constraints related to using the smartphone’s camera allowing better ergonomics for the clinician and increased comfort for the patient, a system better able to address the imaging need while keeping the desirable functions and portability of the smartphone.

7 Supplementary Material

The design files for the LED driver have been released on GitHub under the GPL-3.0 license.25,26

Disclosures

The authors have declared that no competing interests exist.

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