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Usability of a smartphone-compatible, confocal micro-endoscope for cervical cancer screening in resource-limited settings

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Abstract

Background More efficient methods to detect and treat precancerous lesions of the cervix at a single visit, such as low-cost confocal microscopy, could improve early diagnosis and hence outcomes. We piloted a prototype smartphone-compatible confocal micro-endoscope (SCME) among women presenting to a public cervical cancer screening clinic in Kampala, Uganda. We describe the piloting of the SCME device at an urban clinic used by lower cadre staff.

Methods We screened women aged 18 and 60 years, who presented for cervical cancer screening at the Kawempe National Referral Hospital Kampala, and evaluated the experience of their providers (nurses). Nurses received a 2-day training by the study doctors on how to use the SCME, which was added to the standard Visual Inspection with Acetic acid (VIA)-based cervical cancer screening. The SCME was used to take colposcopy images before and after VIA at positions 12 and 6 O'clock if VIA negative, and on precancer-suspicious lesions if VIA positive. We used questionnaires to assess the women's experiences after screening, and the experience of the nurses who operated the SCME.

Results Between November 2021 and July 2022, we screened 291 women with a median age of 36 years and 65.7% were HIV positive. Of the women screened, 146 were eligible for VIA, 123 were screened with the SCME, and we obtained confocal images from 103 women. Of those screened with the SCME, 60% found it comfortable and 81% were willing to screen again with it. Confocal images from 79% of the women showed distinguishable cellular features, while images from the remaining 21% were challenging to analyze. Nurses reported a mean score of 85% regarding the SCME's usefulness to their work, 71% regarding their satisfaction and willingness to use it again, 63% in terms of ease of use, and 57% concerning the ease of learning how to operate the SCME.

Conclusion Our findings demonstrate the feasibility of using the SCME by lower cadre staff in low-resource settings to aid diagnosis of precancerous lesions. However, more work is needed to make it easier for providers to learn how to operate the SCME and capture high-quality confocal images.

Keywords Cervical cancer, Confocal microscopy, Task shifting, Mobile health, User experience, Nurses

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Introduction

Cervical cancer is a significant global health concern, especially in Eastern Africa, where it is the leading cause of cancer-related deaths among women [1]. Mortality after a cervical cancer diagnosis in East Africa is about 10 times higher (28.6 deaths per 100,000 women), than in the U.S. (2.1 per 100,000 women) [1]. In Uganda, 5-year survival after diagnosis of cervical cancer is only 18% [2]. This high mortality can be largely attributed to late presentation since 80% of the women are diagnosed with advanced-stage disease (stage III and IV), which is associated with poor survival [2]. Screening (cytology-based via PAP-smear) combined with treatment of cervical precancer or early-stage cancer has been credited for substantially reducing mortality and morbidity from cervical cancer in resource-rich settings [3, 4]. Conversely in resource-poor settings, however, cytology-based screening is challenging and has not achieved the desired results regarding cervical cancer control [5]. The lack of functional systems with relevant histopathology infrastructure and personnel has made it difficult to use a cytology-based approach. First, the lack of experts, space and ancillary equipment makes women unable to provide samples [6]. Secondly, upon collection, the long turnaround times for results, and the subjective reads lead to loss to follow-up, erroneous results, failed conclusion of diagnosis, and eventually discourage women from seeking routine screening [5, 6].

The 'screen-and-treat' approach using visual inspection with acetic acid (VIA) was adopted in Uganda in 2010 to screen women for precancerous lesions [7]. However, VIA is largely user dependent; is not reproducible, lacks reliable quality control, and has variable sensitivity and specificity [8, 9]. World Health Organization (WHO) therefore currently recommends screening by testing for human papilloma virus (HPV) where feasible [10]. While the HPV test is very sensitive for the presence of oncogenic HPV, [11]. HPV testing alone has very low specificity for the presence of pre-cancerous or cancer states. Using it as the basis of screen-and-treat results in over-treatment [11]. An ideal screening test for cervical pre-cancer in resource-poor settings should therefore have high sensitivity and specificity to minimize false negatives and false positives and resolve the current diagnostic challenges while minimizing costs to both the woman and the health system. Ideally, this test should be a point-of-care test, that can be used by lower cadres staff to screen women and return results the same day to enable prompt treatment [12].

Confocal microscopy, which generates high-resolution images of human tissues in vivo, [13]. could address the challenges above. High-resolution in-vivo microscopy of cellular changes on the cervix provides an opportunity for same-day diagnosis and treatment of women with precancerous lesions. Several studies have shown that confocal microscopy can diagnose cervical pre-cancer with high sensitivity (93–100%) and specificity (93–100%) [14–16]. However, the high cost of these devices, more than $ 50,000, makes it challenging to adopt confocal microscopy in low-resource settings [17]. High-resolution optical coherence tomography (OCT) can provide cross-sectional images of cervical epithelia. Previous studies showed that high-resolution OCT can diagnose cervical pre-cancer with high sensitivity (80–87%) and specificity (89–94%) [18, 19]. However, expensive lasers need to be used in high-resolution OCT, which makes the device as costly as confocal microscopy devices. Low-cost alternatives to confocal microscopy like high-resolution micro-endoscopy (HRME) have shown promising sensitivity of 84–97% and specificity of 54–74%,[20, 21] but they have been reported to face challenges when imaging tissues with high nuclear density due to the lack of confocal optical sectioning capability [22]. These existing challenges with in-vivo microscopy devices show the need to continue developing devices that are affordable and practical for use in low-resource settings where they are needed the most.

Recently, we developed an affordable smartphone-compatible confocal micro-endoscope (SCME) that could visualize cellular details from cross-sections of the tissue in vivo down to the tissue depth of 100 μm of the human epithelium [17]. The SCME has a compact design and is operated from a smartphone which is familiar to many in low-income settings [17]. The SCME is advantageous over standard confocal microscopy and high-resolution OCT devices in terms of low device cost and portability. The SCME's cross-sectional imaging approach with the confocal optical sectioning capability can be useful for examining nuclear features over tissue depth and evaluating epithelial maturation, one of the key histomorphologic aspects when diagnosing high-grade squamous intraepithelial lesion (HSIL). This technology is new and untested in the hands of providers, especially in low-resource settings where the need for such technology is highest. We piloted the use of the low-cost SCME device to detect cervical neoplasia among women screening for cervical cancer at a public facility and report usability, and feasibility of image capture lower cadre staff who typically run cervical cancer screening clinics in low-resource settings.

Methods

Overall design

We conducted a cross-sectional study among adult women (18 to 60 years) attending the Kawempe National Referral Hospital (KNRH) cervical cancer screening and colposcopy clinic in Kampala, Uganda. The KNRH is a government-owned referral health facility, offering

specialized obstetric, gynecologic, and pediatric services to women and children from various parts of the country, especially the urban and peri-urban districts of central Uganda. The cervical cancer screening and colposcopy clinic at KNRH is a high-volume clinic with an average attendance of about 25 to 30 women per day, 5 days a week. The clinic is run by registered nurses who are supervised by gynecologists. During the study period, approximately 3200 women received services from this clinic. All services at this clinic are provided at no cost to patients. The standard of care in this setting is to use HPV testing as the first option for cervical cancer screening. However, VIA is recommended in case HPV testing is not available, or if the risk of loss to follow up is high. For women where the squamocolumnar junction (SCJ) is not visible, the guidelines recommend using a pap smear test. After screening, women with a positive HPV test need to undergo VIA to assess eligibility for ablative therapy or Loop Electrosurgical Excision Procedure (LEEP). Women suspected to have cancer at the time of the VIA procedure will get a biopsy done and sent for histology. For women with no visible SCJ, the PAP smear or endocervical curettage (ECC) results guide the mode of treatment. For this study, we used HPV COBAS 4800 test for HPV testing which was done at the Uganda Cancer Institute (UCI) laboratory.

Study population

During the study period, nurses invited women who were interested to take part in the study through routine health education talks. Given the high volume of work in the clinic, women were only invited to take part in the study on three out of the 5 days of the week. We used consecutive sampling, to identify between 5 and 7 potential study participants after a health education talk, each day the study was conducted. Specifically, we enrolled women aged between 18 and 60 years who presented to the clinic: (i) for routine screening, (ii) with symptoms suggestive of cervical cancer, (iii) with lesions suspicious for cervical cancer, and (iv) with an abnormal screening result (defined as a positive HPV DNA result or VIA test result). The exclusion criteria were women who had no cervix, were pregnant, reported never being sexually active, had known previous diagnosis or treatment for cervical cancer, and with previous history of treatment for cervical dysplasia in the last 12 months. Women enrolled into the study had one study visit (the enrolment visit). We contacted women after 2 weeks to notify them about their biopsy results and the need for further treatment/referral if required following the biopsy results.

Nurses who routinely participate in the cervical cancer screening and oncology clinic were considered as the providers. We included all the 4 nurses who regularly run the clinic as providers in this study. The 4 nurses had no prior experience with the SCME or any confocal device and they were all experienced in screening women and treatment of women with cervical precancerous lesions. These nurses underwent a 2-day training on how to use the SCME by the study doctors. The first day of training consisted of a theory session using videos to show how to connect, operate, disconnect, clean and store the SCME. On the second day, each nurse had a chance to connect, operate and disconnect the SCME for cleaning during a practical session. Thereafter, they had an initial supervised use of the device at which all the steps were clarified. There was no pre- or post-test assessment for the nurses but the study doctors were at hand to clarify on the operation of the SCME as needed.

Smartphone-compatible confocal microscope endoscope (SCME)

Details of the SCME device are described in a prior publication [17]. Briefly, the SCME has a diameter of 11 mm and length of 300 mm produced with a material cost of less than $1,500 (Fig. 1). It achieved a lateral resolution of 2 μm and axial resolution of 4 μm, sufficiently high for visualizing individual nuclei. Cross-sections of the tissue were imaged with the SCME with an imaging speed of 4 frames/sec and over an area of 468 μm (width) x 100 μm (depth), similar to the image width examined during standard histopathologic diagnosis. Image data from the SCME was transferred to a smartphone (Galaxy S8+, Samsung) via a standard USB cable. The smartphone was also used for acquiring colposcopy images in conjunction with magnifying optics composed of a telephoto lens and a planoconvex lens (focal length = 300 mm). Confocal and colposcopy images were displayed and stored in real-time using a custom smartphone app and uploaded for analysis by investigators outside the clinic. The smartphone colposcope provided the magnification of 8.4, visualizing the tissue area with the size of 47 mm x 35 mm, a sufficiently large image size to examine the entire cervix (Fig. 1c).

Confocal images were quantitatively analyzed using a custom algorithm developed in Matlab (Mathworks). For each confocal image, a background map was generated using a moving horizontal line with the width of 50 pixels. The horizontal line was used for the moving window because the background noise varied primarily along the vertical direction and each horizontal line shared a similar background level. Each confocal image was then background-subtracted, noise-reduced with a Gaussian filter with the kernel size of 3 pixels, and binarized for nuclei. The algorithm was tested for 186 manually-labeled nuclei in SCME images, and the accuracy of detecting manually-labeled nuclei was 83% (Fig. 2). The segmented nuclei were analyzed for intensity, density, area, nuclear-to-nuclear distance, and nuclear-to-cytoplasm ratio [23].

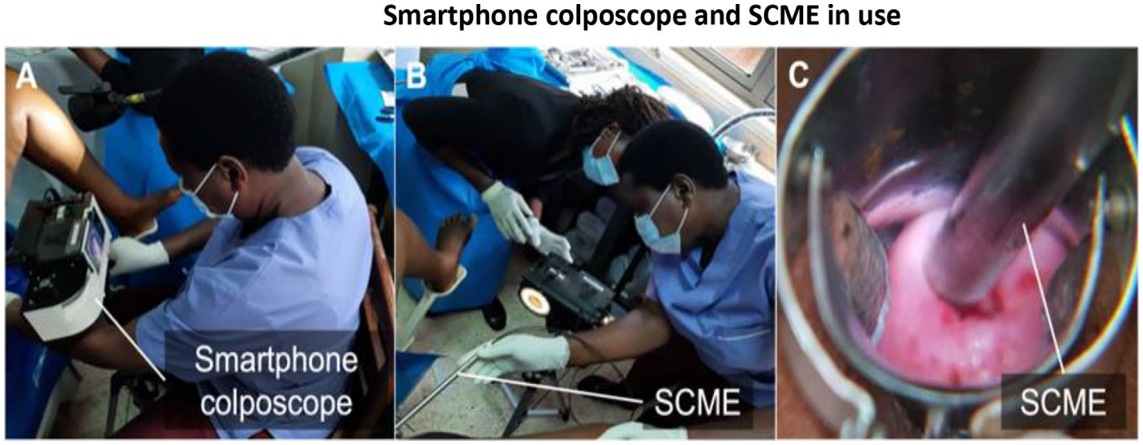

Fig. 1 Photos of the smartphone colposcope and SCME device used in clinic (**A**, **B**) and a representative smartphone colposcopy image showing SCME placed on the cervix (**C**)

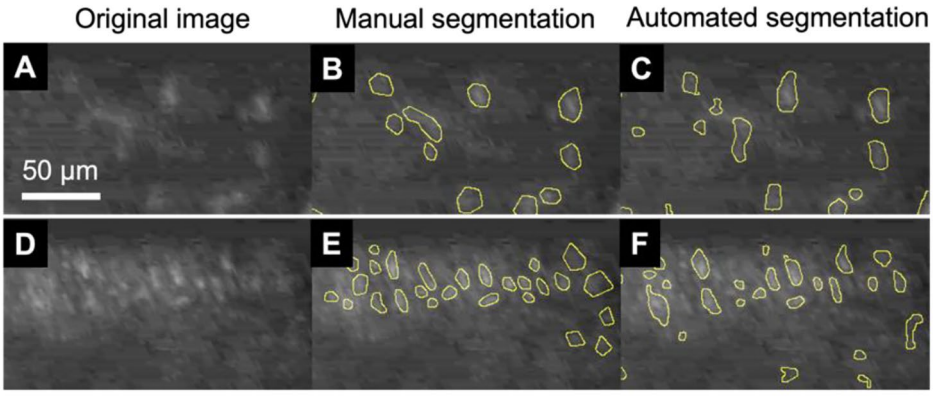

Fig. 2 Representative SCME images (**A**, **D**) and their manually-segmented images (**B**, **E**) and automatically-segmented images (**C**, **F**) for an image with low cell density (**A**, **B**, **C**) and high cell density (**D**, **E**, **F**)

Average of each morphologic feature and the slope of the line fitting the depth-vs-feature curve were calculated. Two-sample t-test was performed for each morphologic feature between high-grade squamous intraepithelial lesion (HSIL) and benign/low-grade squamous intraepithelial lesion (LSIL).

Diagnostic performance was evaluated in two different methods. First, a single feature was used to develop linear discriminator models. 5-fold cross validation was used, where the dataset was divided into 5 folds, with 4 folds used for training and 1-fold for validation. In order to compensate for the data imbalance (less HSIL images than benign/LSIL images), we used a custom optimization cost function that has proportionally larger weight on false negatives than false positives. For each model, a receiving operating characteristic (ROC) curve was generated, and the area under the curve (AUC) was calculated. Sensitivity and specificity were calculated on validation results with the operating point that balances well between sensitivity and specificity. Second, combinations of all or some of the features were evaluated with various classifier models (e.g., linear discriminators, support vector machines, logistic regressions). Models that produced small optimization cost values were further evaluated for AUC, sensitivity, and specificity.

Measurements

Eligible women, willing to participate provided written informed consent prior to the start of study procedures. We used a provider administered interview questionnaire to obtain the women's demographic information (age, education level, marital status), income, HIV status, history of cervical cancer symptoms and screening. All women without an HPV result had HPV testing done using COBAS 4800 at the UCI laboratory. Thereafter, women underwent a pelvic exam that included examination of the abdomen and external genitalia for any abnormalities, followed by a speculum exam to examine the vaginal vault and visualize the cervix. For women with a visible SCJ, colposcopy imaging was done before and after application of 5% acetic acid on the cervix (VIA) as per standard of care. Using the SCME, we obtained

confocal images from all women who underwent VIA. Confocal images were acquired at the 6 and 12 O'clock position of the cervix if VIA was negative. If VIA was positive, confocal imaging was done on the cervical lesions. We also collected colposcopy images of the cervix for these women using the smartphone colposcope (Fig. 1a). Images from the SCME were saved, downloaded from the device and stored in a secured cloud folder at the end of each day by the study team. Women had a biopsy done after confocal image capture. The biopsies were taken from the same tissue locations as the SCME imaging locations, 6 and 12 o'clock for VIA negatives and abnormal lesion sites for VIA positives. We also took colposcopy images before and after each biopsy to document the location where the biopsy was done. If a woman had no visible SCJ, suspicious lesion for cervical cancer, or if the cervix was difficult to visualize, we excluded her from the study and provided her with the standard of care treatment including a biopsy or cervical curettage as needed.

After the procedure, using a 5-point Likert Scale, we assessed the women's screening experience focusing on discomfort and pain, willingness to screen again, and level of satisfaction with the SCME (see additional file 1). We considered responses strongly agree and agree as agreement, neutral as neutral, while strongly disagree and disagree were rated as disagreement. After six months of operating the SCME, providers (nurses) had a user experience interview using a self-administered questionnaire (see additional file 2) that covered 4 domains: ease of use of the SCME, ease of learning how to use the SCME, adequacy/usefulness of the SCME to their screening work, and satisfaction or willingness to use the SCME during routine screening. The domains assessed in this interview were developed based on themes in a questionnaire from a study protocol that sought to validate a prototype double syringe [24]. We measured the responses for each domain using a Likert scale, and rated the responses as: - Strongly Agree=5, Agree=4, Neutral=3, disagree=2, Strongly disagree=1. The total ratings for each domain were obtained for each provider and we used the average score of all providers to determine the overall score for each domain. Using STATA 14 software we provide descriptive statistics for the socio-demographic characteristics of the population as well as those for women who had VIA and a biopsy done for histology.

Results

Description of the study population

Between November 2021 and July 2022, we invited and consented 291 women to participate in the study. The median age of the women was 36 (Interquartile range (IQR): 30, 45) years, and approximately half of them (51.9%) were married (Table 1). Most (45%) of the women had secondary level education and their median personal income per month was $67 (IQR: $40, $107) (Table 1). Majority of the women (65.7%) were HIV positive with a median number of 3 (IQR: 2,4) viable live births. Additionally, only 6 (2.1%) of the women enrolled had previously screened for cervical cancer (Table 1). Regarding HPV testing, of the 291 women we invited for screening assessment and consent, 142(49%) had a positive HPV result, 129 (44%) had a negative HPV result, results were missing for 4 (1%) women, sample failed to run for 8 (3%) women, and HPV was not done for 8 (3%) women (Fig. 3).

VIA and histology examination findings

Of the 291 women screened, 146 (50.2%) were originally eligible for VIA, and 144 (49.5%) were ineligible for various reasons shown in Fig. 3. The most common reason for ineligibility was the absence of the squamocolumnar junction (SCJ). As per the standard of care, these women had ECC done and samples taken for histology and the results were used to guide the choice of treatment. The two women who were ineligible for VIA because of pregnancy/ menses were advised to return for screening after pregnancy/menses. We performed a biopsy on the suspicious lesions and sent this for histology for the 38 women (Fig. 3) who had suspicious lesions on the cervix and were therefore, ineligible for VIA. The histology results were used to guide the treatment plan for these women. Finally, the HPV results were used to determine the management plan for the two women (Fig. 3) for whom we couldn't visualize the cervix. One woman (0.3%) was excluded from the study because she feared the speculum and declined to have a speculum exam (Fig. 3). We did not perform VIA for 7 women who were originally deemed eligible, because of suspicious lesions on the cervix (4 women), old cervical tear (1 woman), warts covering the cervical Os (1 woman) and cervical ectropion (1 woman). On examination with VIA, 61 women were VIA positive (Table 1). Almost half (48%) of the women who had a cervical biopsy done had LSIL (Table 2).

Women's experience with the SCME

Of the 146 VIA-eligible women, 124 (85%) had a screening attempt done with the SCME (Fig. 3). More than half (60%) of these women reported that they were comfortable screening with the SCME device (Table 3). Majority (85%), were satisfied with the care received when screened with the SCME (Table 3) and a similar proportion (85.1%) were willing to screen again with the SCME in future (Table 3). However, some (22.3%) of the women reported experiencing discomfort and 34% were intimidated by presence of the SCME during the procedure (Table 3).

Table 1 Characteristics of the study population

Variable	Total *N* = 291 *n* (%) or Median (IQR)	VIA Not Done *N* = 152† (%) *N* (%) or Median (IQR)	VIA Done *N* = 139*	
			VIA Negative *N* = 78 (%) *n* (%) or Median (IQR)	VIA positive *N* = 61(%) *n* (%) or Median (IQR)
Age categories				
18–30	87 (29.9)	34(22.4)	28(35.9)	25(41.0)
31–40	104 (35.7)	45(29.6)	34(43.6)	25(41.0)
41–49	75(25.8)	52(34.2)	16(20.5)	7(11.5)
50–60	25(8.6)	21(13.8)	0(0.0)	4(6.6)
Education (*N* = 280)*				
No formal education	12 (4.1)	7(4.6)	2(2.6)	3(4.9)
Primary level	112 (38.5)	63(41.5)	22(28.2)	27(44.3)
Secondary level	131 (45.0)	62(40.8)	44(56.4)	25(41.0)
Tertiary/University	25 (8.6)	16(10.5)	5(6.4)	4(6.6)
Marital Status (*N* = 280)*				
Never married	19 (6.5)	5(3.3)	8(10.3)	6(9.8)
Married	151 (51.9)	73(48.0)	41(52.6)	37(60.7)
Widowed	25 (8.6)	16(10.5)	6(7.7)	3(4.9)
Divorced	85 (29.2)	52(34.2)	20(25.6)	13(21.3)
Average personal income categories in USD (*N* = 204)*				
<$27	20 (9.8)	11(10.1)	8(15.7)	1(2.3)
$27–133	161 (78.9)	87(79.8)	38(74.5)	36(81.8)
$134–267	16 (7.8)	7(6.4)	5(9.8)	4(9.1)
$268–533	5 (2.5)	3(2.8)	0(0.0)	2(4.6)
$534–1333	2 (1.0)	1(0.9)	0(0.0)	1(2.3)
> $1334	0 (0.0)	0(0.0)	0(0.0)	0(0.0)
HIV status				
Negative	97 (33.3)	45(29.6)	36(46.2)	16(26.2))
Positive	187 (64.3)	105(69.1)	41(52.6)	41(67.2)
Unknown	7(2.4)	2(1.3)	1(1.3)	4(6.6)
Parity, median (IQR) (*N* = 287)*	3 (2,4)	3,(2,4)	2(2,4)	2(2,4)
Parity categories				
1–3	191 (66.6)	99(66.9)	54(69.2)	38(62.3)
4–5	73 (25.4)	37(25.0)	19(24.4)	17(27.9)
> 5	23 (8.0)	12(8.1)	5(6.4)	6(9.8)
Previous cervical cancer screening, Yes (*N* = 6)*	6(2.1)	3(2.0)	2(2.6)	1(1.6)

†*N* = 152 includes the 7 women who were originally eligible but never had got VIA and 1 woman who declined the speculum exam after consenting

* Missing values: Education and Marital status (*N* = 11, 3.8%), Average personal income (*N* = 87, 29.9%), Parity (*N* = 4,1.4%), and Previous cervical cancer screening (*N* = 285, 97.9%)

Confocal imaging

We successfully obtained confocal images from 103 (83%) of the 124 women (Fig. 3) whom the nurses attempted to image. Confocal images were not obtained in 17% of the women due to occasionally missed procedural steps (e.g., LED not turned on, USB not fully connected) or data communication issues. Among the 103 women with confocal images, 79% (81 cases) showed cellular features (Table 4). The main causes for not visualizing cellular features in 21% of the cases were (i) unstable contact between the confocal endoscope and cervix and (ii) slow imaging speed. Among the 81 cases with cellular details, 15% were diagnosed with HSIL per histology. Figure 4 shows representative confocal endoscopy, histologic, and smartphone colposcopic images for histology-confirmed benign and HSIL tissues. Epithelial cell nuclei are visualized as bright dots in confocal images (Fig. 4a, b). An automated image analysis method was used to identify and highlight nuclei with red (Fig. 4c, d). In the confocal images of the HSIL tissue (Fig. 4b, d), the nuclei were more numerous and larger than those shown in the benign tissue confocal images (Fig. 4a, c). A similar trend is shown in the corresponding histologic images (Fig. 4e, f). Both subjects were VIA negative (Fig. 4g, h) and HIV positive.

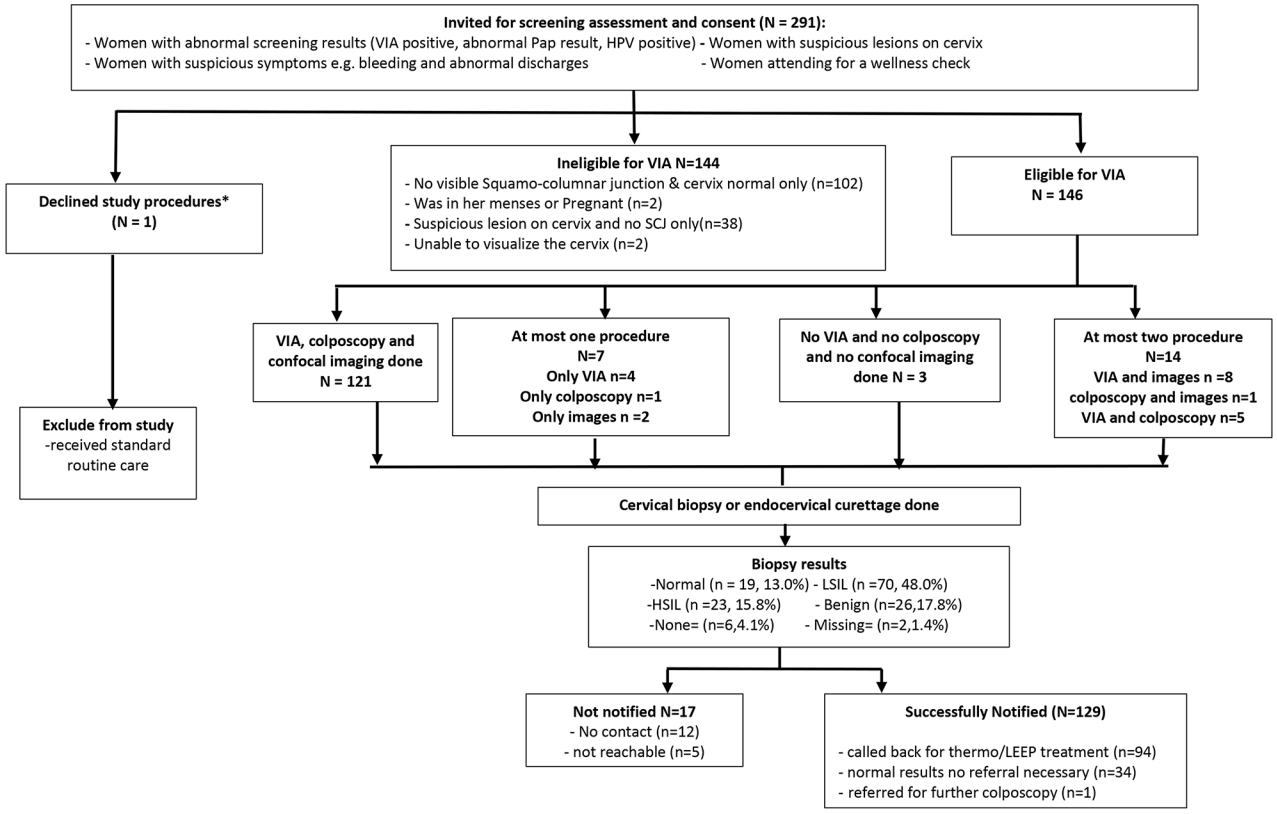

Fig. 3 Study flow diagram. *We invited all women who were interested to consent for the study, and gave them the option to withdraw from the study at any time. All the women accepted to participate and gave written consent. However, one woman later declined to have a speculum exam and did not continue with the subsequent study procedures

Table 2 Histology examination findings for women who had a cervical biopsy done

VIA status	Total *N* = 139 *n* (%)	VIA Negative *N* = 78 *N* (%)	VIA positive *N* = 61 *n* (%)
Normal histology *N* = 18	18(13.0)	13(16.7)	5(8.2)
Benign* *N* = 24	24(17.3)	14(18.0)	10(16.4)
LSIL *N* = 67	67(38.2)	35(44.9)	32(52.5)
HSIL *N* = 22	22(15.8)	10 (12.8)	12(19.7)
None/Missing *N* = 8		6(16.7)	2(3.3)

*Benign category included non-malignant histological findings such as cervical polyps, condyloma acuminatum, and reactive basal hyperplasia

(%) Percent stands for Column percentages

Table 3 Women's experiences screening with the confocal device

Experiences, *N* = 133	Agree *n*(%)	Neutral *n*(%)	Dis-agree *n*(%)
The procedure with the device was comfortable (*N* = 94) *	57(60.6)	25(26.6)	12(12.8)
The procedure with the device caused me some pain (*N* = 94) *	21(22.3)	36(38.3)	37(39.4)
I am satisfied with the care I received when I got screened with the device. (*N* = 93) †	79(85.0)	13(14.0)	1(1.1)
I was intimidated by the presence of the device during the procedure (*N* = 94) *	32(34.0)	23(24.5)	39(41.5)
I am willing to be screened again in future using the device (*N* = 94) *	80(85.1)	11(11.7)	3(3.2)

*:39(29.3) participants did not respond to the question

†:40 (30.8) participants did not respond to the question

Automated, quantitative analysis of morphometric parameters of the confocal images

The automatically-identified nuclei were further analyzed for various morphometric parameters. Among the nuclear features analyzed, average nuclear area, average intensity of nuclei, and estimated nuclear-to-cytoplasm ratio showed significant difference between HSIL and benign/LSIL (Fig. 5). The average nuclear area was significantly larger for HSIL, 35.6 μm [2], than benign/LSIL, 29.6 μm [2] (p=0.0014). A similar trend was previously reported for the average nuclear area measured from histology images, 41–50 μm [2] (HSIL) and 34–40 μm^2 (benign/LSIL) [23]. The average nuclear-to-cytoplasm ratio was higher for HSIL, 0.12, than benign/LSIL, 0.08 (p=0.016), which were also comparable to the values measured with a standard confocal microscope, 0.12 (HSIL) and 0.04 (benign/LSIL) [25]. The slope of these

Table 4 Confocal images quality analysis compared to the histology findings stratified by VIA status

	Cases with distinguishable cellular features *N* = 81 (79%)		Cases with non-distinguishable cellular features*** *N* = 22 (21%)*	
	VIA Negative *N*= (%)	VIA positive *N*= (%)	VIA Negative *N*= (%)	VIA positive *N*= (%)
Normal histology N= (%)	9(11)	3(4)	2(9)	2(9)
Benign N= (%)	11(14)	7(9)	1(5)	1(5)
LSIL N = (%)	19(23)	20(25)	4(18)	4(18)
HSIL N= (%)	6(7)	6(7)	3(14)	5(23)

* Distinguishable confocal images were not obtained due to occasionally missed procedural steps (e.g., LED not turned on, USB not fully connected) or data communication issues

features over depth was not different between HSIL and benign/LSIL (p=0.10, 0.06, and 0.51 for the area, intensity, and nuclear-to-cytoplasm ratio slopes, respectively). The AUC values were 0.80 for nuclear area, 0.71 for nuclear intensity, and 0.70 for nuclear-to-cytoplasm ratio. When the nuclear area of 33 µm [2] is used as the diagnostic threshold, the sensitivity was 83% (95% confidence interval (CI)=52–98%) and specificity 75% (95% CI=64–85%). Compared to the linear discriminator using nuclear area, classifier models using multiple features did not improve the diagnostic performance: the best performance with multi-feature classifiers was achieved with a logistic regression model using nuclear area and intensity, producing the AUC value of 0.74, sensitivity of 83% (95% CI=52–98%), and specificity of 71% (95% CI=59–81%). For the 81 cases with cellular details shown in confocal images, VIA sensitivity was 50% (95% CI=21–79%) and specificity was 57% (95% CI=44–68%).

Providers experience using the SCME

We interviewed all the 4 providers who had used the SCME for 6 months. The median age of the providers was 47 years and their average duration of service was 23 years. Three of the providers have diplomas in nursing and one has a degree in nursing. The mean scores of the nurses' experiences with the device was highest (85%) regarding its usefulness to their work and 71% in terms of their satisfaction and willingness to use the device (Table 5). The lowest rating of the SCME device was a mean of 57% in terms of ease of learning how to use it, and 63% regarding ease of use (Table 5).

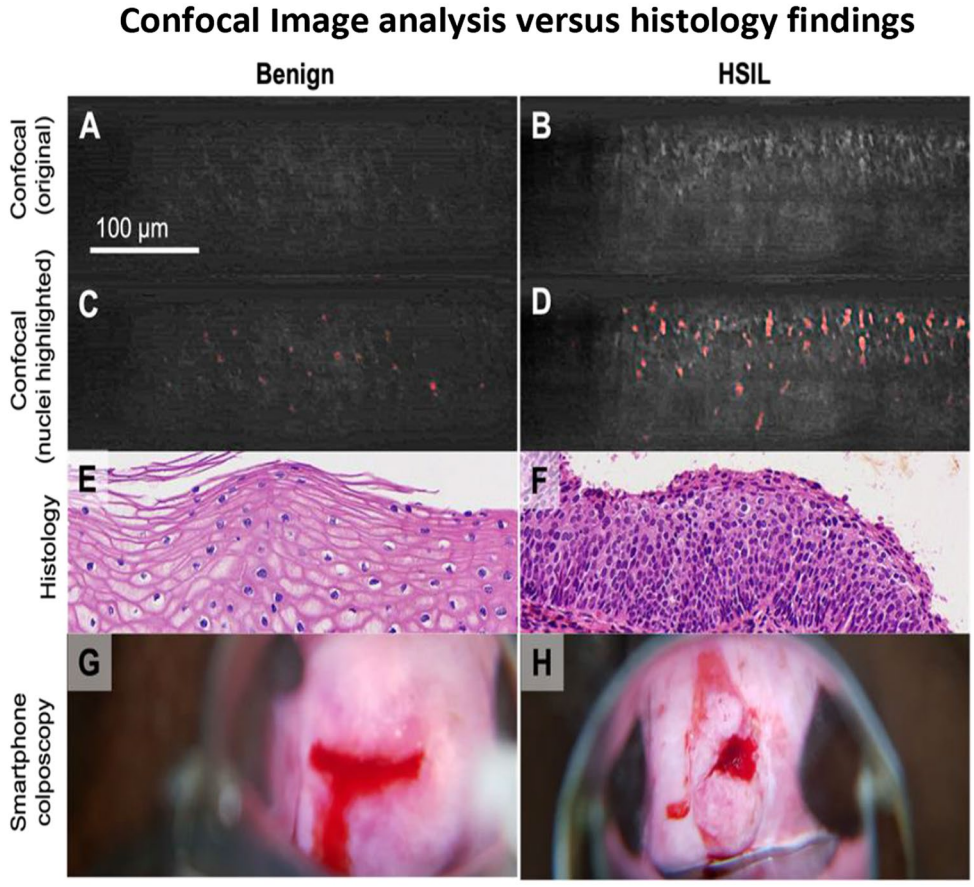

Fig. 4 Representative confocal endoscopy (A-D), histologic (E, F), and smartphone colposcopic (G, H) of benign (A, C,E, G) and HSIL (B, D,F, H) tissues

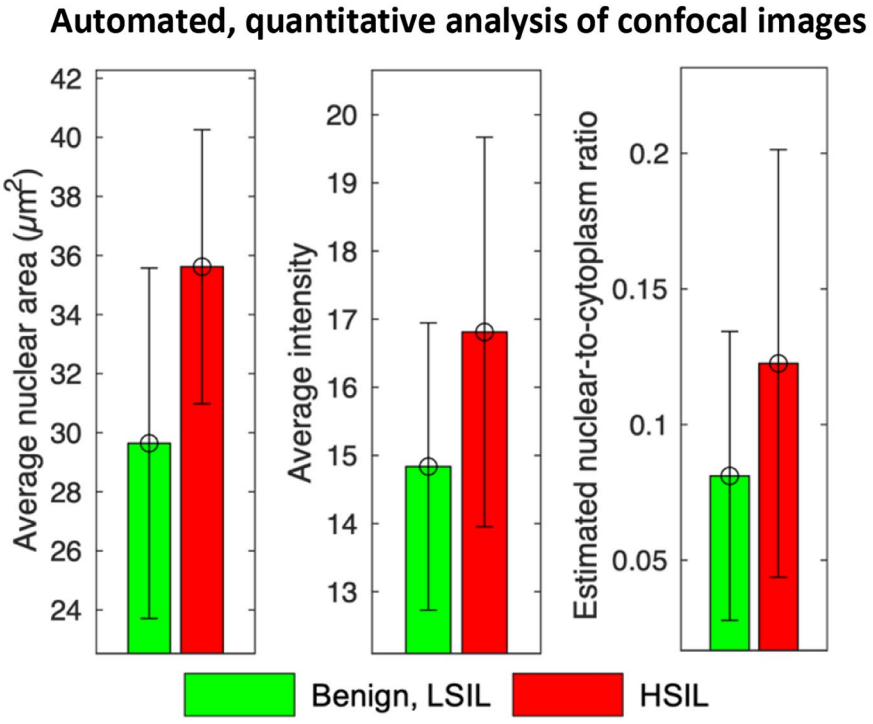

Fig. 5 Morphometric parameters of cell nuclei visualized in confocal images of benign/LSIL and HSIL tissues

Table 5 Provider's rating of their experience using the SCME

Provider	Ease of use of the SCME device	Ease of learning how to use the SCME device	Adequacy/Usefulness of the SCME device in my work	Satisfaction/ willingness to use the SCME device	Overall score
Provider 1	64%	4%	85%	80%	66%
Provider 2	51%	33%	95%	84%	59%
Provider 3	60%	67%	65%	52%	61%
Provider 4	74%	80%	95%	68%	77%
Mean	63%	57%	85%	71%	66%

Discussion

In a high-burden cervical cancer setting, with low screening rates, we successfully implemented the first real-world use of a low-cost SCME device to detect cervical neoplasia. This is the first time this novel imaging tool has been used by lower-cadre providers to screen women for cervical cancer. We found that most of the women were comfortable when screened with the SCME and were willing to be screened with it again in the future. We demonstrated that it is feasible for lower-cadre staff to use the SCME to obtain images that showed promising correlation with histology findings, the gold standard for the detection of cervical neoplasia. In addition, providers were willing to use the SCME in routine work and provided valuable feedback that could be used to further improve the operation of the device.

Women's experience with the SCME

Our findings showed that screening with the SCME was overall acceptable to the women as most found the procedures comfortable and they were willing to screen again with the SCME. However, some of the women reported experiencing discomfort during screening with the SCME. We took the SCME images after colposcopy and VIA and before cervical biopsies, using a probe that is placed in contact with the cervix (Fig. 1c). Some studies have reported pain and discomfort among women who had colposcopy and cervical biopsies [26, 27]. Considering that we interviewed women after colposcopy and all other screening procedures including the cervical biopsy, it is difficult to tell whether the pain and discomfort reported in our study was associated with the SCME, colposcopy, VIA or cervical biopsy. Unfortunately, other studies looking at the use of microscopic endoscopy devices in vivo for the detection of cervical precancerous lesions have also not reported on the patient's experiences [20, 28]. It is important that such a device causes

minimal discomfort since it should be used routinely and acceptability will be influenced by user experience. Therefore, future evaluations of the screening experience should consider this, to confirm if imaging with the SCME is indeed uncomfortable, and the discomfort graded. Since this was the first real-world clinical use of the of the SCME, the feedback from the women is valuable for improving the SCME design features, and the experience of the women should be explored more qualitatively and incorporated into designing similar devices.

Confocal imaging

The SCME demonstrated promising preliminary diagnostic performance (AUC value of 0.80, sensitivity of 83%, and specificity of 75%), albeit the small sample size. The sensitivity and specificity were higher than those of VIA for the same population but lower than those demonstrated by previous studies using confocal microscopy [14–16]. This indicates that the SCME might be potentially beneficial in addition to VIA, but it has not realized the high diagnostic performance that the study originally aimed to achieve. There were several challenges in the current SCME as discussed below.

The main challenges of the SCME device were low signal level and slow imaging speed. These challenges also made SCME images from 21% of the patients not analyzable for cellular details. The SCME image quality can be improved by using an imaging sensor with higher sensitivity and further optimizing the light efficiency of the device.

Another challenge was on assessing the quality of confocal images while maneuvering the SCME over the tissue. Our original plan was to have the nurse use the real-time confocal images to guide the device placement. This plan faced two challenges. First, the smartphone was positioned at a set distance away from the patient and facing the patient, to provide colposcopy images. This arrangement made it challenging for the nurse to be on the same side as the smartphone to view real-time confocal images. Second, the custom smartphone app acquiring confocal images lacked the functionality of assessing image quality in real-time. Future SCME devices can integrate both confocal imaging and colposcopy imaging capabilities into a single endoscopic device, which can facilitate easy and reliable maneuvering of the device [29].

About half of the total number of women screened had no visible SCJ which limited the application of VIA and consequently, the use of the SCME. These women who were ineligible for VIA were within the recommended age group for screening with VIA. A study in Peru showed a similar proportion of women not eligible for VIA because the SCJ was not visible [30]. Potential solutions to this limitation include acquisition of SCME videos while the SCME device is systemically maneuvered over a large area of the cervix and use of deep learning-based image analysis methods for guiding SCME to tissue regions with high probability of risk of having pre-cancer regardless of the visibility of SCJ [31–33].

While three nuclear features (area, intensity, nuclear-to-cytoplasm) showed statistically significant differences ($p<0.05$) between HSIL and benign/LSIL, there were noticeable overlaps for these features between HSIL and benign/LSIL as shown in Fig. 5. Potential causes of the overlaps include moderate-to-low signal levels (causing nuclei difficult to detect) and motion blurs (causing nuclei appear larger). In the future development, we will investigate if improving the image quality could reduce feature overlaps and subsequently improve the diagnostic performance.

We initially expected that the depth-dependent feature changes revealed in cross-sectional SCME images would be useful in distinguishing HSIL from benign/LSIL. However, we found that the features did not change significantly over the imaging depth of 100 μm. This could be because the depth-dependent nuclear changes are subtle in the imaging depth of 100 μm in HSIL or benign mucosa in the transition zone as shown in the histology images (Fig. 4E, F). The resolution and image quality of the SCME might not have been sufficient for examining these subtle changes. A recent study of imaging anal squamous intraepithelial lesions ex vivo with scattering light sheet microscopy also found that the nuclear features are more or less uniform in the superficial lesions [34]. The same scattering light sheet microscopy study, however, demonstrated high diagnostic performance (HSIL sensitivity=91%, specificity=85%), indicating that acquisition of cross-sectional microscopy images of epithelial tissues might be a viable direction for examining squamous intraepithelial lesions, if the images can be acquired with high quality.

The SCME image analysis was conducted post-operatively in this study. This was because the image analysis algorithm needed debugging and tuning to achieve optimal performance. In the future SCME device, the image analysis algorithm can be integrated as part of the smartphone application to provide real-time image analysis results. The image analysis results will include the nuclear morphologic features (nuclear area, intensity, nuclear-to-cytoplasm ratio) and the probability of pre-cancer. The clinician or nurse will then be able to use the SCME results along with other information (e.g. VIA findings) to make care decisions.

In Uganda, most of the cervical cancer screening services are provided by nurses and midwives [7]. It is therefore important for the nurses to be able to use the SCME if it is to be used for cervical cancer screening in this setting. In our task-shifting approach, we used nurses with

no prior experience using the SCME, which is different from work done in Brazil where experienced colposcopists operated HRME devices for in vivo cervical imaging [20]. The task-shifting approach similar to what we used has been found useful in increasing access to diagnostic services for Kaposi Sarcoma in Uganda [35] as well as in screening for cervical cancer [36]. For successful task shifting to occur, however, it is important to have a device that lower cadre staff can learn to operate with minimal training. Our study demonstrated that with minimal training of only 2 days, nurses can successfully use the SCME to obtain confocal images promising for diagnosis of cervical precancer. However, more work needs to be done to ensure that the devices using this technology can be operated easily and can collect high-quality diagnostic images.

Providers' experience with the SCME

The nurses in this study found that the SCME was useful to them when performing routine cervical cancer screening tasks, and they reported willingness to continue using the SCME in the future. However, more work needs to be done to make it easier for the nurses to learn how to operate the SCME. This study was done in a busy clinical setting, with limited space to maneuver the SCME to focus and obtain good images. These challenges of limited space in the facility and the busy clinic environment, are similar to those experienced in other health facilities in Uganda and other resource-poor countries [37]. We suspect that the limited clinic space may have contributed to the difficulty in focusing when using the SCME, leading to difficulty in learning how to operate the SCME. Further investigation of the nurses' experience using qualitative methods is needed to enable us to pinpoint more strategies to improve the operation and ease of learning how to use the SCME. Of all the studies that have used devices with confocal microscopy technology, this is the first study to report on the user experience moreover among lower cadre staff. Our study findings are encouraging as they show the potential for adequately supported lower-cadre staff to use the SCME in our setting despite the challenges that exist in the health facilities.

The successful use of the SCME with minimal training by nurses with no prior experience with the device sets a good precedent for the integration of the SCME into the existing health care system. Although the difficulty in learning how to use the SCME may pose a challenge to integration of the SCME into the health system, we expect that this can be overcome by further improvement in the imaging speed, more practical training, real-time confocal image quality feedback, and automation of more steps in the operation of the SCME.

Study limitations

Some of the limitations of our study were the use of non-probability sampling to identify study participants, as well as the small number of patients and providers interviewed. Also, only a handful of the women (2.1%) in this study had screened for cervical cancer before. This limited history of cervical cancer screening can however be an advantage since these women are less likely to be biased when providing their experience screening with the SCME. The study aimed to assess the feasibility of using the SCME and its acceptability in a real-life clinical setting. Therefore, despite these limitations, our study findings provide useful information for us to improve the operation of the SCME before it is used on a larger scale. The lack of a validated tool to assess the acceptability of women and providers is another limitation in this study. However, the use of the Likert scale in this initial assessment provided insight on which areas to focus on to expound more on the acceptability of the SCME. Despite the use of the Likert scale, further qualitative assessment of the experience of the women and providers will be useful to provide more details that we can use to improve the device and its integration into clinical care. This work was also done as a research study which may have altered the experience of the providers who used the SCME under strict research procedures.

Generalizability of our findings

This study was conducted in a public health facility whose setup and operational challenges like limited space and overcrowding, are similar to those of other public health facilities in the country and other resource-constrained settings. The patient population and the cadre of staff are most likely to be found in other public health facilities where cervical cancer screening is done. The successful use of the SCME to yield useable results for the diagnosis of precancer in this study enhances the generalizability of these findings in similar settings.

Implications

Given the limited capacity of pathology services in our setting, the findings from this study indicate the potential to use the SCME to enable diagnosis of precancerous lesions. This is a great step towards enhancing same-day treatment of women with precancerous lesions in low-resource settings, where screening prevalence is low, loss to follow-up reduces chances of treatment, and allows progression to invasive cancer. Improving the operation of the SCME presents a viable option to enhance the screen and treat approach for cervical cancer prevention and control in low-resource settings.

Conclusion

In conclusion, this study demonstrated the willingness of women and low-cadre providers to use the SCME, and its potential to obtain useable images to facilitate same day diagnosis and treatment of cervical precancerous lesions. While the SCME performance evaluation had several limitations (moderate-to-low signal levels, only imaging patients with visible SCJ, a substantial portion of the SCME images not showing cellular features), this study provides important datapoints on the preliminary diagnostic performance and patient and user acceptance. These datapoints are important in developing affordable in-vivo microscopy tools that enhance screening and treatment of women with precancerous lesions in our setting. Our next steps will include refining the SCME to improve the image quality and diagnostic performance, and qualitative assessment to further explore the experience of women and providers.

Abbreviations

AUC	Area under the curve
HPV	Human Papilloma Virus
HRME	High-resolution micro-endoscopy
HSIL	High-grade Squamous intra-epithelial lesions
KNRH	Kawempe National Referral Hospital
LSIL	Low-grade intra-epithelial lesions
SCJ	Squamocolumnar junction
SCME	Smartphone Confocal Micro-Endoscope
SSA	Sub-Saharan Africa
UCI	Uganda Cancer Institute
VIA	Visual Inspection with Acetic acid
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12905-024-03323-5.

Supplementary Material 1-Confocal Device Patient Interview

Supplementary Material 2-Confocal Device Provider Interview

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Author contributions

PKM: participated in the conceptualization of this work, project administration, data collection and analysis, and writing—wrote and performed all revisions to the main manuscript text. AS: participated in the acquisition of funding, conceptualization, project administration, data collection and analysis, and writing—reviewed and edited the manuscript. MLO: participated in the acquisition of funding, conceptualization, project administration, data collection, and writing—reviewed and edited the manuscript. MM: participated in project administration, data collection, and writing—reviewed and edited the manuscript. RL: participated in project administration, data collection, analysis of histology samples and data, and writing—reviewed and edited the manuscript. MH: participated in funding acquisition, project administration, and writing—reviewed and edited the manuscript. EF: Participated in funding acquisition, project administration, and writing—reviewed and edited the manuscript. NK: participated in conceptualization, data analysis, analysis of confocal images, and writing—reviewed and edited the manuscript. JM: participated in the acquisition of funding, conceptualization, project administration, data collection, and writing—reviewed and edited the manuscript.DK: participated in the acquisition of funding, conceptualization, project administration, data collection and analysis, image analysis, prepared Figs. 4 and 5, and writing—reviewed and edited the manuscript. MN: participated in the acquisition of funding, conceptualization, project administration, data collection and analysis, and writing—reviewed and edited the manuscript.

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Data availability

The datasets that were analyzed to obtain the results of this study are available from the corresponding author upon reasonable request. These data sets are not publicly available to protect the privacy of the study participants.

Declarations

Ethics approval and consent to participate

The conduct of this study was approved by the Makerere University School of Biomedical Sciences Research and Ethics Committee (SBSREC) under reference number SBS 774. The SBSREC is the research ethics committee for the School of Biomedical Sciences which is one of the schools under the Makerere University College of Health Sciences. The study was also approved by the Uganda National Council for Science and Technology (Ref: HS1161ES). All study participants provided written informed consent before enrolment into the study.

Consent for publication

All study participants Provided written informed consent to have their data used, without any identifiers, for any publications resulting from this study. The study nurses also provided written informed consent to have their images and personal data published as part of this manuscript.

Author information (optional)

Not applicable.

Competing interests

DK and NK have declared a conflict of interest due to an outside interest in ArgosMD. DK and NK are the inventors of the patent application related to the confocal endoscopy technology used in the Smartphone Confocal Mirco-Endoscope (SCME) device used in this study. NK and DK have the right to receive royalties as a result of a technology licensing agreement between the University of Arizona and Argos MD. DK also serves as a scientific advisor to ArgosMD.All the other authors declare that they have no competing interests.

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