

Research paper

Utility of a low-cost 3-D printed microscope for evaluating esophageal biopsies

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ABSTRACT

In this manuscript we assessed the utility of a low-cost 3D printed microscope to evaluate esophageal biopsies. We conducted a comparative analysis between the traditional microscope and our 3-D printed microscope, utilizing a set of esophageal biopsy samples obtained from patients undergoing screening endoscopy. Two pathologists independently examined 30 esophageal biopsies by light microscopy and digital images obtained using a low-cost 3D printed microscope (Observer 1 and 2). The glass slide consensus diagnosis was compared to the findings of 2 additional pathologist who independently just reviewed the digital images (Observer 3 and 4). The intra-observer agreement was substantial to almost perfect for observer 1 (k:0.64) and 2 (k:0.84). All four observers had 100 % sensitivity and negative predictive value, whereas specificity ranged from 59 % to 100 % and positive predictive value ranged from 21 % to 100 %. The PPV and specificity were lower for the two Observers (3 and 4) who just examined the digital images. Overall, our results suggest that telepathology may be used with high sensitivity and specificity, utilizing the pictures produced by our 3D-printed microscope.

Introduction

A 3D printed microscope is a type of microscope that is created using 3D printing technology. Unlike traditional microscopes, which are typically manufactured using complex and expensive processes, 3D printed microscopes can be designed and fabricated using computer-aided design (CAD) software and manufactured using a 3D printer [1]. This allows for greater flexibility and customization in the design of the microscope, as well as lower costs and faster prototyping [2]. The microscope, for example, can be motorized to enable automatic whole-slide scanning, autofocus, Z-stacking, fluorescence microscopy, and phase contrast imaging [3].

Telepathology is a subfield of pathology that involves the use of telecommunication and information technologies to diagnose and manage pathology cases. This technology enables pathologists to consult on and interpret digital pathology images, such as those obtained from a

biopsy, from a remote location. Telepathology can be used in a variety of settings, including remote consultations between pathologists, second opinions, remote review of slides for quality control, and remote analysis of pathology specimens in remote or underserved areas [4]. By leveraging advances in digital imaging and telecommunications technology, telepathology has the potential to improve the quality and efficiency of pathology services and increase access to pathology expertise in areas where it may be limited. Despite its many benefits, telepathology is not without its challenges and limitations. Equipment cost, operating costs, IT infrastructure, and network limitations are some barriers that impede long distance and international telepathology collaboration [5]. In this paper we assessed the utility of a low-cost 3D printed microscope to evaluate esophageal biopsies and conducted a literature review.

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Material and methods

Low-cost 3D printed microscope

The OpenFlexure microscope (openflexure.com) was printed with a Creality CR10S 3D printer (Creality, Shenzhen, China) using black and white PLA filament (eSun3D.net, Hubei Province, China). Microscope assembly was performed using the fixing hardware recommended in the developer's instructions (<https://openflexure.org/projects/microscope/build>). The electronic parts consisted of a 5 mm white LED (3 V, 20 mA, 3000 K), Raspberry pi camera module V2 (Raspberry Pi Foundation, 37 Hills Road, Cambridge, UK), Raspberry pi 4 model B, three 28BYJ-48 micro stepper motors 5 V with ULN2003 driver board, and one Arduino Nano controller (Arduino.cc). The basic optics module was built by detaching the raspberry camera lens and mounting it backward on the 3D printed lens spacer (Fig. 1). This low-cost version of the optics module turns the Raspberry Pi camera to provide a field of view about 400 micrometers across and a resolution of around 2 μ m.

Patient samples

Patients who underwent upper endoscopy at the Department of Gastroenterology of the University of São Paulo were included in this study. Biopsy samples were acquired as part of a larger clinical trial [6] involving screening of subjects who had a history of oropharyngeal cancer. All subjects were ≥ 18 years of age and were required to sign an informed consent form. Study exclusion criteria included known cancer or a nodule or ulcer greater than 2 cm, allergy to the fluorescent agent proflavine or Lugol's iodine solution, active gastrointestinal bleeding, and contraindication to endoscopy.

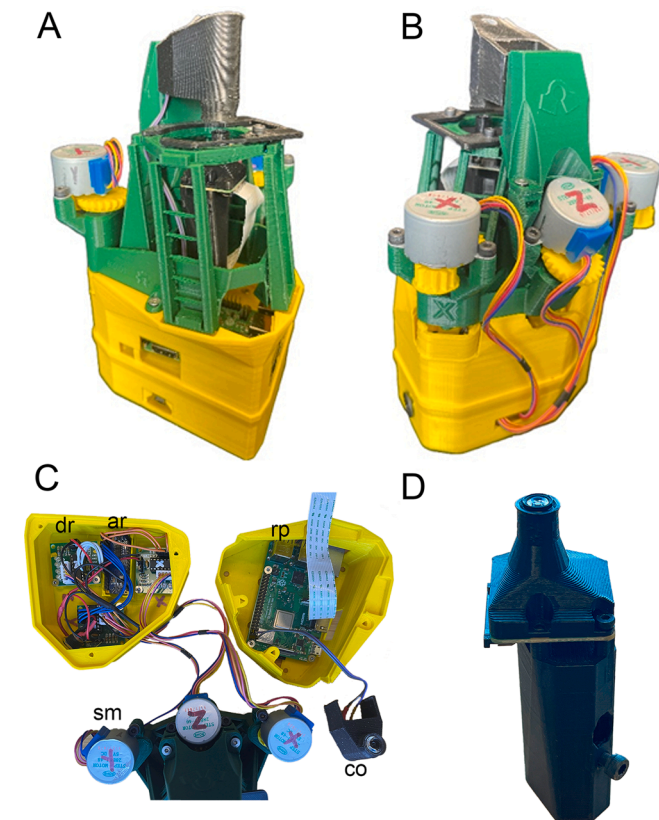


Fig. 1. Low-cost 3D printed microscope. A) front and B) back image of the low-cost 3D printed OpenFlexure microscope. C) electronic housing showing stepper motors (sm), motor drivers (dr), arduino board (ar), raspberry pi (rp), and condenser (co). D) Low-cost magnification objective using the raspberry pi camera and lens.

Sample evaluation

Thirty cases, corresponding to 20 patients, were examined. Routinely stained hematoxylin and eosin samples were examined under a light microscope by a local pathologist as the standard of care (Observer 1). Glass slides were also reviewed on site by a second board certified pathologist, who was blinded to the endoscopic, HRME and local pathologist results (Observer 2). The results were recorded on an electronic spreadsheet, and cases were assigned consecutive numbers. Reclassification was performed by consensus review of the two pathologists in cases of disagreement. Each glass slide contained a minimum of three sections; however, only one representative section was selected for image scanning.

Next, the slides were scanned using a 3D printed microscope, and filenames were assigned based on the Excel spreadsheet number to correlate with the diagnoses. Image stitching to create a whole-slide image was performed using the grid/collection stitching plugin in FIJI (ImageJ 1.53q, NIH, USA). <http://imagej.nih.gov/ij>). Microscopic pictures were also captured for comparison using an Opticam 0500R microscope with a connected Opticam LOPT10003 10MP camera at 4x and 20x objective magnification. Examples of the images at low and high power are shown in Fig. 2. The digital slides were then uploaded to a secure server and reviewed by Observers 1 and 2 after a washout period of at least two weeks. Both Observers were blinded to the original glass slide diagnoses. The percentage of tissue scanned was estimated by comparing the glass slide sections with the acquired digital images.

In addition, the digital slides were reviewed by two additional expert gastrointestinal pathologists (Observer 3 and Observer 4). Both Observers were blinded to clinical information, imaging studies, and pathology results, and did not review the original glass slides.

All Observers rated the digital image quality as poor, bad, average, good or excellent, using a Likert scale, and the diagnosis categories as shown on Table 1.

Literature review

An online literature review was conducted using PubMed and google scholar searching for the terms “low-cost microscope”, “affordable microscope”, “scanner” and “3D printed”.

Statistics

Data was analyzed using Cohen [kappa] statistic, a measure of agreement between observations, the magnitude of which reflects the strength of the agreement. Interpretation of strength of agreement was analyzed according to Douglas and Altman, where kappa value over 0.8 indicated excellent agreement, good level of agreement for kappa ranging between 0.6 and 0.8, moderate level of agreement for kappa ranging from 0.4 to 0.6, reasonably fair level of agreement for kappa between 0.4 and 0.2, and poor level of agreement for kappa < 0.2 . The analysis of intraobserver agreement compared the glass slide and digital image results for Observers 1 and 2, separately. The interobserver agreement compared the digital image results for Observers 3 and 4 with the glass slide consensus diagnoses from Observers 1 and 2.

Calculated sensitivity refers to the percentage of true positive results that a diagnostic test or screening tool correctly identifies as positive. When sensitivity and NPV both reach 100 %, it means that the test accurately identifies all individuals who do not have the condition (true negatives) and all individuals who have the condition (true positives). In other words, the test has no false negatives (individuals with the condition who test negative) or false positives (individuals without the condition who test positive).

Results

Overall image quality was rated as average (score 3) by all Observers.

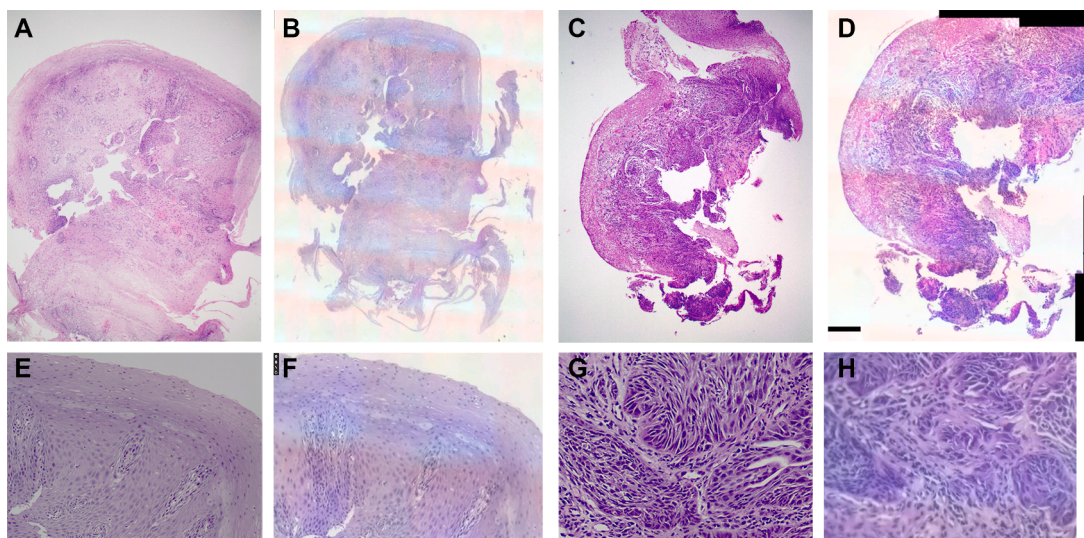


Fig. 2. Image comparison using low-cost 3D printed microscope and standard microscopy. A) reactive squamous mucosa light microscopy (40x), B) reactive squamous mucosa low-cost 3D printed microscope, C) squamous cell carcinoma using light microscope (40x) and D) squamous cell carcinoma using low-cost 3D printed microscope; E) reactive squamous mucosa light microscopy (200x), F) reactive squamous mucosa low-cost 3D printed microscope, G) squamous cell carcinoma using light microscope (200x) and H) squamous cell carcinoma using low-cost 3D printed microscope.

Table 1

Diagnostic categories used to evaluate digital images.

Diagnosis
Negative/reactive/reflux
Low grade dysplasia
Moderate dysplasia
High grade dysplasia
Invasive SCC
Cannot rule out LGD
Cannot rule out HGD
Cannot rule out invasion

Image size range from 0.18 Gigapixels to 0.74 Gigapixels (average 0.2 Gigapixels). The average sample was 10.4 mm (3–23 mm) (Table 2). In 19 samples (63 %) more than 90 % of the tissue was digitally scanned, whereas the remainder had less than 85 % acquired. Two samples (6.6 %) had approximately 60 % of tissue acquired (Fig. 3).

The details of the consensus glass slide and digital image interpretation for all four observers are listed in Table 2. In the consensus glass slide, 27 cases were interpreted as negative, 1 as LGD, 1 as HGD, and 1 as invasive SCC. Digital image interpretation showed three discrepancies for Observer 1, one for Observer 2, eleven for Observer 3, and seven for Observer 4. A consensus diagnosis of LGD was interpreted by one observer as MD, and consensus diagnosis of HGD was interpreted by one observer as LGD. All 4 observers interpreted the consensus diagnosis case of INV SCC as such. Dysplasia on the digital images was correctly interpreted by all four observers. However, there was discrepancy about the grade. The Intra-observer agreement between the glass slide consensus and digital images for Observers 1 and 2 is shown in Fig. 4A and 4B. The intra-observer agreement was substantial to almost perfect for observer 1 and 2 respectively (k : 0.64–0.84). The correlation between digital image diagnosis and consensus glass slide diagnoses for observers 3 and 4 was fair to moderate (k : 0.48–0.39) and is shown in Fig. 4C and D. The calculated sensitivity and negative predictive value reached 100 % for all 4 observers while the specificity ranged from 59 % to 100 % and the positive predictive value between 21 %–100 %. Observers 3 and 4 who did not evaluate the glass slides had a lower PPV and specificity compared to Observers 1 and 2 who did review the glass slides. (Table 3)

Literature review revealed 3 other similar low-cost 3D printed

devices (Table 4), consisting of a miniature low-cost portable digital microscope scanner prototype used for detecting breast cancer metastasis (MoMic) [7], the open-source PUMA microscope [8], and the UC2 3D printed modular microscopy toolbox[9].

Discussion

In this pilot study we investigated the potential of using a 3D printed microscope to evaluate esophageal biopsies. Our findings suggest that telepathology evaluation using this low-cost microscopy equipment can achieve high sensitivity and specificity.

Esophageal cancer is the eighth most frequent cancer worldwide and the sixth leading cause of cancer-related mortality [10]. In contrast with the western world, high-incidence regions for esophageal squamous cell carcinoma have been identified and investigated in northern China, northeastern Iran, southern South America, South Africa, and the eastern corridor of Africa (extending from Ethiopia to South Africa) [11, 12] Early detection, accurate diagnosis, and surgical intervention are crucial steps in reducing esophageal cancer mortality, making strong and reliable pathology services crucial. Yet, there is a critical shortage of anatomical pathologists both locally and globally, which has caused overworked workforces and decreased access to laboratory diagnosis. [13,14] In this context, digital pathology has the potential to improve patient care and support the pathology workforce by making the diagnosis and monitoring of disease much more efficient. Telepathology offers several advantages over traditional pathology. Increased access to pathology services allows pathologists to diagnose and consult on pathology cases from a distance, expanding access to pathology services in distant or underserved locations. This can improve diagnostic quality and efficiency, reduce the requirement for physical pathology specimen transportation, and save time and lower the danger of specimen deterioration. Telepathology also has the potential to enhance patient care by allowing faster diagnosis and decreasing the need for repeat biopsies. It can lower pathology service costs by eliminating the requirement for physical specimen transportation and eliminating the need for pathologists to commute to remote sites. Furthermore, telepathology allows pathologists to cooperate and consult with other professionals from a distance, enhancing diagnosis quality and overall level of care and extending access to education and enhancing the quality of pathology training programs.

Despite its many benefits, telepathology is not without its challenges

Table 2
Detail of consensus glass slide and digital image interpretation for all 4 observers.

Patient #	Sample #	Sample size (mm)	Consensus glass slide read	Digital image interpretation			
				OBS 1	OBS 2	OBS 3	OBS 4
1	1	16	NEG	NEG	NEG	NEG	NEG
2	2	15	NEG	NEG	NEG	NEG	NEG
3	3	10	NEG	NEG	NEG	NEG	NEG
3	4	8	NEG	NEG	NEG	NEG	NEG
3	5	8	NEG	NEG	NEG	NEG	NEG
3	6	6	NEG	NEG	NEG	NEG	NEG
4	7	23	NEG	NEG	NEG	NEG	NEG
5	8	20	NEG	NEG	NEG	NEG	NEG
5	9	16	NEG	NEG	NEG	NEG	NEG
6	10	17	NEG	NEG	NEG	NEG	NEG
6	11	6	NEG	NEG	NEG	NEG	NEG
6	12	7	NEG	NEG	NEG	LGD	NEG
7	13	17	NEG	NEG	NEG	NEG	NEG
7	14	15	NEG	NEG	NEG	NEG	NEG
7	15	16	NEG	NEG	NEG	LGD	R/O LGD
8	16	10	LGD	LGD	LGD	LGD	MD
9	17	13	NEG	NEG	NEG	LGD	R/O LGD
10	18	10	NEG	NEG	NEG	LGD	NEG
11	19	13	NEG	NEG	NEG	LGD	NEG
11	20	13	NEG	HGD	NEG	MD	R/O LGD
12	21	10	NEG	NEG	NEG	HGD	NEG
12	22	7	NEG	NEG	NEG	MD	NEG
13	23	3	NEG	NEG	NEG	HGD	NEG
14	24	5	NEG	R/O LGD	NEG	HGD	MD
15	25	5	NEG	NEG	NEG	NEG	R/O LGD
16	26	6	NEG	R/O LGD	NEG	MD	R/O HGD
17	27	3	HGD	HGD	LGD	HGD	HGD
18	28	7	NEG	NEG	NEG	NEG	NEG
19	29	4	INV SCC	INV SCC	INV SCC	INV SCC	INV SCC
20	30	5	NEG	NEG	NEG	NEG	NEG

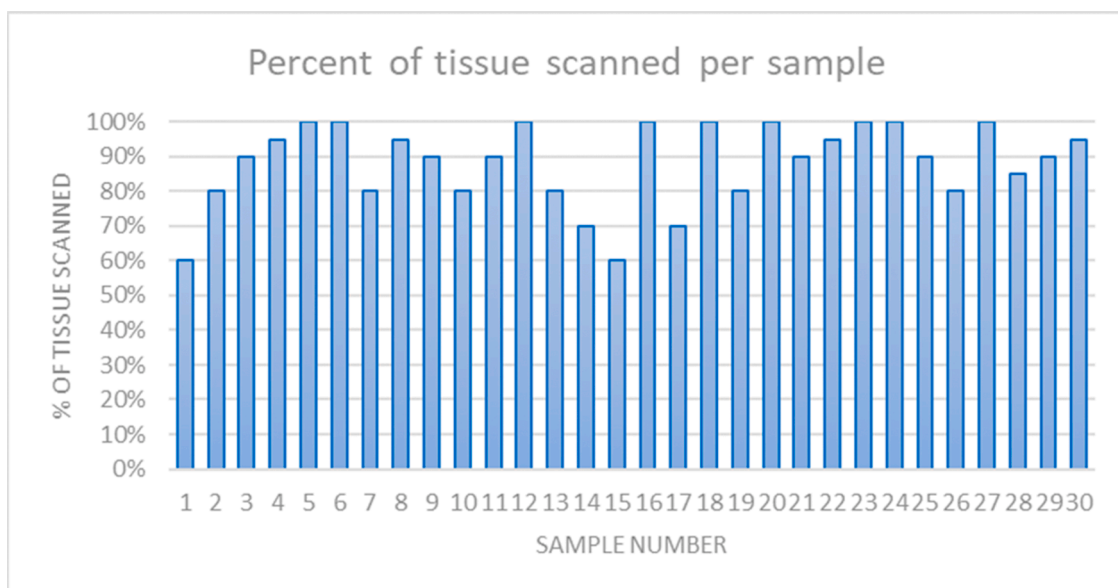


Fig. 3. Percent of tissue digitally scanned per sample.

and limitations. Telepathology requires dependable and fast internet access, as well as specialized software, and hardware. The quality of images can be influenced by factors such as the quality of the digital microscope, specimen preparation, and the technical skill of the person producing the slides. There are also legal and regulatory concerns, including data privacy, data security, and intellectual property. Furthermore, telepathology is a substantial shift from conventional pathology, and some pathologists may be resistant to embracing this new technology. Telepathology can also be costly since it demands specialized hardware and software, as well as telecommunications and

information technology infrastructure. Lastly, telepathology requires training and expertise for reliable diagnosis.

The Openflexure Microscope (OFM) has evolved over the course of 6 years into a mature and well-tested laboratory device [1–3]. This 3D printed low-cost microscope consists of a high precision translation stage, a small and sturdy optics module, and an integrated digital camera and embedded computer. It can be easily customized to meet specific requirements, such as changing the magnification level, adjusting the size and shape of the stage, or modifying the optics. When compared to traditional microscopes, 3D printed microscopes are often

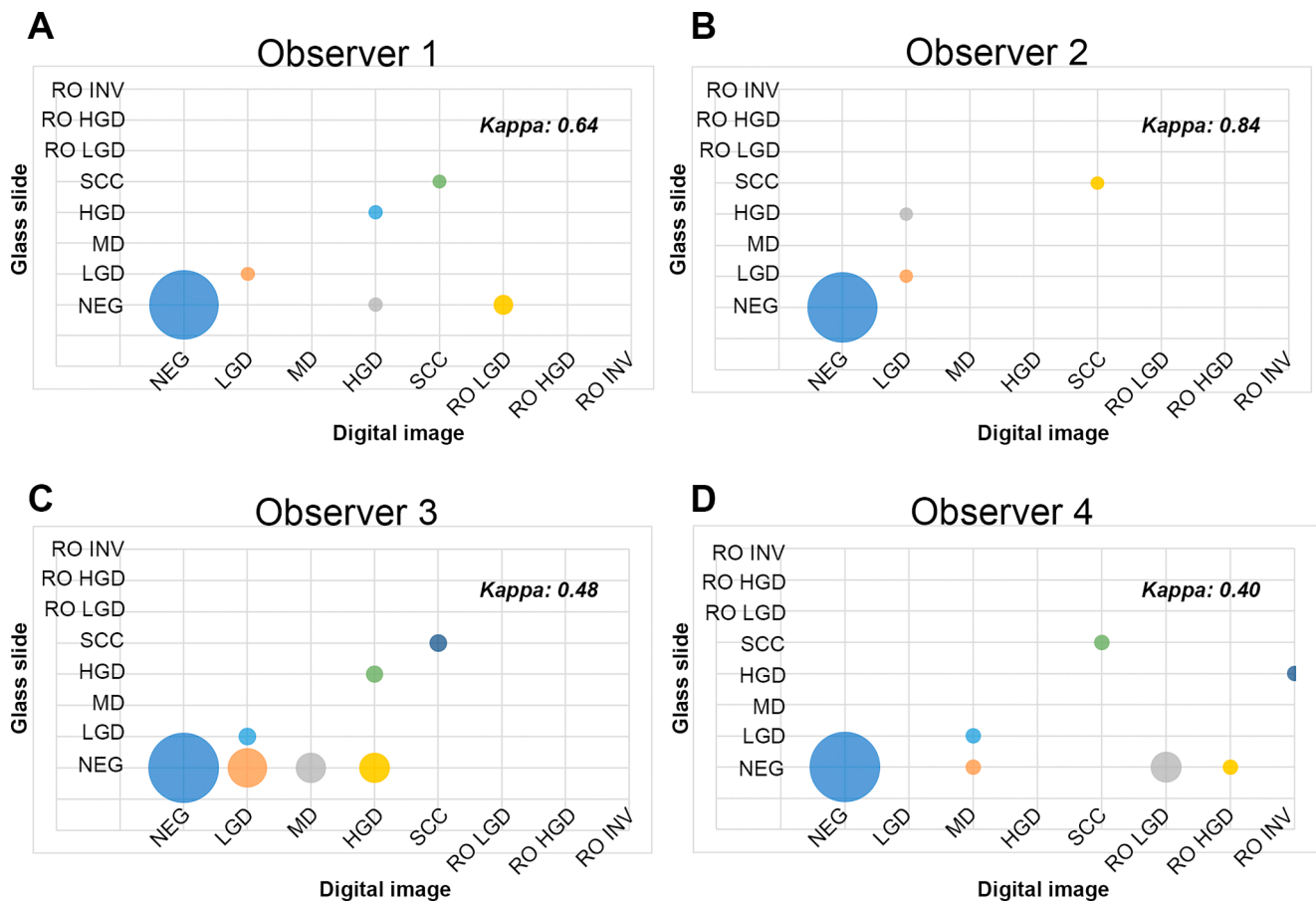


Fig. 4. Intra-observer agreement between the glass slide consensus and digital images for A) Observers 1, B) observer 2, C) Observer 3, and D) Observer 4. (NEG= Negative, LGD: Low grade dysplasia, MD: moderate dysplasia, HGD: High grade dysplasia, SCC: squamous cell carcinoma, RO LGD: cannot rule out low grade dysplasia, RO HGD: cannot rule out high grade dysplasia, RO INV: cannot rule out invasion.).

Table 3

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for all four observers for identifying dysplasia. *The consensus glass slide diagnosis between observers 1 and 2 was used as the gold standard.

	Observer 1	Observer 2	Observer 3*	Observer 4*
Sensitivity	100 %	100 %	100 %	100 %
Specificity	90 %	100 %	71 %	81 %
PPV	50 %	100 %	21 %	33 %
NPV	100 %	100 %	100 %	100 %
Accuracy	90 %	100 %	73 %	83 %

Table 4

Comparison of low-cost 3D printed systems.

	MoMic	PUMA	UC2	OpenFlexure
Goal	Whole slide scanner	Open-source 3D printed microscope for direct	Modular open-source 3D printed microscope	Customizable, open-source optical microscope
Camera	13MP	5MP	8MP	8MP
Battery powered	Yes (5v)	Yes (9–12 V)	Yes (5v)	Yes (5v)
Cost (USD)	\$500–1000	\$47–228	\$100–300	\$200–300
Resolution	0.9 μm	0.9 μm	<2.2 μm	<2 μm*
Slide scanner	Yes	No	No	Yes
Multiple optic modalities	No	Yes	Yes	Yes
Key features	Low-cost microscopy could enable telepathology	Visual observation and manual slide screening	Accessible modular platform for microscopy education and research	Low-cost microscopy, that enables telepathology

*magnification calculated using low resolution optics. The microscope can achieve up to 0.35 μm using a 100 × 1.25NA objective.

remote or rural areas where healthcare infrastructure may be limited. Moreover, they can be used as educational tools to train healthcare providers in low- and middle-income countries, helping to build capacity and improve the quality of care. Lastly, 3D printed microscopes can be used to conduct research on a range of diseases and conditions, allowing for more targeted and effective interventions. However, there are some limitations to 3D printed microscopes; the resolution of the print may be limited by the quality of the 3D printer and the materials used. Additionally, 3D printed microscopes may not be as durable as traditional microscopes and may require more frequent maintenance and replacement of parts. Lastly, 3D printing a microscope can be a time-consuming process, which may not be practical for researchers with time constraints or tight deadlines.

Other low-cost 3D printed microscopes have been published in the literature. These devices have been developed to address different aspects of diagnostics, research, and education. The MoMic focuses specifically on telepathology showing 91 % sensitivity and 99 % specificity compared to light microscopy. The PUMA microscope is an open-source device designed for direct visual observation and screening of standard microscope slides. The UC2 3D printed modular microscopy toolbox offers a versatile solution for different microscopy needs, with a modular design allowing for customization and adaptability for research and education. Except for the MoMic, the Openflexure, PUMA and UC2 devices are open-source and can be manufactured using off the shelf components and a typical FDM 3D printer.

There is currently no minimum criteria for picture capture and viewing [12]. The OFM can generate images that are 0.7 $\mu\text{m}/\text{pixel}$ with is close to the recommended 0.5 $\mu\text{m}/\text{pixel}$ [15]. In this paper the image quality was scored as average. We speculate that the main reason was that the wide-angle lens from the Raspberry Pi camera was used as the objective to lower the cost of the microscope. Using this approach, the lens detached and turned around producing a field of vision measuring 400 micrometers wide and a resolution of around 2 $\mu\text{m}/\text{pixel}$. Instead of the low-cost objective, further investigations utilizing higher magnification objectives are required.

One limitation of the 3d printed microscope is the restricted range of motion. The microscope is a 3D printed monolithic flexure translation mechanism that provides 3-axis positioning. The restrictions of machined mechanisms are eliminated by exploding the plastic compliance of the 3D printed model. This means that the 3D printed model will be more adaptable and flexible, allowing for a broader range of movements and functions. Because of the increased plastic compliance, the model can withstand greater stress and strain without breaking or malfunctioning, making it more durable and reliable. This provides sub-micron-scale motion over a range of $12 \times 12 \times 4 \text{ mm}$ on X, Y and Z axis respectively. This mechanical range limitation can be a challenge for bigger samples or multiple tissue samples on one slide spanning over the range limit. However, in this study we were able to acquire over 80 % of the diagnostic tissue in most of our samples.

In the context of our results, the calculated sensitivity indicates that all cases showing any grade of dysplasia or invasive carcinoma were correctly identified using digital images (sensitivity= 100 % and NPV=100 %). Furthermore, the specificity values ranged from 59 % to 100 %, which means that the test correctly identified a high percentage of individuals who did not have the condition (true negatives). The low positive predictive value in our study suggests that there may be a higher false positive rate, where individuals are identified as positive for dysplasia even though they do not have it. This was more evident for the observers 3 and 4 who only evaluated the digital images. Based on these findings, cases that are determined negative for dysplasia have a very high likelihood of being accurately identified, but those classified with dysplasia or above may be triaged for additional assessment using

traditional light microscopy. Overall, our results suggest that telepathology may be used with high sensitivity and specificity, utilizing the pictures produced by our 3D-printed microscope.

In general, 3D printed microscopes are affordable and adaptable and may improve access to healthcare, enhance the quality of care, and drive innovation particularly in low- and middle-income countries. Further research with a larger sample size is necessary to validate these preliminary findings and establish the efficacy of 3D printed microscopes in clinical settings.

Declaration of competing interest

The authors have declared no conflicts of interest. All co-authors have read and approved the article, and there are no financial conflicts to disclose. We certify that the submission is unique and is not currently under consideration by another publisher.

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