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ORIGINAL ARTICLE

Computer-assisted assessment of colonic polyp histopathology using probe-based confocal laser endomicroscopy

Pushpak Taunk[1] · Christopher D. Atkinson[2] · David Lichtenstein[3] · Eladio Rodriguez-Diaz[4] · Satish K. Singh[2,5]

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Abstract

Introduction Probe-based confocal laser endomicroscopy (pCLE) is a promising modality for classifying polyp histology in vivo, but decision making in real-time is hampered by high-magnification targeting and by the learning curve for image interpretation. The aim of this study is to test the feasibility of a system combining the use of a low-magnification, wider field-of-view pCLE probe and a computer-assisted diagnosis (CAD) algorithm that automatically classifies colonic polyps.

Methods This feasibility study utilized images of polyps from 26 patients who underwent colonoscopy with pCLE. The pCLE images were reviewed offline by two expert and five junior endoscopists blinded to index histopathology. A subset of images was used to train classification software based on the consensus of two GI histopathologists. Images were processed to extract image features as inputs to a linear support vector machine classifier. We compared the CAD algorithm's prediction accuracy against the classification accuracy of the endoscopists.

Results We utilized 96 neoplastic and 93 non-neoplastic confocal images from 27 neoplastic and 20 non-neoplastic polyps. The CAD algorithm had sensitivity of 95%, specificity of 94%, and accuracy of 94%. The expert endoscopists had sensitivities of 98% and 95%, specificities of 98% and 96%, and accuracies of 98% and 96%, while the junior endoscopists had, on average, a sensitivity of 60%, specificity of 85%, and accuracy of 73%.

Conclusion The CAD algorithm showed comparable performance to offline review by expert endoscopists and improved performance when compared to junior endoscopists and may be useful for assisting clinical decision making in real time.

Keywords Confocal laser endomicroscopy · Colorectal cancer · Polyp histology · Machine learning

Introduction

Worldwide, colorectal cancer (CRC) is the fourth most common malignancy [1]. Sporadic CRC occurs through an accumulation of mutations whereby adenomatous polyps progress to adenocarcinoma [2]. The removal of premalignant adenomatous polyps appears to prevent colon cancer [3] such that colonoscopy with polypectomy dominates the procedure volumes of most gastroenterologists in the USA and Europe. However, most removed polyps are diminutive in size (≤ 5 mm) with negligible malignant potential. This is particularly true in the distal colon where the great majority of diminutive

✉ Satish K. Singh
Satish.Singh@va.gov

Pushpak Taunk
ptaunk@health.usf.edu

Christopher D. Atkinson
christopher.atkinson2@va.gov

David Lichtenstein
David.Lichtenstein@bmc.org

Eladio Rodriguez-Diaz
Eladio.Rodriguez-Diaz@va.gov

[1] Division of Digestive Diseases and Nutrition, University of South Florida Morsani College of Medicine, Tampa, FL, USA

[2] Department of Medicine, Section of Gastroenterology, VA Boston Healthcare System, Boston, MA, USA

[3] Boston Medical Center, Boston University School of Medicine, Boston, MA, USA

[4] Research Service, VA Boston Healthcare System, Boston, MA, USA

[5] Boston University School of Medicine & College of Engineering, Boston University, Boston, MA, USA

polyps are hyperplastic (i.e., non-neoplastic) [4–7]. Nonetheless, the real clinical impact, as it relates to diminutive polyps, lies in the identification of adenomas to guide future surveillance intervals [8, 9]. Thus, the current practice of detecting and removing all polyps would be more efficient if the histology of diminutive polyps was known in situ during colonoscopy, whereby histopathological analysis—and even resection—could be avoided. This concept has been suggested as a paradigm for the purely colonoscopic management of diminutive polyps referred to as "resect and discard" [10, 11]. To this end, the American Society for Gastrointestinal Endoscopy (ASGE) put forth Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) guidelines and performance thresholds to obviate the need for universal polypectomy with histopathology [11].

This said, adoption of a "resect and discard" approach requires the capability for in situ assessments of diminutive polyps in real time during colonoscopy. Several recent advances in endoscopic imaging have shown promise for enabling real-time polyp histology including elastic-scattering spectroscopy [12–14], standard and high-definition white light endoscopy (WLE) [10, 15, 16], and electronic/virtual chromoendoscopy, encompassing narrow band imaging (NBI; Olympus America Inc., Center Valley, PA, USA) [17–21], Fuji Intelligent Chromo Endoscopy (FICE, Fujinon Inc., Wayne, NJ, USA) [22, 23], and i-Scan (Pentax America Inc., Montvale, NJ, USA) [24, 25].

Confocal laser endomicroscopy (CLE) is another such modality, one which enables high-resolution fluorescence microscopy of the mucosa in real-time. This technology employs local and/or intravenous contrast agents to generate high-quality images comparable with traditional histologic examination. Studies have shown CLE to be useful for a variety of gastrointestinal applications including improving the detection of Barrett's dysplasia in the esophagus [26, 27], classifying changes associated with inflammatory bowel disease [28–33] and assessing biliary strictures [34]. In particular, probe-based confocal laser endomicroscopy (pCLE) has been promising for assessing colorectal polyps. High magnification miniprobes (Cellvizio UHD; Mauna Kea Technologies, Allston, MA) enable real-time imaging of the mucosa with a 1000× magnification, 20-μm optical slice thickness, 1-μm lateral resolution, and a 240-μm field of view [35–39] usable with any existing colonoscope with a biopsy channel.

Use of high magnification pCLE miniprobes has been shown to provide highly accurate, near-histopathology-grade diagnosis in reports that examined polyps of all sizes [35, 37, 38, 40]. However, performance appears to be hampered in diminutive polyps, likely due to probe stability and targeting efforts at high magnification. In addition, the external validity of these reports is limited by discrepancies with image interpretation between experts and non-experts [35]. Due to issues of operator expertise and image quality due to poor probe stability and mistargeting [37, 38], pCLE has yet to meet PIVI thresholds for a resect and discard strategy. The use of computer algorithms that provide real-time diagnostic assistance may be one approach to overcome the abovementioned issues related to the clinical use of pCLE. Development of such algorithms has been investigated using image and video data acquired with the high magnification UHD pCLE miniprobe [41, 42], and while the results showed the potential of the approach, it was observed that larger fields of view lead to improved diagnostic performance.

The aim of the present study was to develop and assess the accuracy of a computer assisted diagnostic algorithm to classify polyps from pCLE images and compare this performance against that of endoscopists trained in pCLE image interpretation. Based on the suggestion that wider fields of view enhance the performance of diagnostic algorithms, we employed a lower magnification pCLE probe (Cellvizio Type-Z probe, Mauna Kea Technologies, Allston, MA), which provides a larger field of view at the expense of microscopic detail compared to the high magnification UHD pCLE probe used in previous studies (Fig. 1).

Materials and methods

Probe-based confocal laser endomicroscopy

We used the Cellvizio™ pCLE system (Mauna Kea Technologies, Allston, MA) for our study. The main components of the system are a laser-scanning unit and a miniprobe with an external diameter of 2.5 mm that was passed via a standard biopsy channel and placed in contact with the mucosa under direct endoscopic visualization (EVIS EXERA II 190 series high-definition colonoscope, Olympus America, Center Valley, PA). The miniprobe that we employed (ColoFlex Z-probe™) consists of a bundle of approximately 30,000 optical fibers terminated by a miniaturized microscope objective. The miniprobe provides a depth of imaging of 70 to 130 μm, the maximal field of view is 600 μm, and the lateral resolution is 3.5 μm. The laser-scanning unit houses and controls a 488-nm semiconductor laser that illuminates the mucosa via the miniprobe. Photons emitted from the mucosa by fluorescence are collected by the miniprobe, processed, and rendered as digitized images on a computer monitor at a frame rate of 12 per second. Because the autofluorescence of gastrointestinal tract mucosae is low, intravenous sodium fluorescein was used as an imaging contrast agent. In this manner, pCLE provides real-time, in vivo histopathological imaging during standard endoscopic procedures. Figure 2 illustrates different pathologies as seen using pCLE with the lower-magnification ColoFlex Z-probe that was employed in the present study.

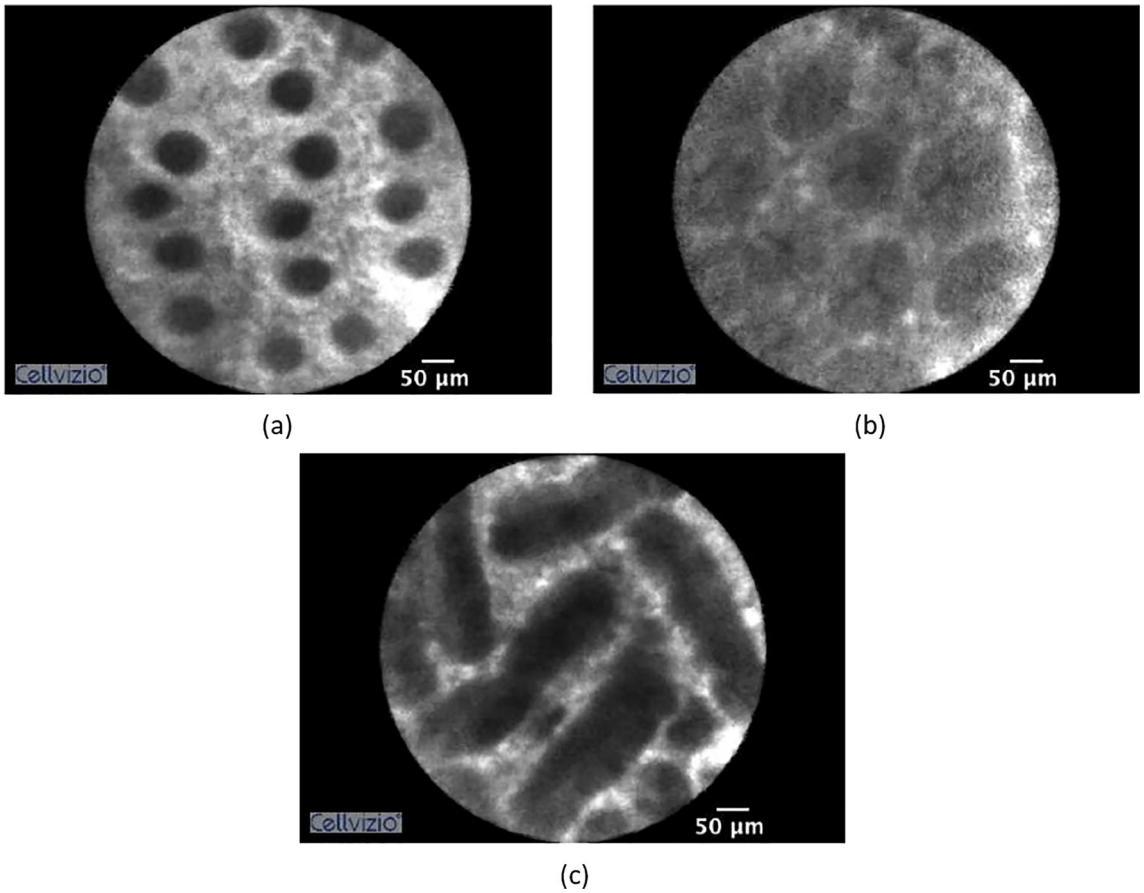

Fig. 1 pCLE images of normal (**a**), hyperplastic (**b**), and neoplastic (**c**) mucosa

Data collection

The study protocols were reviewed and approved by the VA Boston Healthcare System (VABHS) institutional review board. This study collected and analyzed data from patients receiving standard care at VA Boston that required screening or surveillance colonoscopy. Women of childbearing age, patients younger than 18 years of age, and patients with an allergy to fluorescein sodium were excluded from the study.

At total of 26 patients with a median age (and range) of 64.5 (52–82) years were studied. Of these, 25 were Caucasian (one African-American) and 25 patients were males. All patients were prepared for routine colonoscopy by ingesting the standard prescribed oral electrolyte lavage solution. A pCLE trained expert endoscopist (SKS) performed confocal laser endomicroscopy. Once a polyp was identified using standard white-light endoscopy, the patient was subsequently given 3.0–5.0 mL of fluorescein sodium solution 10% (100 mg/mL) intravenously. This enabled near-instantaneous high-quality mucosal imaging that lasted up to 20 min, thus far-exceeding the typical target withdrawal time of 6–12 min for a high-quality colonoscopy. The confocal miniprobe was inserted through the working channel of the endoscope and used to examine macroscopically visible lesions. The distal tip of the confocal probe was placed in gentle contact with the identified tissue. Video loops of each colonic polyp were obtained and stored as digital files using the Cellvizio platform. After completion of confocal imaging, the appropriately indicated clinical procedure was performed. None of the patients experienced any endoscopic complications or adverse reaction to sodium fluorescein. Two independent experienced GI pathologists reviewed the mucosal specimens in a blinded fashion.

Dataset

A total of 47 polyps from 26 patients were imaged. Histopathological consensus confirmed 27 neoplastic and 20 hyperplastic polyps. Polyp size distribution is summarized in Table 1. Endomicroscopic “still frames” of satisfactory quality were extracted from the stored video loops. Images that revealed crypt and vessel architecture and did not have any motion artifacts were selected for computer analysis. A total of 314 distinct confocal images were obtained, 159 from neoplastic lesions and 155 from non-neoplastic tissue (normal mucosa and hyperplastic polyps). A training set was created by randomly selecting

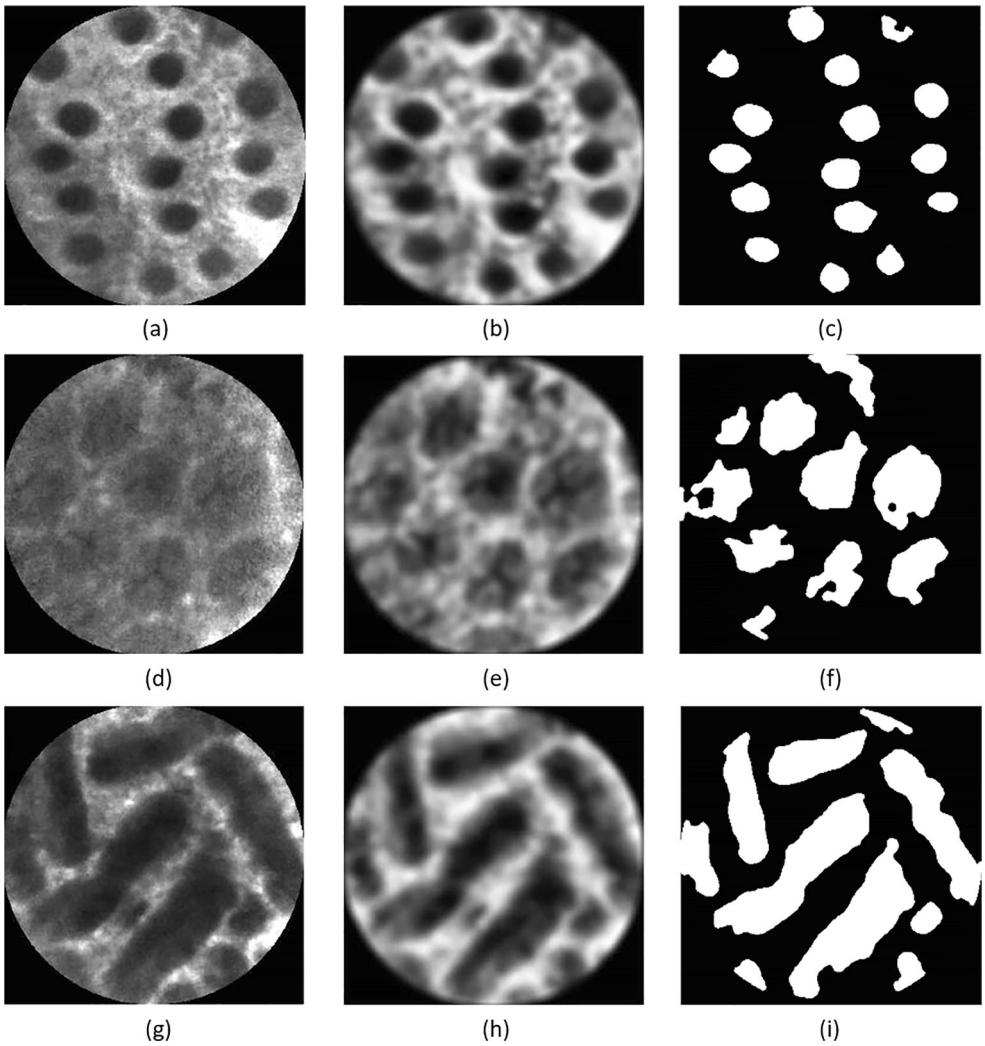

Fig. 2 Original pCLE images of normal (**a**), hyperplastic (**d**), and neoplastic (**g**) mucosa. Pre-processed images (**b**, **e**, **h**). Segmented images (**c**, **f**, **i**)

40% of the images, 63 neoplastic and 62 non-neoplastic, and allocating the remaining images as the testing set. The testing set consisted of 189 images, 96 from neoplastic polyps (34 images from neoplastic polyps ≤ 5 mm), 53 images from hyperplastic polyps (46 from hyperplastic polyps ≤ 5 mm), and 40 images from normal colonic mucosa. The training set was used to tune classifier parameters, while the testing set was used to evaluate the algorithm's performance as well as the interpretation by endoscopists.

Table 1 Polyp size distribution

	Neoplastic	Non-neoplastic
Total	27	20
≥ 1 cm	7 (26%)	0
6–9 mm	7 (26%)	5 (25%)
≤ 5 mm	13 (48%)	15 (75%)

Computer-aided diagnostic algorithm

The diagnostic algorithm consists of three components: image segmentation, where crypts are automatically detected in each image; feature extraction, where diagnostically relevant features are automatically extracted from the detected crypts; and classification, where a decision about the underlying pathology is made based on those extracted features. In order to perform image segmentation, each frame was automatically pre-processed to enhance contrast and reduce variable speckle and pixilation, leading to a more homogenous image pattern. Segmentation followed by thresholding the image, the result being a binary image where only the crypts remain, as seen in Fig. 3. Thresholding was accomplished by using the expectation-maximization (EM) [43] algorithm to find three intensity distributions from the overall image intensity histogram. These correspond to dark, midrange, and bright intensity values. Noticing that the crypts, in general, are the darkest components in the images, the threshold was selected as the intersection of the dark and midrange intensity distributions

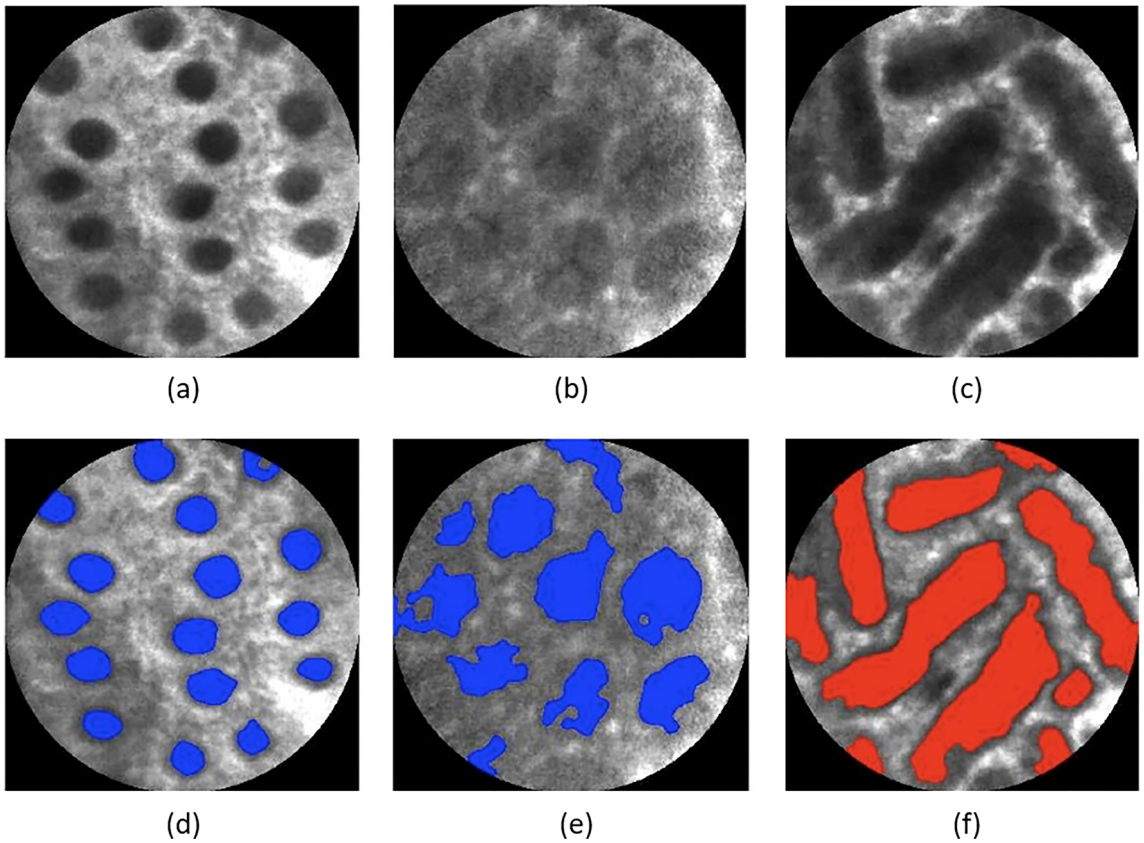

Fig. 3 Original frames for normal (**a**), hyperplastic (**b**), and neoplastic (**c**) mucosa. Highlighted crypts as found by the CAD algorithm for normal (**d**), hyperplastic (**e**), and neoplastic (**f**) mucosa

estimated with the EM algorithm. Morphological features were then extracted from each detected crypt in the binarized images [44]. These included crypt area, major axis, minor axis, and perimeter, as well as "roundness" metrics such as eccentricity, ratio of minor axis to major axis, compactness, and the ratio of the area to the area of the circle described by major axis. Essentially, crypt features characterized by a more elliptical shape were likely to indicate a neoplastic pattern, while features characterized by more circular shape were likely to indicate a non-neoplastic pattern. Extracted features served as inputs to a linear support vector machine classifier [45].

Image interpretation by endoscopists

We compared the prediction accuracy of the computer algorithm to the classification accuracy of two expert endoscopists (SKS and DL) versus five junior endoscopists with no prior experience with confocal laser endomicroscopy. Prior to the study, the expert endoscopists had participated in a standardized education and training program based on the manufacturer's atlases, while the junior endoscopists were not trained on pCLE interpretation in any way. Based on pCLE images, the endoscopists, blinded to histopathology as well as to the computer algorithm, classified mucosal images as normal, neoplastic, or non-neoplastic.

Statistical analysis

We used sensitivity, specificity, and overall accuracy obtained from the testing set as the primary diagnostic performance measures for both the diagnostic algorithm and the endoscopists' image interpretation. Exact binomial confidence intervals of 95% are provided with reported performance estimates. The kappa (κ) statistic was used to assess the interobserver agreement between the expert endoscopists and the CAD algorithm in predicting polyp histology from the pCLE images. Finally, we used McNemar's test to compare the accuracy between the endoscopists interpretation and the results from the diagnostic algorithm.

Results

Probe-based confocal laser endomicrosopic images were selected, including images of normal colon, hyperplastic and adenomatous polyps, from 26 patients. Results reported were obtained from the testing set, which consisted of 96 neoplastic and 93 non-neoplastic images. The images

underwent diagnostic evaluation using the CAD algorithm described above and were compared to index histopathology. This comparison showed that neoplastic changes could be predicted using the newly developed computer algorithm with a sensitivity of 95%, specificity of 94%, and an accuracy of 94%. As a point of comparison, the pCLE trained endoscopists classified images as neoplastic and non-neoplastic with a sensitivity of 98% and 95%, a specificity of 98% and 98%, and accuracy of 98% and 96%, respectively. Results are summarized in Table 2 including the performance obtained when the analysis was restricted to only pCLE images of hyperplastic and neoplastic polyps, and of polyps ≤ 5 mm in size. Interobserver agreement between both expert endoscopists, measured with the kappa statistic (κ), was $\kappa = 0.93$, suggesting strong agreement in their classification of the images. The CAD algorithm also displayed strong agreement with the endoscopists, with $\kappa = 0.85$ and $\kappa = 0.82$ resulting from the images classified by the algorithm and each of the endoscopists, respectively.

When considering the pCLE image evaluations made by the group of five junior endoscopists, on average, a sensitivity of 60% (range of 51 to 67%), specificity of 85% (range of 71 to 98%), and accuracy of 73% (range of 61 to 82%) was observed. The differences in classification performance between the diagnostic algorithm and the expert endoscopists were not significantly different based on McNemars's test, with $p \gg 0.05$ when comparing the diagnostic algorithm's performance versus each of the endoscopists interpretation, while differences in performance between the CAD algorithm and the five junior endoscopists' evaluations were found to be statistically significant ($p \ll 0.01$) in all five cases. Table 3 summarizes the diagnostic performances of the CAD algorithm and the endoscopists, including results from McNemar's test.

Discussion

In the current study, we sought to establish the feasibility of using pCLE images, acquired with a lower magnification, wider field of view confocal probe (Cellvizio ColoFlex type Z-probe), in conjunction with a CAD algorithm to assess the histology of polyps. Compared to the expert endoscopists' interpretation of the pCLE images, the developed CAD algorithm was able to achieve equivalent performance. This level of accuracy was also observed when limiting the analysis to diminutive polyps, i.e., those ≤ 5 mm in size. The CAD algorithm achieved expert levels of performance when compared to the evaluations made by junior endoscopists. Thus, were the CAD algorithm used to assist junior endoscopists, their performance could be brought up to an expert level immediately without any additional training.

Previous studies with the Cellvizio UHD probe, which has higher magnification than the ColoFlex Z-probe used in this study, have shown pCLE to be a viable platform for real-time histology of colorectal polyps. Buchner et al. reported an accuracy of 87% for differentiating neoplastic from non-neoplastic lesions based on offline blinded interpretation of confocal images [35]. More recently, Shahid et al. obtained an accuracy of 82% when blinded endoscopists interpreted offline video sequences of neoplastic and non-neoplastic polyps, with an accuracy of 80% when limiting the analysis to polyps ≤ 5 mm [38]. Another study by Shahid et al. sought to compare the accuracy of real-time interpretation of polyp histology during endoscopy with that of blinded offline interpretation [37]. Results showed a decrease in overall accuracy when interpretation of pCLE videos was performed in real time during endoscopy, accuracy of 79%, compared to an accuracy of 83% when videos where interpreted offline by the same endoscopist. Other studies have sought to investigate interobserver agreement among multiple interpreters of pCLE

Table 2 Performance differentiating neoplastic from non-neoplastic polyps based on size

		Sensitivity, % (95% CI)	Specificity, % (95% CI)	Accuracy, % (95% CI)
All images ($N = 189$)	Endoscopist 1	97.9 (92.6–99.7)	97.8 (92.4–99.7)	97.9 (94.6–99.4)
	Endoscopist 2	94.8 (88.2–98.2)	97.8 (92.4–99.7)	96.3 (92.5–98.5)
	CAD	94.8 (88.2–98.2)	93.5 (86.4–97.6)	94.2 (89.8–97.1)
Images HP and neoplastic polyps ($n = 149$)	Endoscopist 1	97.9 (92.6–99.7)	96.2 (87.0–99.5)	97.3 (93.3–99.3)
	Endoscopist 2	94.8 (88.2–98.2)	96.2 (87.0–99.5)	95.3 (90.5–98.1)
	CAD	93.8 (86.9–97.7)	94.3 (84.3–98.8)	94.0 (88.8–97.2)
Images HP and neoplastic polyps ≤ 5 mm ($n = 80$)	Endoscopist 1	94.1 (80.3–99.3)	95.7 (85.2–99.5)	95.0 (87.7–98.6)
	Endoscopist 2	88.2 (72.5–96.7)	97.8 (88.5–99.9)	93.8 (86.0–97.3)
	CAD	91.2 (76.3–98.1)	93.5 (82.1–98.6)	92.5 (84.4–97.2)

Table 3 Comparison between performances of CAD, expert endoscopists, and junior endoscopists. McNemar's test was performed for each endoscopist against the CAD algorithm

	CAD	Expert 1	Expert 2	Junior 1	Junior 2	Junior 3	Junior 4	Junior 5
Sensitivity, %	94.8	97.9	94.8	51.0	66.7	61.5	55.2	66.7
Specificity,%	93.5	97.8	97.8	71.0	90.3	88.2	79.6	97.8
Accuracy, %	94.2	97.9	96.3	60.8	78.3	74.6	67.2	82.0
p value McNemar's test	1	0.08	0.36	« 0.01	« 0.01	« 0.01	« 0.01	« 0.01

videos [35, 36], finding moderate agreement between multiple blinded endoscopists interpreting offline pCLE videos of colorectal lesions, using standardized criteria of diagnostic pCLE features. Based on the total assessment time that a given operator took to assess all images, CAD made a diagnosis on a static image under 1 s, experts made their diagnostic call within 3–5 s, and junior endoscopists took 10–15 s to make their assessments. Thus, a CAD algorithm could be expected to shorten required interpretation time while improving performance accuracy, the net result being a more efficient use of pCLE for real-time histology of colorectal polyps.

While these studies have shown the potential for the clinical use of pCLE for assessing polyp histology, some limitations have been encountered. it has been speculated that the classification accuracy, especially in the smaller polyps, could be improved if greater stability could be achieved when placing the pCLE probe onto the polyp [37], which is compounded by the limited field of view provided by the high magnification Cellvizio UHD probe [38]. Thus, for real-time use of pCLE, an endoscopist has to concentrate on maintaining steady contact with the polyp in question, while at the same time attempting to interpret frequently unstable image sequences. The use of some sort of computer-aided diagnostic system has been suggested as a possible approach to reliably use pCLE for polyp classification [37, 41, 42]. By having an automated CAD algorithm assist in the interpretation of the pCLE data, the endoscopist could focus on maintaining stable probe contact with the lesion, improving image quality and possibly accuracy. In addition, the use of a validated CAD system could, in theory, reduce or eliminate the interobserver variability currently observed among endoscopists using this imaging modality.

The development and use of a CAD algorithm for classifying pCLE image and video data of colorectal polyps has been investigated previously by André et al. [41, 42]. In their work, the authors used a bag-of-visual-words approach, a method used for content-based image retrieval, modified for use with pCLE images and videos. That approach was further extended by utilizing the resulting image descriptors to classify the pathology of an imaged lesion based on their similarity to descriptors obtained from validated images using a nearest-neighbor classification scheme. When applied to individual frames, this approach yielded an accuracy of 84%. In addition, the authors applied their scheme to mosaics created from contiguous frames to address the lack of field of view inherent in the high magnification pCLE images. These mosaics were created by stitching together several individual frames in order to achieve an image of a larger mucosal area. An improved classification accuracy of 90% was then achieved when their approach was applied to the mosaic images. Finally, the authors further extended their approach to video sequences of polyps by obtaining a descriptor signature for each video, in part, by including the possible spatial overlap between images in the same video, resulting in an accuracy of 94% again using a nearest-neighbor approach.

Our approach to CAD of polyps using pCLE images follows, in principle, a similar structure to the one presented by André et al. [41, 42]. In our work, image descriptors (i.e., features) were obtained automatically by analyzing the morphology of the imaged crypts after segmentation. These image features then served as inputs to a classification scheme in order to provide a diagnosis of the underlying pathology captured by the pCLE image frame. By using the lower magnification Cellvizio Type-Z probe, we sought to take advantage of the increased mucosal area imaged in each frame, when compared to the higher magnification Cellvizio UHD probe (Fig. 1), without the need of additional processing of images or increased algorithmic complexity. We hypothesize that analyzing the morphology of greater number of crypts per image frame contributed to the accurate classification results obtained in the current study, not only by the developed algorithm but by the endoscopist as well. As was shown by the work of André et al. [41, 42], increasing the imaged field of view trends to improved classification accuracy, as has also been suggested in other pCLE clinical studies [37, 38].

While the results obtained in the current study suggest the development an accurate CAD algorithm for polyps imaged with pCLE, our results should be viewed in the context of the inherent limitations of a feasibility study. A data-driven approach, such as the one utilized in the study, would benefit from a larger cohort of patients, permitting algorithms to better learn, test and validate diagnostic patterns. In addition, preselection of frames used in the study based on the quality of the imaged mucosa could serve to add an optimistic bias to the observed results. Ideally, and most likely necessary for clinical implementation of this approach, the algorithm should be

designed in such way as to automatically differentiate between high and low-quality frames before a frame is analyzed for diagnosis. Another limitation of the study is the absence of sessile serrated adenomas (SSAs) in the dataset. Serrated polyps present a unique challenge due to their morphologic similarity to hyperplastic polyps. Future work will need to examine the performance of CAD algorithms and whether distinct features can be extracted to modify them.

In summary, results from our study establish the feasibility of developing a CAD algorithm for the prediction of colorectal neoplasia based on low magnification pCLE images obtained using the Cellvizio Type-Z probe. Highly accurate classification results were obtained when images were interpreted by endoscopists, as well as when the CAD algorithm was applied, as compared to index histopathology. In addition, strong interobserver agreement was observed between the endoscopists and the computer-aided algorithm. The combination of this computer-aided algorithm with the larger mucosal area imaged with Cellvizio Type-Z probe has the potential to address some of the barriers for pCLE adoption in clinical practice, mainly by increasing accuracy of diagnostic predictions and reducing, or even eliminating, interobserver variability.

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Compliance with ethical standards

Disclosure of financial arrangements The authors do not have any relevant disclosures to report.

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