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ORIGINAL ARTICLE

Artificial Intelligence-Based Assessment of Colorectal Polyp Histology by Elastic-Scattering Spectroscopy

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Abstract

Background Colonoscopic screening and surveillance for colorectal cancer could be made safer and more efficient if endoscopists could predict histology without the need to biopsy and perform histopathology on every polyp. Elastic-scattering spectroscopy (ESS), using fiberoptic probes integrated into standard biopsy tools, can assess, both in vivo and in real time, the scattering and absorption properties of tissue related to its underlying pathology.

Aims The objective of this study was to evaluate prospectively the potential of ESS to predict polyp pathology accurately.

Methods We obtained ESS measurements from patients undergoing screening/surveillance colonoscopy using an ESS fiberoptic probe integrated into biopsy forceps. The integrated forceps were used for tissue acquisition, following current standards of care, and optical measurement. All measurements were correlated to the index pathology. A machine learning model was then applied to measurements from 367 polyps in 169 patients to prospectively evaluate its predictive performance.

Results The model achieved sensitivity of 0.92, specificity of 0.87, negative predictive value (NPV) of 0.87, and high-confidence rate (HCR) of 0.84 for distinguishing 220 neoplastic polyps from 147 non-neoplastic polyps of all sizes. Among 138 neoplastic and 131 non-neoplastic polyps ≤ 5 mm, the model achieved sensitivity of 0.91, specificity of 0.88, NPV of 0.89, and HCR of 0.83.

Conclusions Results show that ESS is a viable endoscopic platform for real-time polyp histology, particularly for polyps ≤ 5 mm. ESS is a simple, low-cost, clinically friendly, optical biopsy modality that, when interfaced with minimally obtrusive endoscopic tools, offers an attractive platform for in situ polyp assessment.

Keywords Artificial intelligence · Colorectal neoplasm · Colonic polyps · Colonoscopy · Machine learning · Spectroscopy

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Abbreviations

AI	Artificial intelligence
ASGE	American Society for Gastrointestinal Endoscopy
CADx	Computer-aided diagnosis
CRC	Colorectal cancer
DL	Deep learning
ESS	Elastic-scattering spectroscopy
HCR	High confidence rate
IRB	Institutional review board
LIFS	Laser-induced fluorescence spectroscopy
ML	Machine learning
NBI	Narrow-band imaging
NPV	Negative predictive value
PIVI	Preservation and incorporation of valuable endoscopic innovations
RTH	Real-time histology
SSAP	Sessile serrated adenomas/polyps
VA	Veterans affairs
VABHS	Veterans Affairs Boston Healthcare System

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer death in the USA, with nearly 150,000 new cases and 50,000 deaths annually [1]. In an effort to continually improve primary and secondary prevention, colonoscopy with polypectomy of neoplastic polyps remains the gold standard for CRC screening and surveillance [2, 3] since removal of neoplastic polyps during colonoscopy modifies disease outcomes and informs subsequent management. However, the endoscopist's ability to distinguish neoplastic from non-neoplastic polyps in real time, during standard white-light colonoscopy, has known limitations [4, 5]. As a result, standard practice continues to favor submission of all resected polyps for histopathological assessment, despite estimates that nearly half of these polyps may be non-neoplastic [6]. Studies have shown that reliable, real-time histology (RTH) of polyps could result in substantial improvement in the cost-effectiveness of colonoscopy for CRC screening and surveillance [7–9].

In recognition of the current need for more efficient endoscopic colonic polyp management, the American Society for Gastrointestinal Endoscopy (ASGE) developed the Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) initiative to guide emerging endoscopic technologies [10]. The PIVI for diminutive colorectal polyps (≤ 5 mm) establishes performance thresholds against which novel endoscopic technology is judged in order to be considered comparable to the current standard of care. In the US, these criteria afford the possibility of a real-time "resect-and-discard" and/or "leave-behind" approach for diminutive polyps. Economic models indicate that real-time, in situ assessment of polyp histology without separate confirmation by histopathology improves the cost-effectiveness of CRC screening and surveillance while decreasing additional risk [7–9]. However, a recent ASGE meta-analysis of endoscopic technologies applying the previously described PIVI thresholds [11], found that in academic centers, with or without the benefit of expert operators, only narrow-band imaging (NBI) met PIVI performance thresholds for RTH. Underperformance in community settings was attributed to learning curve limitations, interobserver variability, and the subjective nature of histology assessments made by endoscopists in real time [11–13].

Computer-aided diagnosis (CADx) has been proposed as a solution to overcome the challenges of adopting RTH or optical biopsy more widely. CADx typically leverages machine learning (ML) approaches applied to endoscopic visualization or in situ measurements of polypoid mucosa to provide an objective histology assessment of the lesion in question. The feasibility and utility of machine learning-based CADx approaches have been investigated previously utilizing enhanced endoscopic imaging modalities such as probe-based confocal laser endomicroscopy [14, 15], endocytoscopy [16], autofluorescence imaging [17, 18], and laser-induced autofluorescence spectroscopy [19, 20]. However, the most promising application of CADx has been one formulated with NBI, leveraging advances in ML, specifically in the fields of deep learning (DL) [21–23].

In this study, we present results obtained from a prospective data analysis study with a different form of spectroscopy, elastic-scattering spectroscopy (ESS), in conjunction with CADx, for colorectal polyp histology assessment. ESS is a point-spectroscopic measurement, rather than an imaging modality, taken over a broad wavelength range (typically 320–800 nm) that samples a tissue volume of ≤ 0.05 mm. The tip of the ESS fiberoptic probe is placed in optical contact with the tissue and incorporates separate illuminating and collecting fibers. When performed with specific fiberoptic geometries, ESS is sensitive to both the absorption spectra of major chromophores, such as oxy-/deoxy-hemoglobin, and the micromorphological features of superficial tissues. ESS spectra derive from the wavelength-dependent optical scattering efficiency (and the effects of changes in the scattering phase function) caused by optical refractive index gradients associated with cellular and subcellular structures. Unlike Raman and fluorescence spectroscopies, ESS provides largely structural, not biochemical, information. Thus, ESS is sensitive to features such as nuclear size, crowding, chromaticity, chromatin granularity, and mitochondrial and organellar size and density [24]. Because abnormal tissues are often associated with changes in subcellular, nuclear and organellar features, scattering signatures represent the spectroscopic counterpart of a histopathological interpretation.

The ESS method senses those morphological changes in a semi-quantitative manner, without actually imaging the microscopic structure. Typically, clinical studies have leveraged ML and artificial intelligence (AI) to interpret ESS measurements as meaningful pathologies [25–30], with studies showing the viability of ESS for classification of pathologies related to colorectal neoplasms [31–33].

Methods

Instrumentation

The ESS system and probes have been described previously [32]. Briefly, the ESS system consists of a broadband pulsed xenon arc lamp (Hamamatsu Corp., Bridgewater, NJ, USA), spectrometer/microcontroller board (Avantes Inc., Louisville, CO, USA), power supply, and built-in computer with custom software, housed in a clinically friendly, compact enclosure. ESS measurements involve short pulses of light (~ 50 microseconds) spanning the near-ultraviolet spectral region (~ 300 nm) through the visible to the near-infrared spectral region (~ 900 nm), coupled with a detector array, incorporating a fast electronic shutter. For in vivo measurements, ultraviolet light below 320 nm is filtered out to avoid potential risk to patients. The combination of short pulses and time-gated detection reduces the effect of ambient light, allowing measurements to be acquired irrespective of lighting condition.

The ESS optical probes consist of two identical adjacent fibers with 200-µm cores (one for illumination, the other for detection), with a numerical aperture of 0.22 in air. The center-to-center separation between the fibers is ~ 250 µm. With this probe configuration, a tissue depth of ~ 350 µm and a tissue volume ≤ 0.2 mm^3 are interrogated. In addition, an ESS fiberoptic probe with a pair of 200-µm core fibers was integrated into the polypectomy device. In one 'optical biopsy' forceps design, the optical probe was built into a hollow central channel extending into the space between the jaws (ESCO Medical Instruments, Stony Brook, NY). This design was capable of accommodating the 0.47-mm outer diameter of the hypotube encasing the fiber probe (Fig. 1a). In another design used in the study, the pair of optical fibers was enclosed in a polyimide jacket, resulting in a probe with outer diameter of ~ 1 mm. This probe was then affixed along standard 2.3-mm biopsy forceps (Fig. 1b), though its use is restricted to colonoscopes with 3.7-mm instrument channels. Before each procedure, a white-reference measurement was recorded from a spectrally flat diffuse reflectance standard (Spectralon®, Labsphere Inc., North Sutton, NH). This reference measurement was used to calibrate subsequent measurements for system response, taking into account spectral variations due to the light source, spectrometer, fiber transmission, and fiber coupling.

Clinical Measurements

The study was reviewed and approved by the Institutional Review Board (IRB) of the Veterans Affairs Boston Healthcare System (VABHS; IRB# 2898, 3273). Subjects were recruited prospectively from individuals undergoing CRC screening/surveillance colonoscopies at VABHS. Informed consent was obtained prior to enrollment in the study. Patients at increased risk for developing CRC, including those with genetic predispositions and/or chronic colonic inflammation, were excluded. All endoscopic examinations and biopsies were clinically indicated and performed by endoscopists in a routine manner.

The only deviation from standard colonoscopic examination was the acquisition of ESS measurements on identified polyps prior to polypectomy. Endoscopists were instructed to open the jaws and place the integrated ESS probe in gentle contact with the center or apex of identified polypoid lesions to acquire spectral data (Fig. 1c). After contact, the forceps jaws were closed immediately to obtain a physical biopsy. By using forceps with integrated ESS optics, precise co-registration of optical readings and physical biopsies was assured. For a given polyp, the "optical biopsies" were then correlated to index pathology results.

Data Analysis

The ESS measurements were pre-processed prior to spectral analysis. Raw ESS spectra consisted of 1347 bands, corresponding to the pixel density of the detector in the spectrometer, covering the wavelength range of 300–900 nm. Spectral bands were averaged to the nearest integer wavelength value, resulting in 601 bands in that range. Smoothing was performed using a moving average with a window of five bands. Dimensionality was further reduced by smoothing and downsampling the resulting measurements by averaging blocks of two bands and by limiting the spectral range used in subsequent analyses to the wavelength range of 330–760 nm. The resulting spectral measurements consisted of 215 bands. These pre-processing steps were performed to reduce high-frequency noise variations and to remove the regions of the spectra with a low signal-to-noise ratio arising from combined detector sensitivity and to lower source light intensity at the extremes of its output spectrum. These spectra were then normalized to the area under the curve to enhance spectral shape, independent of relative intensities (Fig. 2).

Machine learning was used to develop a diagnostic algorithm to classify the measured spectra, an approach previously used by our group in similar applications [15, 26–28,

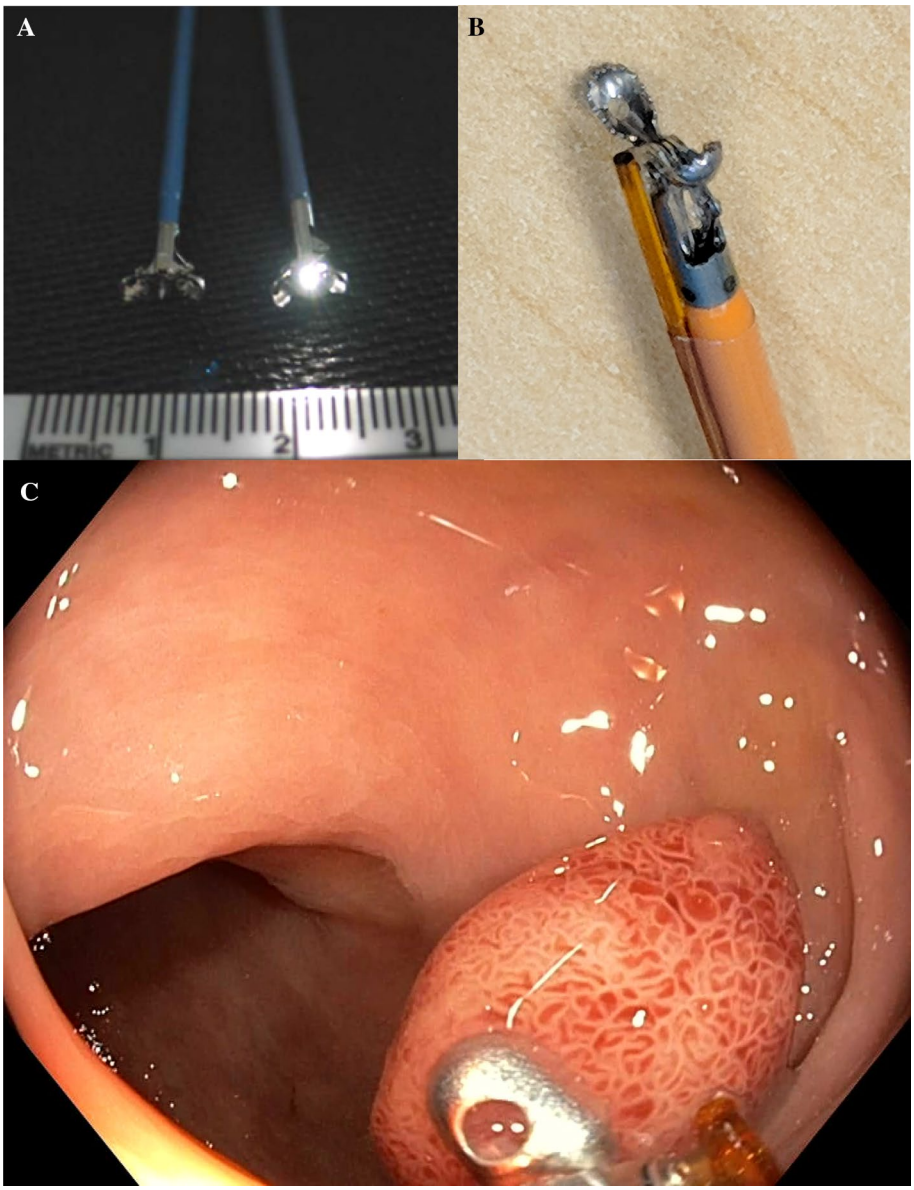

Fig. 1 **a** ESS optical biopsy forceps with built-in optical fibers. **b** Optical biopsy forceps with ESS optics attached along standard forceps. **c** Polyp interrogation with ESS optical biopsy forceps

32, 34]. The model was trained to provide a binary histopathological prediction as the output: (1) neoplastic, which included tubular adenomas, tubulovillous adenomas, adenocarcinomas; (2) non-neoplastic, which included hyperplastic polyps and polypoid-appearing normal colonic mucosa. In this study, sessile serrated adenomas/polyps (SSAP) were excluded from the training process. The training set consisted of 512 ESS measurements from 294 polyps (113 neoplastic, 181 non-neoplastic) collected during the study, a portion of which was previously reported in [32]. The classification model was designed using support vector machines with a Gaussian kernel [35]. *K*-fold cross-validation with ten folds was used to tune classifier parameters and determine high/low confidence level during the training process. As such, the resulting output of the classifier for each polyp measured with ESS is a neoplastic/non-neoplastic designation accompanied by a high/low confidence level. We used sensitivity, specificity, and negative predictive value (NPV) as the primary diagnostic performance measures based on a given high-confidence decision rate (HCR), defined as the number of high-confidence decisions over the total number of decisions. Exact binomial confidence intervals of 95% are provided with reported performance estimates (Table 1).

Results

A total of 367 polyps in 169 patients were interrogated optically with ESS and used as a prospective testing set. The testing set included 147 non-neoplastic polyps and 220

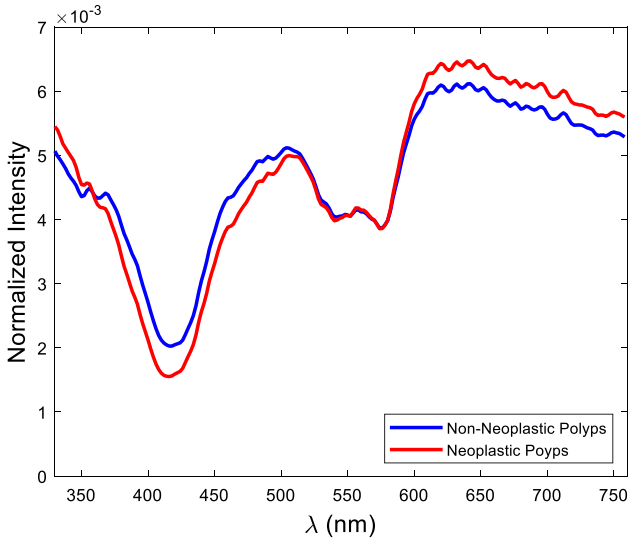

Fig. 2 Characteristic ESS spectra for neoplastic and non-neoplastic polyps

neoplastic polyps, including SSAPs. Categorized by size, 315 polyps were < 1 cm of which 143 were non-neoplastic and 172 were neoplastic, and a subset of 269 polyps was ≤ 5 mm, of which 131 were non-neoplastic and 138 were neoplastic. Table 2 summarizes the polyp distribution by histology, size, and location.

Performance results from prospective validation of the diagnostic approach based on polyp sizes are summarized in Table 3. Analysis of ESS measurements of all colonic polyps yielded a sensitivity of 0.92, specificity of 0.87, negative predictive value (NPV) of 0.87, and HCR of 0.84 for distinguishing neoplastic from non-neoplastic polyps. Similar performance levels were observed when restricting the analysis to polyps < 1 cm, with a sensitivity of 0.90, specificity of 0.87, NPV of 0.87, and HCR of 0.83. For all diminutive polyps (≤ 5 mm), ESS achieved a sensitivity of 0.91, specificity of 0.88, NPV of 0.89, and HCR of 0.83. When results of polyps ≤ 5 mm are parsed based on location, proximal colonic polyps had slightly better diagnostic rates with ESS than rectosigmoid colonic polyps. In proximal polyps, ESS

Table 1 Training set polyp characteristics by histology, size, and location

	Proximal			Rectosigmoid		
	N = 134			*N* = 160		
	Polyps ≥ 1 cm	5 mm > polyps < 1 cm	Polyps ≤ 5 mm	Polyps ≥ 1 cm	5 mm > polyps < 1 cm	Polyps ≤ 5 mm
Tubular adenomas	27	10	40	15	2	14
Tubulo-villous adenoma/adenocarcinoma	0	0	0	5	0	0
Hyperplastic/normal colonic mucosa	4	5	48	5	18	101

Table 2 Prospective test set polyp characteristics by histology, size, and location

	Proximal			Rectosigmoid		
	N = 188			*N* = 179		
	Polyps ≥ 1 cm	5 mm > polyps < 1 cm	Polyps ≤ 5 mm	Polyps ≥ 1 cm	5 mm > polyps < 1 cm	Polyps ≤ 5 mm
Tubular adenomas	23	19	97	14	11	35
Tubulo-villous adenoma/adenocarcinoma	4	0	0	6	0	0
Sessile serrated polyps	1	4	6	0	0	0
Hyperplastic/normal colonic mucosa	2	3	29	2	9	102

Table 3 Performance of ESS for differentiating neoplastic from non-neoplastic polyps based on size

	All polyps *N* = 367	Polyps < 1 cm *N* = 315	Polyps ≤ 5 mm *N* = 269
Neoplastic polyps	220	172	138
Non-neoplastic polyps	147	143	131
Sensitivity (95% CI)	0.92 (0.87–0.96)	0.90 (0.84–0.94)	0.91 (0.84–0.95)
Specificity (95% CI)	0.87 (0.80–0.93)	0.87 (0.79–0.93)	0.88 (0.80–0.93)
NPV (95% CI)	0.87 (0.80–0.93)	0.87 (0.79–0.93)	0.89 (0.82–0.95)
HCR (95% CI)	0.84 (0.80–0.88)	0.83 (0.78–0.87)	0.83 (0.78–0.87)

achieved a sensitivity of 0.91, specificity of 0.93, NPV of 0.76, and HCR of 0.90. As for rectosigmoid polyps, ESS achieved a sensitivity of 0.88, specificity of 0.86, NPV of 0.96 and HCR of 0.76. Table 4 summarizes the classification results by polyp size and location.

Results based on histopathological groupings, summarized in Table 5, showed encouraging findings regarding the use of ESS for distinguishing neoplastic polyps. Overall, 43 advanced adenomas, defined as adenomas ≥ 1 cm, with or without villous elements/high-grade dysplasia, were correctly classified in high confidence. Tubular adenomas < 1 cm were classified with an accuracy of 0.91 (125/137). On the other hand, SSAPs, sampled entirely from the proximal colon, were classified with an accuracy of 0.70 (7/10).

Discussion

In the current study, we sought to evaluate prospectively the performance of ESS as an endoscopic modality for real-time polyp histology. Our ESS-based approach combined optical scattering measurements of mucosa obtained with probes integrated into tissue-sampling tools and the use of AI to provide objective polyp histology assessments. The results of the study indicate that our ESS platform can accurately distinguish neoplastic from non-neoplastic polyps, with an observed sensitivity of 0.92 and specificity of 0.87 among polyps of all sizes. In particular, the performance obtained on polyps ≤ 5 mm was especially encouraging, as it appears capable of achieving PIVI thresholds for diminutive polyps. Our ESS method was able to classify prospectively polyps ≤ 5 mm with a sensitivity of 0.91 and specificity of 0.88. When further restricting the analysis to diminutive rectosigmoid polyps of ≤ 5 mm, the NPV obtained was 0.96. While further prospective validation with larger, more diverse sample sets is still required, these results position ESS as a viable platform for real-time histological assessment of polyps in clinical practice.

In recent years there has been great interest in endoscopic technologies aimed at improving the endoscopic visualization of colorectal neoplasia as well as technologies that can assist endoscopists in performing in situ histology assessments of visualized lesions with increasing accuracy. Laser-induced fluorescence spectroscopy (LIFS) is a form of spectroscopy that has been investigated for endoscopic RTH. LIFS uses the autofluorescence response of the measured tissue following excitation with laser light. This response

Table 4 Performance of ESS for differentiating neoplastic from non-neoplastic polyps based on size and location

	Proximal			Rectosigmoid		
	All polyps	Polyps < 1 cm	Polyps ≤ 5 mm	All polyps	Polyps < 1 cm	Polyps ≤ 5 mm
	N = 188	*N* = 158	*N* = 132	*N* = 179	*N* = 157	*N* = 137
Neoplastic polyps	154	126	103	66	46	35
Non-neoplastic polyps	34	32	29	113	111	102
Sensitivity (95% CI)	0.92 (0.86–0.96)	0.90 (0.83–0.95)	0.91 (0.84–0.96)	0.92 (0.81–0.98)	0.88 (0.73–0.97)	0.88 (0.70–0.98)
Specificity (95% CI)	0.93 (0.78–0.99)	0.93 (0.77–0.99)	0.93 (0.76–0.99)	0.85 (0.76–0.92)	0.85 (0.76–0.92)	0.86 (0.76–0.92)
NPV (95% CI)	0.72 (0.55–0.85)	0.71 (0.54–0.85)	0.76 (0.58–0.89)	0.95 (0.88–0.99)	0.95 (0.87–0.99)	0.96 (0.88–0.99)
HCR (95% CI)	0.89 (0.84–0.93)	0.89 (0.83–0.94)	0.90 (0.84–0.95)	0.78 (0.71–0.84)	0.76 (0.69–0.83)	0.76 (0.68–0.83)

Table 5 High-confidence accuracy of ESS based on size and location for each pathology grouping

	Proximal			Rectosigmoid		
	Polyps ≥ 1 cm	5 mm > polyps < 1 cm	Polyps ≤ 5 mm	Polyps ≥ 1 cm	5 mm > polyps < 1 cm	Polyps ≤ 5 mm
Tubular adenomas	1	0.87	0.93	1	0.87	0.88
	21/21	14/16	81/87	13/13	7/8	23/26
Tubulo-villous adenoma/adenocarcinoma	1	N/A	N/A	1	N/A	N/A
	4/4			5/5		
Sessile serrated polyps	1	0.75	0.60	N/A	N/A	N/A
	1/1	¾	3/5			
Hyperplastic/normal colonic mucosa	1	1	0.93	1	0.75	0.86
	1/1	2/2	25/27	2/2	6/8	67/78

then serves as an optical marker used to distinguish among different tissue types. Similar to our system, the necessary optics are embedded into tissue-sampling tools for ease of use and minimal disruption of clinical workflows [19]. Rath et al. conducted a pilot study using LIFS for predicting polyp histology in real time [20], assessing the histology of 137 polyps ≤ 5 mm from 27 patients. Their results showed a sensitivity of 0.82, specificity of 0.85, and NPV of 0.96.

Our work in the present study follows recent studies investigating the use of AI models in providing quantitative and accurate RTH. Similar to LIFS, ESS, as practiced in the current study, would be highly familiar and simple to use for most endoscopists. Since the ESS probe is integrated into the tissue sampling tools, there would be no additional endoscopic technique to master beyond that of standard polypectomy. In addition, quantitative histology assessments made by the system would be displayed to the user in less than 1 s, decreasing the need for operator interpretation, along with the inherent learning curve and/or operator bias that has hindered wider adoption of real-time histology based on other methods [11–13]. While LIFS and ESS share similar endoscopic probe interfaces, the improved diagnostic performance driven by ESS sets it apart as a spectroscopy-based RTH modality. In addition, and particularly encouraging, the diagnostic performance achieved by ESS is comparable to that reported by NBI-based CADx RTH, which is thought to be one of the most promising applications of CADx [21–23]. From a practical perspective, NBI CADx has the advantage of not requiring added capital equipment or specialized tools for its use, as it passively analyzes endoscopic video frames while assessing polyp histology, thereby requiring minimal operator manipulation. In general, CADx based on specific enhanced endoscopic imaging will be limited to endoscopes with such capabilities. Whereas NBI CADx is limited to Olympus endoscopes with NBI capabilities, ESS is endoscope-agnostic.

ESS and imaging-based CADx are potentially complementary. We envision a multi-modal approach where ESS could serve an adjunctive role for other minimally obtrusive, readily accessible, and high-performing technologies such as NBI. As an example, in the "resect and discard" paradigm, an initial histology assessment would be made with an imaging-based CADx, such as NBI CADx, and subsequently confirmed with ESS, as the tissue sampling tool is deployed for polypectomy. Our group is currently investigating the feasibility of this combined modality approach, and we are designing clinical studies to quantify what improvement in diagnostic performance would be gained as well as assess the potential impact on clinical flow and cost-effectiveness of these methods.

Future work will focus on addressing the limitations of the current study. First, as in any approach using ML, ongoing acquisition of labeled data will serve to enrich the development and validation of prediction models based on ESS spectral measurements. Second, we plan to further analyze the capability of ESS in predicting the histology of SSAPs. These types of polyps were excluded from the training process because of their underrepresentation in our data set as well as the inherent challenge presented by sessile serrated polyps. While morphologically similar to hyperplastic polyps, SSAPs are clinically managed as premalignant because of an increased risk of future neoplasia [36]. A positive finding in this study was that ESS classified the majority of these lesions as "neoplastic." Additional studies with a larger representation of this specific pathology grouping as well as other unique pathologies of interest, would serve to develop more robust prediction models and improve histology assessments across all pathology groupings. Finally, the current work is the result of prospective data analysis, not in situ predictions. To this end, our group is designing clinical studies to evaluate ESS performance with prediction made in situ and in real time using the PIVI thresholds as benchmarks, with a re-engineered system that will be more compact, user-friendly, and easily deployable than predecessor technologies.

In summary, we have presented ESS as a viable platform for endoscopic RTH. Particularly encouraging was the performance obtained in polyps ≤ 5 mm, with the promise for meeting both of the PIVI "resect and discard" and "leave-behind" thresholds. We believe that ESS continues to be a promising tool for RTH assessment of colorectal polyps and that our continued efforts in developing this technology will provide a clinically friendly, minimally obtrusive endoscopic tool for in situ CRC management.

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Compliance with Ethical Standards

Conflict of interest All authors disclosed no financial relationships or conflicts of interest relevant to the work presented in this publication.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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