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ABOUT COVER

Editorial board member of *Artificial Intelligence in Gastrointestinal Endoscopy*, Professor Yirupaiahgari KS Viswanath is an upper gastrointestinal (GI) Consultant Surgeon and Visiting Chair at Teesside University, who works at James Cook University Hospital over 20 years. He is the Programme Director for MCh postgraduate surgical specialties works in collaboration with Teesside University. His research interests mainly focused in upper GI cancer, acid reflux and Barrett's. He has supervised PhD, MSc MCh and MPhil students. He oversees dissertations every year and presents and publishes articles in GI surgery. Last 2 years, he have put efforts in developing a team of clinical and data scientists in artificial Intelligence in upper GI endoscopy. He remains active in clinical, radiological and lab-based research. His other noteworthy interests are on cancer immunology and molecular biology. He has received national and international accolades over years.

AIMS AND SCOPE

The primary aim of *Artificial Intelligence in Gastrointestinal Endoscopy* (*AIGE*, *Artif Intell Gastrointest Endosc*) is to provide scholars and readers from various fields of artificial intelligence in gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

AIGE mainly publishes articles reporting research results obtained in the field of artificial intelligence in gastrointestinal endoscopy and covering a wide range of topics, including artificial intelligence in capsule endoscopy, colonoscopy, double-balloon enteroscopy, duodenoscopy, endoscopic retrograde cholangiopancreatography, endosonography, esophagoscopy, gastrointestinal endoscopy, gastroscopy, laparoscopy, natural orifice endoscopic surgery, proctoscopy, and sigmoidoscopy.

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EDITORIAL

Application of convolutional neural networks for computer-aided detection and diagnosis in gastrointestinal pathology: A simplified exposition for an endoscopist

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Abstract

The application of artificial intelligence (AI), especially machine learning or deep learning (DL), is advancing at a rapid pace. The need for increased accuracy at endoscopic visualisation of the gastrointestinal (GI) tract is also growing. Convolutional neural networks (CNNs) are one such model of DL, which have been used for endoscopic image analysis, whereby computer-aided detection and diagnosis of GI pathology can be carried out with increased scrupulousness. In this article, we briefly focus on the framework of the utilisation of CNNs in GI endoscopy along with a short review of a few published AI-based articles in the last 4 years.

Key words: Convolutional neural network; Gastrointestinal endoscopy; Artificial intelligence; Deep learning; Machine learning

Core tip: The convolutional neural network (CNN), a deep learning model, has gained immense success in endoscopy image analysis, with its application to diagnose and detect gastrointestinal (GI) pathology at endoscopy. This article shares a basic framework of the utilisation of CNNs in GI endoscopy, along with a concise review of a few published AI-based endoscopy articles in the last 4 years.

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INTRODUCTION

The role of artificial intelligence (AI), specifically machine learning (ML) or deep learning (DL), in medicine is evolving and studies have surfaced beholding its advantages in performing gastrointestinal (GI) endoscopy[1,2]. The pace of AI utilisation in medicine will further increase, especially in the coming years as a "new normal" is established post-coronavirus disease 2019 (COVID-19). Already, there is evidence of the advantages of AI utilisation in the diagnosis of various pathologies such as colonic polyps, esophagitis and GI cancer. It is also a fact that the translation of gained experience and skills over many years to a novice trainee is not easy and bound with initial problems, and raises errors whether in diagnosis or decision making. We believe that ML could play a resolute role in passing on this knowledge and facilitate better patient management.

Though computer programmes mimicking human cognitive functions have existed since the 1950s, it is only in the 1980s onwards that ML, followed by DL, applications have been studied in medical fields[3]. The future is looking likely to be increasingly automated and therefore driving AI research safely and fairly, with increased accuracy and interpretability, would reduce the dependency on skilled professionals, while concurrently aiding patient management at an early stage. There is increasing evidence that these results in a reduction in time-to-treatment and facilitate early patient management. However, AI in gastroenterology comes with some assurance as well as drawbacks.

Recent advances in AI as applied to medicine have largely come through ML, in which mathematical computer algorithms learn to interpret complex patterns in data. Specifically, DL, a subclass of ML originally inspired by the brain, uses layers of artificial neurons to form a "neural network" which maps inputs to an output. Typically, these networks are "trained" on large amounts of manually labelled data, in which example input-output pairs are provided to the model to enable it to "learn". Of most interest to us in this article are the DL models which have achieved great success in image analysis tasks, namely convolutional neural networks (CNNs)[1-3]. We briefly focus on a high-level outline of the utilisation of CNNs in a simplified form to enable an endoscopist to cognize, along with a concise review of a few published GI endoscopy articles on AI in the last 4 years.

CONVOLUTIONAL NEURAL NETWORKS

CNN's are a type of DL model, commonly used to analyse endoscopy images.

Figure 1 illustrates the CNN training method where ultrasound scan images have been used, highlighting the salient steps of the DL framework. At a high level, the CNN is a parametric model which maps an input - in this case, an image - to an output. The output can take a variety of forms: from a classification (a label of the image containing or not containing a tumour); to a detection (a bounding box around the tumour); to a segmentation (specification of exactly which pixels in the image contain the tumour)[4]. The model is "trained" by giving the model multiple (usually, thousands) of examples of input-output pairs.

This training (Figure 2) involves, given an input image, computing the error between the model's prediction and the manual label, with the parameters of the model then adjusted to reduce this error. This process is repeated numerous times until the performance of the model is acceptable, with its final accuracy computed on a held-out "test set" of manually labelled images which it has not seen during training. Figure 1 illustrates the CNN framework, with the process rephrased in words in Figure 3. Figure 2 expands upon the training process specifically, in which the CNN parameters are iteratively updated so that its predictions are in closer alignment with the manual expert annotations. We highlight that the process involves partitioning the dataset into "training" and "testing" data, with the final model evaluation done on the

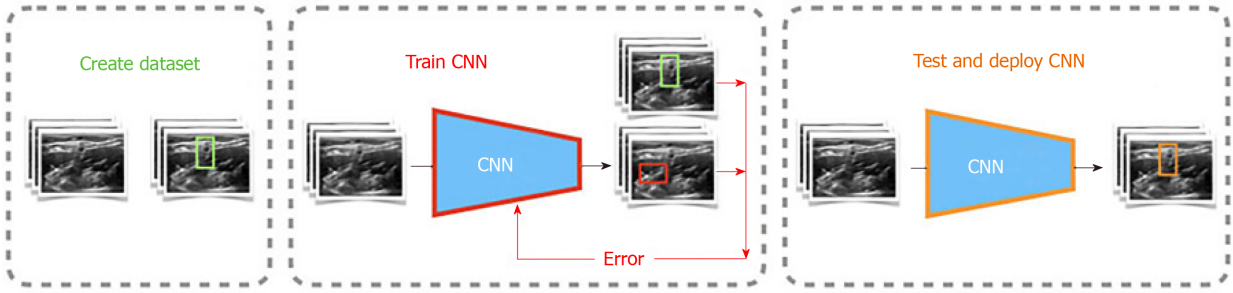

Figure 1 Illustrated convolutional neural network framework. CNN: Convolutional neural network.

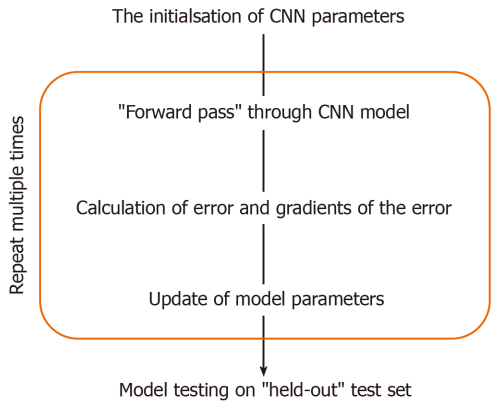

Figure 2 Convolutional neural network training; further defined. CNN: Convolutional neural network.

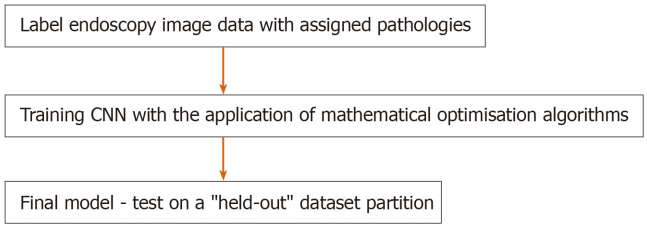

Figure 3 The convolutional neural network framework simplified. CNN: Convolutional neural network.

"held-out" test set - on images which the CNN has not seen during training. In this way, the model's performance on this test set can be used to approximate how well the model generalises to images, not in the dataset.

The training has been well described in the recent article[2], where authors have highlighted splitting the computer learning model into training followed by validation set and then the test set. The initial game was to train the model to predict labelled image pathology followed by validation. This will allow the model to detect unseen pathology and lastly evaluate the outcomes of the trained model with optimal hyperparameters.

It can be seen, here, that by ensuring that the manual labels are generated by expert physicians, the model could encode this knowledge and be used to transfer it to trainees. The validation of this idea is an interesting avenue of research, in which two sets of labels could be collected for the "test-set", from both experts and non-experts, to see if the CNN predictions can better align with the experts' annotation than those of the less experienced physicians.

Data augmentation is one technique that can be used to supplement and amplify a small or limited dataset[2,4]. This can be beneficial in increasing data variability, thus exposing CNN to more examples to learn from and improve final model accuracy. Traditional augmentation methods on image data include image scaling and rotation,

as well as manipulation of an images' brightness, contrast or saturation. Synthesised images generated from a class of DL algorithms known as generative adversarial networks have also augmented data used to train CNNs, Frid-Adar *et al*[5].

We also highlight the potential risks of the naive implementation of this technology. The model will encode and operate well on patterns seen in the training data but will fail (often catastrophically and uninterpretably) when exposed to unseen patterns. As such, researchers and clinicians must carefully ascertain whether biases are encoded into the curated datasets. These biases may be clinical (*e.g.*, omitted pathologies in the data) but also socio-technical (*e.g.* underrepresentation of sub-groups according to age, ethnicity, gender *etc.*). We direct the reader to further work on this topic[6].

CNN'S IN GI ENDOSCOPY

The CNN training process has been well described in a recent article[2] where the authors have highlighted splitting the dataset into training, validation and test sets. The initial game was to train the model to predict labelled image pathology followed by validation.

The use of CNN's in the early detection of oesophageal carcinoma has been published by Medel *et al*[7]. Here, the authors concluded improvement in sensitivity to 0.94 and specificity to 0.88. They defined C0 as a non-cancerous area and C1 as a cancerous area, highlighting the two regions and ultimately classified images as cancerous or non-cancerous using a patch-based approach. They concluded that future studies should include a greater number of images in the training set. Though adenoma detection rates at colonoscopy is variable with human interpretation, polyps' localisation and detection rate using a CNN has been shown to improve accuracy to 96.4%. This, in turn, can affect a reduction in colorectal interval cancers and associated cancer mortality[8].

The CNN can be used as an image feature extractor along with a support vector machine (SVM) as an aid for polyp classification. Shape, size and surface characteristics guide the attending gastrointestinal physician to identify and differentiate benign and malignant polyps. The accuracy of detection and diagnosis is variable depending on the experience of the endoscopist and the equipment. It has been shown that AI-based systems increase the accuracy of diagnosis and detection rate of polyps.

A Japanese team published an article on polyp classification in 2017, where they used a CNN to extract features from the endoscopic image and an SVM to classify colonic polyps. The SVM algorithms are used primarily for classification and regression analysis. In this study, the authors noted increased accuracy by using multiple CNN-SVM classifiers[9]. A further improvement in the detection and classification can be achieved through improved extraction methods such as wavelet colour texture feature extraction. This is nicely illustrated in an article by Billlah *et al*[10]. In another study, authors showed an accuracy of 78.4% to differentiate adenomatous vs non-adenomatous colonic polyps[11]. The system used linked colour imaging and showed a sensitivity of 83% and specificity of 70.1%[9]. Likewise, AI has been used to classify inflammatory bowel disease with 90% accuracy[12]. In another study authors collected and tagged 6 colorectal segments from 100 patients - they inferred the computer-aided detection system has potential for automatic identification of persistent histological inflammation in patients with ulcerative colitis[13].

CONCLUSION

AI use in medicine is likely to rise fast along with its endoscopy applications, followed by a noticeable surge in investment by big industry players. Gastrointestinal physicians will witness many breakthroughs in the coming years; however, a lack of proper legislation and clinical governance structure needs to be addressed soon. This requires evidence-based consensus and acceptable international standards without compromising a patient's safety in the coming years. Likewise, several technical issues within AI must be addressed, such as algorithm interpretability, fairness in results, and diverse representation in the dataset. However, reduction of errors due to endoscopist fatigue, inter-observer variability and learner endoscopist misconception are few rewards of AI; all these can no-doubt be leveraged to improve patient management. One cannot answer, whether, in the coming years, AI will replace

humans in performing the endoscopies themselves! Indisputably, AI is here to stay and will play a vital role in the post-COVID-19 "new normal" era.

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MINIREVIEWS

Emerging artificial intelligence applications in gastroenterology: A review of the literature

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Abstract

Artificial intelligence (AI) allows machines to provide disruptive value in several industries and applications. Applications of AI techniques, specifically machine learning and more recently deep learning, are arising in gastroenterology. Computer-aided diagnosis for upper gastrointestinal endoscopy has growing attention for automated and accurate identification of dysplasia in Barrett's esophagus, as well as for the detection of early gastric cancers (GCs), therefore preventing esophageal and gastric malignancies. Besides, convoluted neural network technology can accurately assess *Helicobacter pylori (H. pylori)* infection during standard endoscopy without the need for biopsies, thus, reducing gastric cancer risk. AI can potentially be applied during colonoscopy to automatically discover colorectal polyps and differentiate between neoplastic and non-neoplastic ones, with the possible ability to improve adenoma detection rate, which changes broadly among endoscopists performing screening colonoscopies. In addition, AI permits to establish the feasibility of curative endoscopic resection of large colonic lesions based on the pit pattern characteristics. The aim of this review is to analyze current evidence from the literature, supporting recent technologies of AI both in upper and lower gastrointestinal diseases, including Barrett's esophagus, GC, *H. pylori* infection, colonic polyps and colon cancer.

Key words: Artificial intelligence; Machine learning; Deep learning; Computer-aided

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diagnosis; Gastroenterology; Endoscopy

Core tip: Artificial intelligence (AI) allows machines to provide disruptive value in a multitude of industries and knowledge domains. Applications of artificial intelligence techniques, specifically machine learning and more recently deep learning, are arising in gastrointestinal endoscopy. Computer-aided diagnosis has been performed during upper gastrointestinal endoscopy for the automated identification of dysplastic lesions in Barrett's esophagus for preventing esophageal cancer, as well as in lower gastrointestinal endoscopy for detecting colorectal polyps to prevent colorectal cancer. The aim of this review is to investigate current data from the literature, supporting recent technologies of AI both in upper and lower gastrointestinal diseases, including Barrett's esophagus, gastric cancer, *Helicobacter pylori* infection, colonic polyps and colon cancer.

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INTRODUCTION

Artificial intelligence (AI) is based on intelligent agents performing functions associated with human mind, such as learning and problem solving[1,2].

In endoscopy, AI has begun to assist the improvement of colonic polyp detection and adenoma detection rate (ADR), to discriminate between benign and precancerous lesions based on the interpretation of their superficial patterns.

Machine learning (ML) and deep learning (DL) can be considered subfields of AI. ML is a form of AI that can support decision process allowing the improvement, without any Programmation, of the algorithms applied, including data testing and the implementation of descriptive and predictive models (Figure 1).

ML is distinguished into supervised and unsupervised methods. An instance of supervised ML, artificial neural networks (ANN), mirror the scheme function of the brain. Each neuron is a computing unit and all neurons are connected to produce a network. ML and convoluted neural network (CNN) algorithms have been created to train software to discriminate normal from abnormal regions in the lumen of the gut. For polyp detection, ML uses a fixed number of characteristics, such as polyp size, shape, and mucosal patterns.

A variety of deep learning neural network architectures are included in DL-based methods that automatically extract relevant imaging features without the human perceptual biases[3].

AI, BARRETT'S ESOPHAGUS AND ESOPHAGEAL CANCER

Barrett's esophagus (BE) is characterized by an unusual (metaplastic) transformation of the mucosal cells, lining the lower part of the esophagus, from normal stratified squamous epithelium to columnar one and associated with interspersed goblet cells[4]. This condition represents a risk factor for esophageal adenocarcinoma (EAC) whose most serious prognosis is related to the late diagnosis[4]. Moreover, 93% of patients can achieve a complete disease remission after a regular surveillance during 10 years and treatment[5-7]. Promising techniques for the management of BE with the potential of reducing the cancer risk by an accurate diagnosis of dysplasia, are being developed.

However, despite some limitations in interventional therapies, such as endoscopic resection (ER) and ablation techniques (radiofrequency ablation or cryoablation) they can help preventing the evolution into malignancy[8-11].

The recognition of neoplastic changes in BE patients is crucial and innovations in endoscopic imaging have worked for early detection of minimal epithelial neoplastic lesions based on distinct mucosal features.

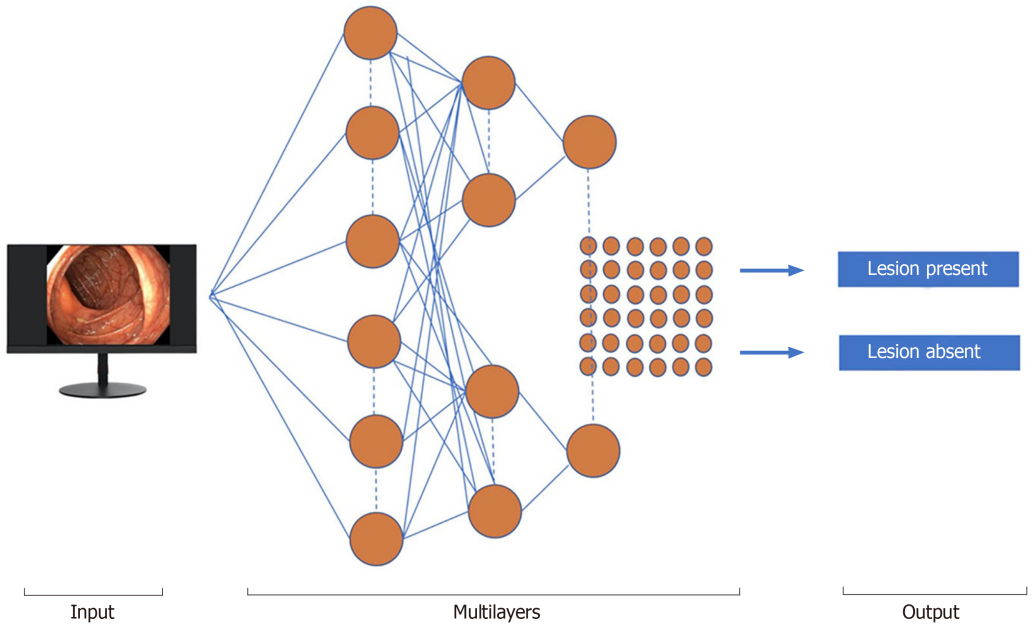

Figure 1 Schematic model of the deep learning algorithm in endoscopy.

In a first study, Mendel *et al*[12], introduced a useful method for generating an automatic classification based on endoscopic white light images through the learning of specific features helped by a pretrained deep residual network, instead of handcrafted texture features. The study used a data set of 100 high-resolution endoscopic images from 39 patients supplied by the Endoscopic Vision Challenge Medical Image Computing and Computer-Assisted Intervention (MICCAI). While 22 BE patients had cancerous lesions, 17 had non-cancerous BE.

The endoscopic images were independently evaluated by five experts and then compared with probability maps provided by AI, showing a strong correspondence. Since the significant of manual segmentations vary significantly, their intersection was considered as a cancerous region (C1-region) within each C1-image.

Ebigbo *et al*[13], employed two data sets to train and validate a computer-aided diagnosis (CAD) system relying on a deep CNN with a residual net (ResNet) architecture. Images consisted of 148 high-definition white light endoscopy (WLE) and narrowband imaging (NBI) images regarding 33 EAC and 41 areas of non-neoplastic BE in the Augsburg data set, while the MICCAI data set comprised 100 high-definition WLE images, 17 early EAC and 22 areas of non-neoplastic BE. CAD-DL system diagnosed EAC with a sensitivity of 97% and a specificity of 88% for WLE images, whereas a sensitivity and specificity of 94% and 80% for NBI images, respectively. CAD-DL reached a sensitivity and specificity of 92% and 100%, respectively, for the MICCAI images.

In these beginning studies, the authors developed a CAD model and displayed promising performance scores in the classification/segmentation areas during BE assessment.

However, these results were achieved using high-quality endoscopic imaging that cannot always be obtained during daily clinical practice. This system was previously developed to further increase the speed of image analysis for classification and the resolution of the dense prediction, displaying the color-coded spatial distribution of cancer probabilities.

Still based on deep CNNs and a ResNet architecture with DeepLab V.3+, a state-of-the-art encoder-decoder network was readjusted. To transfer the endoscopic Livestream to our AI system, a capture card (Avermedia, Taiwan) for image aquisition was incorporated into the endoscopic monitor[14] and the AI system was trained by using 129 endoscopic images. All AI-image outcomes were confirmed by pathological examination of resection specimens (EAC), as well as forceps biopsies (*i.e.*, normal BE). The AI system showed high performance scores in the categorization task with a sensitivity and specificity of 83.7% and 100%, respectively.

CNN was also used by Horie *et al*[15], that retrospectively collected 8428 training images from esophageal cancer of 384 patients through CNNs. CNN took 27 seconds to analyze 1118 test images and correctly detected esophageal cancer cases with a

sensitivity of 98%. CNN detected every 7 small cancer lesions lower than 10 mm in size. This system facilitated early and rapid malignancy detection leading to a better prognosis of these patients.

AI can assist endoscopists to make targeted biopsies with high-accuracy, saving work/time-intensive random sampling, with a low sensitivity (64%) for the detection of dysplasia. An international, randomized, crossover trial[16], compared high-definition white-light endoscopy (HD-WLE) and NBI for detecting IM and malignancy in 123 patients with BE (mean circumferential and maximal sizes, 1.8 and 3.6 cm, respectively).

Both HD-WLE and NBI detected 104/113 (92%) patients with IM, but NBI required fewer biopsies per-patient and exhibited a significantly higher dysplasia detection rate (30% *vs* 21%). During endoscopic examination with NBI, all areas of HGD and cancer presented an irregular mucosal or vascular pattern. Regular NBI surface patterns did not harbor HGD or cancer, suggesting that biopsies could be potentially avoided in the latter cases. Besides, in a multicenter, randomized crossover study[17], using endoscopic trimodal imaging (ETMI) for detection of early neoplasia in BE, ETMI showed no improvement in overall dysplasia detection than standard video endoscopy. The diagnosis of dysplasia was still made in a significant number of patients by random biopsies, and patients with a confirmed diagnosis of LGIN had a significant risk of HGIN/carcinoma.

Van der Sommen *et al*[18] used a computer algorithm to detect early neoplastic lesions in BE and employed specific texture, color filters, and ML-based on 100 images from 44 patients with BE. This system identified early neoplastic lesions on a patient-level with a sensitivity and specificity of 86% and 87%, respectively. The author assumed that the automated computer algorithm implemented for this study was able to identify early neoplastic lesions with reasonable accuracy.

De Groof *et al*[19] developed a CAD system using endoscopic images of Barrett's neoplasm based on the endoscopic images of 40 Barrett's neoplastic lesions and 20 non-dysplastic BE, reaching a sensitivity and specificity for the detection of such lesions of 95% and 85%, respectively.

AI technology was applied for volumetric laser endomicroscopy (VLE) in 2017. VLE with laser marking is a broad field of advanced imaging technology that was commercially available in the United States in 2013 to facilitate dysplasia detection.

VLE can enhance the detection of neoplastic lesions in BE by performing a circumferential scan of the esophageal wall layers. Sixteen patients with BE were included in the study and a total of 222 laser markers (LMs) were placed, 97% of them were visible on WLE. All LMs were evident on VLE directly after marking, and 86% were confirmed during the post hoc analysis. LM targeting held an accuracy of 85% of cautery marks. This original study applied to humans showed that VLE-guided LM can be a possible and secure procedure[20].

In another study[21] the same authors used a database of VLE images from BE endoscopic resection specimens with/without neoplasia, precisely correlated them with histology to develop a VLE prediction score. The receiving operating characteristic curve of this prediction score showed an area under the curve (AUC) of 0.81. A value ≥ 8 correlated with an 83% sensitivity and 71% specificity.

Optical coherence tomography (OCT) is a technique that produces high-resolution esophageal images through endoscopy. OCT can recognize specialized IM from epithelial squamous cells, but image criteria for distinguishing intramucosal carcinoma (IMC) and HGD from LGD, indeterminate-grade dysplasia (IGD), and specialized IM without dysplasia have not been approved yet.

Evans *et al*[22], examined 177 OCT images from patients with a histological diagnosis of BE. The histopathology analysis was IMC/HGD in 49 cases, LGD in 15, IGD in 8, specialized IM in 100, whereas gastric mucosa in 5 patients. A meaningful correlation was found between the MC/HGD histopathologic result and scores for each image feature, surface maturation, and gland architecture. When a dysplasia index determination of ≥ 2 was used, an 83% sensitivity and 75% specificity were determined for diagnosing IMC/HGD.

In a tertiary-care center, 27 BE patients underwent 50 EMRs imaged by VLE and pCLE, and were classified into neoplastic/non-neoplastic on the basis of histology result. The sensitivity and specificity of pCLE for detecting BE dysplasia, was 76% and 79%, respectively. The OCT-SI showed a sensitivity of 70% and a specificity of 60%. Moreover, the novel VLE-DA showed a sensitivity of 86%, specificity of 88% and a diagnostic accuracy of 87%[23].

Esophageal squamous cell carcinoma (SCC) is the sixth malignant cause of mortality worldwide and a greater percentage affect developing countries due to a delayed diagnosis[24]. Lugol's chromoendoscopy currently represents the gold standard

technique for identifying SCC during gastroscopy, despite a low specificity (about 70%) but a higher sensitivity (over 90%).

Among non-invasive tests, NBI is another approach that has a low diagnostic specificity as displayed in a randomized controlled trial (RCT), related to the physician's experience[25].

High-resolution microendoscopy (HRME) has shown the potential to enhance esophageal SCC detection during screening. An automated, real-time analysis algorithm has been developed and assessed using training tests, and validation images derived from a previous *in-vivo* study including 177 subjects involved for screening/surveillance programs. In a post hoc analysis, the algorithm recognized malignant tumors with a 95% sensitivity and 91% specificity, in the validation dataset, while 84% and 95% in the original study. Therefore, this technology could be applied in settings with less expertise operators in interpreting HRME images[26].

Kodashima *et al*[27] realized a computer system architecture to simplify the differentiation among neoplastic features and healthy tissues as a result of analyzing images in endocytoscopy of esophageal tissue from histopathological analysis, by analyzing the nuclear area of the collected images from 10 patients, to achieve an accurate and automatic diagnosis[27].

Shin *et al*[28] developed a quantitative image analysis algorithm that was able to recognize squamous dysplasia from non-neoplastic mucosa. They completed an image interpretation of 177 subjects undergoing upper endoscopy for SCC screening or surveillance, by using HRME. Quantitative data from the high-resolution images were used to create an algorithm to identify high-grade squamous dysplastic lesions or invasive SCC on histopathology.

The highest performance was gained using the mean nuclear area as the input for classification, resulting in a sensitivity and specificity of 93% and 92% in the training set, 87% and 97% in the test set, 84% and 95% in an independent validation set, respectively. ER is a technique employed for treating tumors with submucosal invasion depth 1 (SM1), whereas surgical removal with/without chemo-radiotherapy is usually used for SCC cases with a tumor infiltration deeper than SM2.

Accordingly, the preoperative endoscopic estimation of the ESCC invasion depth is critical. Recently, a rapid improvement in the application of AI with DL in medicine has been realized. A study by Tokai *et al*[29], evaluated the efficacy of AI in measuring ESCC invasion depth in a set of 1751 ESCC training images. AI recognized 95.5% (279/291) of the ESCC in the 10 test images when analyzing the 279 images it correctly predicted the invasion depth of the ESCC with an 84.1% sensitivity and an 80.9% accuracy in 6 seconds, much more precise for the estimation of ESCC invasion depth from endoscopists.

AI AND GASTRIC CANCER

Gastric cancer (GC) ranks third main cause of malignancy mortality worldwide, and esophagogastroduodenoscopy (EGD) is considered the best diagnostic tool for neoplasms at their early stages. The treatment of gastric tumors depends on the depth of the submucosal invasion; indeed, for differentiated intramucosal tumors (M) or those that invade the superficial submucosal layer (≤ 500 lm: SM1) ER is provided, while those with a deep submucosal invasion (> 500 lm: SM2) should be surgically treated for the potential risk of local invasiveness and metastases. Magnifying endoscopy combined with NBI or FICE (flexible color enhancement of spectral imaging) is clinically useful in discriminating gastric malignant from non-malignant areas[30-34]. However, this optical diagnosis strictly depends on the expertise and the experience of the operator, which prevents its general use in clinical practice.

Two RCTs examined the performance of endoscopy with/without the support of AI algorithms. The first research estimated the performance of a real-time DL system, WISENSE, to control the presence of blind spots during EGD. Overall, 324 patients randomly performed endoscopy with or without the use of WISENSE that monitored blind spots with a 90% average accuracy, and a separate accuracy for each site ranging 70.2%-100% in the 107 live endoscopic videos.

The average sensitivity and specificity were 87.6% and 95%, ranging between 63.4%-100% and 75%-100%, respectively. For timing endoscopic procedure, WISENSE accurately predicted the start and end times in 93.5% (100/107) and 97.2% (104/107) videos, respectively[35].

Miyaki *et al*[36], developed software allowing a quantitative evaluation of mucosal GCs on magnifying gastrointestinal endoscopy images obtained with FICE. They

adopted a set of features framework having densely sampled scale-invariant feature transform descriptors to magnifying FICE images of 46 intramucosal GCs then compared with histologic findings. The CAD system allowed an 86%detection accuracy, a sensitivity and specificity of 85% and 87% for a cancer diagnosis, respectively.

In the study by Kanesaka *et al*[37], a total of 127 patients with EGC contributed to 127 cancerous M-NBI images, while 20 not-EGC patients provided to 60 not-cancerous M-NBI images. The authors created software that allowed both the identification of GC and outlined the edge between malignant and non-malignant regions. This CAD algorithm was designed to investigate grey-level co-occurrence matrix characteristics of partitioned pixel slices of magnifying NBI images, and a support vector machine was used for the ML method. The models showed a 97% sensitivity and 95% specificity in distinguishing cancer, while the performance for area concordance displayed a sensitivity and specificity, of 81% and 66% respectively.

In 2018, Hirasawa *et al*[38], elaborated an AI-based diagnostic system to detect GC, using a CNN simulating the human brain.

A total of 714 among 2,296 test image sets (31.1%) confirmed GC presence, and 84.1% had moderate/severe gastric atrophy. The CNN employed 47 seconds to analyze the 2,296 test images, diagnosing overall 232 GCs, 161 as non-malignant lesions, 71 of 77 as GC lesions with a sensitivity of 92.2%. The majority of gastric lesions (98.6%) with a diameter ≥ 6 mm were precisely identified by CNN, additionally to all invasive carcinomas (T1b or deeper). The undiagnosed lesions had a superficial depression and were more frequently intramucosal cancers with a differentiated-histotype, whose discrimination from gastric inflammation was challenging also for experienced endoscopists. Another usual reason for misdiagnosis was the anatomical sites of the cardia, incisura angularis, and pylorus.

Zhu *et al*[39] examined the potential of AI to address the prediction of invasion depth of early GC. In particular, they developed and validated an AI model CNN-CAD that used a deep learning algorithm for determining EGC invasion depth ("M/SM1" *vs* "SM2 or deeper").

A total of 790 endoscopic images of GCs were employed for ML, while an additional 203 images, completely autonomous from the learning material, were handled as a test set. The AI model exhibited a sensitivity and specificity of 76% and 96%, respectively in distinguishing SM2 or deeper cancer invasion, with a higher diagnostic performance as compared to the one reached by endoscopists. This high specificity could lessen the overestimation of tumoral invasion, which would contribute indirectly to reduce avoidable surgeries for M/SM1 malignancies. Moreover, in this study, the CNN-CAD system also achieved significantly greater accuracy and specificity than both expert and junior trained endoscopists.

AI might assist physicians to predict prognoses of patients with GC. Some crucial clinical trials evaluating adjuvant strategies of advanced GC were produced over the past decade, but the most suitable therapy for GC is so far uncertain. Besides, two contemporary molecular landscape studies proved the presence of various molecular GC subtypes[40,41].

A DL-based model (survival recurrent network, SRN) was developed to predict survival events for a total of 1190 GC patients, based on clinical/pathology data as well as therapy regimens, predicting the outcome at each-time point during a 5-year surveillance time.

The SRN showed that the mesenchymal subtype of GC should stimulate a tailored postoperative therapeutical strategy as a consequence of its great risk of recurrence rate. Conversely, the SRN observed that GCs with microsatellite instability and the papillary type displayed significantly more favorable prognosis after chemotherapy including capecitabine and cisplatin. SRN reached a survival of 92%, 5 years after curative gastrectomy resection[42].

ANN model was used to evaluate 452 GC patients, determining survival times with approximately 90% accuracy, and focusing on producing an adequate ANN structure with the capacity to handle censored data[43]. In detail, 5 sets of single time-point feed-forward ANN models were generated to predict the outcomes of GC patients at regular time intervals (every year) until the fifth year after gastrectomy. Hence, the ANN prediction models exhibited accuracy, sensitivity, and specificity ranging as follows 88.7%-90.2%, 70.2%-92.5%, and 66.7%-96.2%, respectively.

AI IN THE IDENTIFICATION OF *HELICOBACTER PYLORI* INFECTION

Helicobacter pylori (*H. pylori*) infects the epithelial gastric cells and is associated with functional dyspepsia, peptic ulcers, mucosal atrophy, intestinal metaplasia, and GC[44]. *H. pylori*-associated chronic gastritis may also raise the risk of GC[45,46]. CNN technology can accurately assess *H. pylori* infection during conventional endoscopy without needing biopsies. In a pilot study by Zheng *et al*[47], the authors produced a Computer-Aided Decision Support System that uses CNN to estimate *H. pylori* infection based on endoscopic images. From 1959 patients, 77% were assigned to the derivation cohort (1507 patients; 11729 gastric images) and 56% of them had *H. pylori* infection (847), while 23% were selected for the validation cohort (452) and 69% of patients were *H. pylori* infected (310; 3755 total images).

Huang *et al*[48] applied neural networks (refined feature selection with a neural network, RFSNN) to predict *H. pylori*-related gastric histological hallmarks based on standard endoscopic images. The authors trained the model using endoscopic images of 30 patients and used image parameters taken from a different cohort of 74 patients to generate a model to predict *H. pylori* infection, showing an 85% sensitivity and a 91% specificity for identifying *H. pylori* infection. Moreover, RFSNN revealed an accuracy higher than 80% in predicting the presence of gastric atrophy, IM, and *H. pylori*-related gastritis severity.

Shichijo *et al*[49] produced a 22-layer deep CNN to predict *H. pylori* infection during real-time endoscopy. A dataset including 32208 images of 735 *H. pylori*-positive and 1015 *H. pylori*-negative patients was handled. The sensitivity/specificity/accuracy, were 81.9/83.4/83.1%, respectively, for the first CNN, and 88.9/87.4/87.7%, respectively, for the secondary CNN, employing in both cases a similar time (198 seconds and 194 seconds, respectively).

Another study group developed a CNN, preparing 179 endoscopic images obtained from 139 patients (65 were *H. pylori*-positive and 74 *H. pylori*-negative). One hundred and fifty-nine of all images were adopted as training for a standard neural network, and the remaining 30 (15 of *H. pylori*-negative and 15 of *H. pylori*-positive patients) as test images. CAD model showed an 87% sensitivity and specificity to detect *H. pylori* infection with an AUC of 0.96[50].

Nakashima *et al*[51] used blue laser images (BLI)-bright and linked color imaging (LCI) on 162 patients as learning material and those from 60 patients as a test data set. From each patient, three white-light images (WLI), three BLI, and three linked color images (LCI; Fujifilm Corp.) were obtained, respectively. For WLI, the AUC was 0.66.

AI FOR COLONIC POLYPS AND COLON CANCER

Colorectal cancer (CRC) is the third most frequent malignancy in males and second in females, and the fourth most frequent cause of cancer fatality[52]. The National Polyp Study registered that 70%-90% of CRCs can be prevented by routine endoscopic surveillance and removal of polyps[53], but 7%-9% of CRCs can occur despite these measures[54].

Around 85% of "interval cancers" are due to missed polyps or inadequately removed polyps[55]. Adenomas are the most common precancerous lesions throughout the colon. The ADR measures the endoscopist ability to identify adenomas. The ADR ranges between 7%–53% among endoscopists making depending on their training, endoscopic removal technique, withdrawal time, quality of bowel preparation, and other procedure-dependent determinants[56,57].

Several endoscopic innovations have been promoted to increase the ADR[58,59].

A review including 5 studies on the effect of high-resolution colonoscopes on the ADR showed conflicting results; a study concluded that the ADR is raised exclusively for endoscopists with an ADR lower than 20%[60].

CAD analysis has the potential to aid adenoma detection further.

Urban *et al*[61], used a different and representative set of 8641 hand-labeled images from screening colonoscopies handled among over 2000 patients. They tested the models on 20 colonoscopy videos with a whole duration of 5 hours. Expert colonoscopists were asked to identify all polyps in 9 de-identified colonoscopy videos, which were selected from archived video studies, with/without the benefit of the CNN overlay. Their findings were correlated with those of the CNN using CNN assisted expert review as the reference. The CNN identified polyps with an AUC of 0.99 and an accuracy of 96.4%. Indeed, in the analysis of colonoscopy videos involving the removal of 28 polyps, 4 expert reviewers identified 8 further (missed) polyps

without CNN assistance and recognized an additional 17 polyps with CNN support. All polyps removed and recognized by the expert review were discovered by CNN, which showed a 7% false-positivity rate. This strategy could improve the ADR and lower interval cancers but it requires further studies to be adequately implemented.

AI can be used during endoscopic assessment to automatically recognize colorectal polyps and distinguish between malignant and non-malignant lesions. CAD is based on the latency time between the image acquisition to its processing for the ultimate visualization on the screen. This model was able to detect polyps with a 96.5% sensitivity[62,63].

A recent RCT estimated the impact of an automatic polyp detection system based on DL during real-time endoscopy. This study enrolling 1058 patients demonstrated that the AI system enhanced ADR of almost 10%[64].

A prospective study of 55 patients used a prototype of a novel automated polyp detection software (APDS) for automated image-based polyp detection and with overall real-time polyp detection of 75%[65]. Smaller polyp size and flat polyp morphology were associated with insufficient polyp detection by the APDS.

Aside from CADe machinery, CADx has been used for differentiating between adenomas and hyperplastic polyps.

Byrne *et al*[66] suggested the use of computerized image analysis to diminish the variability in endoscopic detection and histological prediction. This AI model was trained using endoscopic videos and was able to discriminate among diminutive adenomas and hyperplastic polyps with high accuracy. Additionally, it predicted histology with a 94% accuracy, 98% sensitivity, 83% specificity, a negative and positive predictive value of 97% and 90%, respectively.

Moreover, an AI-assisted image classifier, based on non-optical magnified endoscopic NBI, has been employed to predict the histology of isolated colonic lesions[67], following the evaluation of 3509 colonic lesions. The most prevalent histological types were tubular adenoma (47.6%), carcinoma with deep invasion (15.9%), carcinomas with superficial invasion (7.9%), hyperplastic polyps (14.3%), sessile serrated polyps (7.9%) and tubulovillous adenomas (6.6%). The sensitivity of hyperplastic and serrated polyps was 96.6%, although it was lower for tubular adenoma and cancer. When investigating only diminutive colonic polyps, the correlation of surveillance colonoscopy interval using AI image classifier and histology was 0.97. Moreover, this classifier also showed high accuracy (88.2%) in the prediction of carcinoma with deep invasion, which is not endoscopically curable, and the HNPV and accuracy for carcinoma with deep invasion also suggested that it can assist to select treatable lesions.

The same author assessed the use of AI-assisted image classifiers in determining the feasibility of ER of large colonic lesions based on non-magnified images. The independent testing set included 76 large colonic lesions that fulfilled the indications for endoscopic submucosal dissection. Overall, the trained AI image classifier showed a 88.2% sensitivity (95%CI: 84.7-91.1%) in differentiating endoscopically curable *vs* incurable lesions with a 77.9% specificity (95%CI: 70.3-84.4%) and 85.5% accuracy (95%CI: 82.4-88.3%). This study determined a high accuracy of the trained AI image classifier in predicting the feasibility of curative ER of large colonic lesions. While the progress of AI using CNN is great for the recognition of specific mucosal patterns and image classification, in the next future the prediction performance might outperform an expert endoscopist[68].

Hotta *et al*[69] aimed to validate the effectiveness of endocytoscopy (EC)-CAD in diagnosing malignant or non-malignant colorectal lesions, by comparing diagnostic ability between expert and non-expert endoscopists, by using web-based tests. A validation test was produced using endocytoscopic images of 100 small colorectal lesions (< 10 mm). Diagnostic accuracies and sensitivities of EB-01 and non-expert for stained endocytoscopic images were 98.0% *vs* 69.0%, showing a diagnostic accuracy and sensitivity significantly higher to non-expert endoscopists when diagnosing small colorectal lesions.

A single-group open-label prospective study assessed the performance of real-time EC-CAD on 791 consecutive patients undergoing colonoscopy and 23 endoscopists to differentiate neoplastic polyps (adenomas) requiring resection from non-neoplastic polyps not requiring treatment, potentially reducing cost[70]. The results revealed a 96.4% negative predictive value of CAD with stained mode in the best-case whereas 93.7% in the worst-case scenario. Wile by using NBI, 96.5%, and 95.2% in the best and worst-case scenario.

Another study developed an automatic quality control system (AQCS) and assessed a hypothetical improvement of polyp and adenoma detection in clinical practice based on deep CNN. The primary outcome of the study was to assess the ADR in the 308

AQCS and 315 control group patients. AQCS significantly increased the ADR than the control group. A significant improvement was similarly seen in the polyp detection rate and the mean number of polyps identified per-procedure[71].

Finally, in a study including 117 patients with stage IIA CRC after radical surgery, an ANN-based scoring system, based on the tumor molecular features, recognized those with a high, moderate, and low probability of survival at 10-year surveillance interval[72]. The 10-year overall survival rates were 16.7%, 62.9%, and 100% ($P < 0.001$), whereas the 10-year disease-free survival rates were 16.7%, 61.8%, and 98.8%, respectively. This study revealed that the scoring system for stage IIA CRC high-risk individuals for a more aggressive therapeutic approach.

DL distinguishes patients with a complete response to neoadjuvant chemoradiotherapy for locally advanced rectal cancer with an 80% accuracy. This technology support might allow to choose patients particularly benefitting the conservative treatment than complete surgical resection[73]. This is the first study using DL to predict total pathological response after neoadjuvant chemoradiotherapy in locally advanced rectal cancer.

DISCUSSION

AI could represent an essential diagnostic method for endoscopists and gastroenterologists for the patient's treatments tailoring and prediction of their clinical outcomes.

AI seems particularly valuable in gastrointestinal endoscopy, to improve the detection of premalignant lesions and malignant, or inflammatory lesions, gastrointestinal bleeding, and pancreaticobiliary diseases[74].

However, current limitations of AI include the lack of high-quality datasets for ML development. Moreover, a substantial evidence used to elaborate ML algorithms comes only from preclinical studies[74]. Potential selection biases cannot be excluded in such cases. In this setting, a rigorous validation of AI performance before its employment in daily clinical practice is necessary.

A real measure of AI accuracy, should include as a side effect in the performances overfitting and spectrum bias[75].

Overfitting occurs when a learning model tailors itself too much on the training dataset and predictions are not well generalized to new datasets[75,76]. This effect is in open contradiction with the problem-solving principle of Occam's razor, which states that simpler theories have a higher quality of prediction[77]. In worst cases of AI algorithm application, underfitting can occur, obtaining models that cannot evidence accurately the underlying structure of the dataset, thus obtaining also bad predictivity model features[78].

On the other hand, spectrum bias happens when the dataset used for model development is not representative of the target population[75,79]. To avoid an overestimation of the accuracy and generalization, an external validation dataset collected in a way that minimizes the spectrum bias, should be guaranteed. Besides, well-designed multicenter observational studies, are required for a stronger validation.

Certainly, it is also noteworthy to acknowledge ethical issues since AI is not aware of the patient's choices or legal liabilities. The privacy issues could be addressed using federated datasets that don't involve centralized servers.

Future randomized studies could directly increase the overall value (quality *vs* cost) of the CNN by examining its effects on surveillance colonoscopy, endoscopic time, polyps and ADR, and pathology charges.

Since AI science is in progress, the current limitations must be considered as a future challenge, so actually they are inherited also in the medicine applications, including difficult predictability of situations characterized by some uncertainty.

In general, AI is revolutionizing the technology and impacting also other ethical aspects like human work replacement by machines, but this has always been an open question since the industrial revolution.

What can be done is to promote the mutual collaboration through gastrointestinal endoscopy applications, to reciprocally benefit from the achievements in both science fields.

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MINIREVIEWS

Techniques to integrate artificial intelligence systems with medical information in gastroenterology

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Abstract

Gastrointestinal (GI) endoscopy is the central element in contemporary gastroenterology as it provides direct evidence to guide targeted therapy. To increase the accuracy of GI endoscopy and to reduce human-related errors, artificial intelligence (AI) has been applied in GI endoscopy, which has been proved to be effective in diagnosing and treating numerous diseases. Therefore, we review current research on the efficacy of AI-assisted GI endoscopy in order to assess its functions, advantages and how the design can be improved.

Key words: Gastrointestinal endoscopy; Artificial intelligence; Diagnosis; Advantages

Core tip: Artificial intelligence (AI) has been the center of medical information in the 21st century and we have witnessed the tremendous change it has triggered in the diagnosis and treatment of many diseases. Gastrointestinal endoscopy is the core element of clinical procedures in modern gastroenterology as it provides direct evidence and guides precise diagnosis and treatment. Therefore, in this article, we review the latest findings on AI-assisted gastrointestinal endoscopy concerning its applications in the diagnosis and treatment of gastrointestinal diseases.

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INTRODUCTION

The 21st century has witnessed a tremendous revolution in life sciences. Targets within cells are increasingly being found so that targeted therapiesc, which will provide the maximum benefits while causing minimum or even no damage, are available to treat difficult miscellaneous diseases; hereditary information is continuously being deciphered in order that much more in-depth information on the mechanism of disease occurrence and progression can be established and interpreted. In addition, the first 20 years of the 21st century has also experienced the combination of computer science and clinical medicine, or what we call the application of artificial intelligence (AI) in the diagnosis and treatment of diseases. With the help of machine learning and deep learning algorithms, the sensitivity and specificity of diagnosis involving morphological judgement has rapidly increased, such as the diagnosis of diabetic retinopathy and breast cancer screening using mammography[1-3]. Moreover, incorporated with convoluted neural network (CNN) technology, automated classification of the condition of skin lesions is even possible by experts from a distance[4]. Thus, with the development of network technology to change from 4G network to 5G or an even more advanced network, the addition of AI in medicine will play a more important role in helping clinicians to more accurately combat diseases[5].

The diagnosis and treatment in gastrointestinal (GI) diseases has become more accurate and evidence-based since the popularization of GI endoscopy, which helps detect early-stage lesions and malignancies and thus guide the subsequent intervention[6]. In addition, GI endoscopy also contributes to the removal of early-stage lesions, which results in minuscule operative wounds and prevents further malignant change[7]. However, despite the fact that an increasing number of physicians are trained to operate a GI endoscope, a number of mis-diagnoses are reported annually due to physicians' incompetence, carelessness and visual fatigue[8]. AI-assisted GI endoscopy has been proved to have considerable potential in reducing the number of errors in order to optimize clinical performance by establishing a more suitable treatment strategy and improving long-term prognosis. As many clinical studies have been carried out in recent years, some of the basic disciplines and information concerning the area are known; however, global research is still in a very early phase[9]. Gastroenterology is regarded as a field where AI could have a significant impact and shape the future diagnosis and treatment pattern as both rely greatly on image- or video-based investigations[10]. Some of the research carried out so far has demonstrated that AI-guided endoscopy provides more solid evidence of suspicious neoplasia during examinations and assists optical biopsy to determine the features of lesions and subsequently integrate genomic and epigenomic information to provide optimal therapeutic plans[11]. Therefore, this review aims to summarize high-quality studies completed so far in order to assess the efficiency of the latest AI technology incorporated into GI endoscopy and determine how this technology can be improved.

THE ROLE OF AI IN GI ENDOSCOPY

To date, AI has proved efficient in aiding endoscopic examination and the treatment of GI lesions with high sensitivity, specificity and a successful treatment rate. These lesions include polyps, acute bleeding, precursor lesions and early-stage malignant tumors, especially tumors invading the mucosal and submucosal layers[12]. Without AI, observer variation and errors due to limited experience and expertise occur every now and then. AI-assisted GI endoscopy, is believed to largely reduce these errors and prevent visual fatigue. Among its applications, AI-guided identification and characterization of polyps is the earliest established and the best understood[13]. A team of physicians reported that their AI-guided model could not only accurately recognize the presence of polyps, but could also distinguish hyperplastic and adenomatous polyps based on the assessment of video images under GI endoscopy with a high sensitivity of 98% and a relatively satisfactory specificity of 83%. Their study indicated that AI-guided GI endoscopy was unlikely to miss possible malignant lesions[14]. Misawa *et al*[15] reported that AI-guided endoscopic optical biopsy based on the

EndoBRAIN system could identify and characterize the pathological features of polyps with the aid of indigo carmine dye. If this technology was further improved, it could increase the detection rate of small polyps as well as judge their pathological features, which could lead to correct decision-making regarding resection of the polyps[15]. Similarly, another team used a different algorithm based on CNN to train an AI system using archived images from endoscopic videos. Their test results indicated that the accuracy was as high as 96.4% with an area under the curve (AUC) of the receiver operating characteristics (ROC) of 0.991. They even found that AI-guided GI endoscopy was capable of identifying small adenomas of 1-3 and 4-6 mm in size, and that the number of polyps identified by AI-guided GI endoscopy was much higher than that identified by human-operated GI endoscopy[16]. In 2019, a research group also demonstrated that AI-guided GI endoscopy showed higher efficiency in detecting small adenomas. This research group conducted an open and non-blinded trial with over 1000 patients, who were later randomly divided into 2 groups who underwent GI endoscopy with or without the aid of AI. It was found that AI-guided GI endoscopy increased the identification rate from 20.3% to 29.1% and increased the number of identified adenomas from 0.31 to 0.53 per patient. However, in this study, GI endoscopy with and without AI showed no difference when examining patients with diminutive polyps, as human eyes were also unlikely to miss such apparent lesions[17]. Interestingly, AI-guided GI endoscopy was found to be even more efficient when used by less competent endoscopists and it was reported to be able to increase the skills of these physicians, which might be of significant help in continuous education and promote the popularization of GI endoscopy[18]. Besides the detection of polyps, AI experts along with physicians are now able to detect pre-malignant or early-stage malignant lesions in the GI tract using the latest AI technology, which was a huge challenge as senior endoscopists would sometimes mistakenly ignore such tiny mucosal or submucosal changes[19]. According to a recent study, when used to detect gastric precursor and early-stage malignancy, AI-guided GI endoscopy had the capability of less diagnostic time but resulted in greater sensitivity (65.6% *vs* 31.9%) and a higher positive predictive value (PPV) (41.9% *vs* 36.7%) compared with the naked eye[20]. With the increased prevalence of gastroesophageal junctional diseases, such as gastroesophageal reflux disease and others, gastroesophageal junctional adenocarcinoma has been the focus of attention in many gastroenterologists. AI-guided GI endoscopy was demonstrated to be effective in aiding physicians to detect underlying problems in the gastroesophageal junction and judge their pathological features. Moreover, some technologies have even made it possible for an AI-guided endoscopic resection for early-stage lesions in the gastroesophageal area[21]. In addition to the identification of neoplasms and their pathological features, some recent AI-assisted programs have made it possible to evaluate the depth of cancer invasion, which is of great help to clinicians as the invasion depth is difficult to evaluate with the naked eye. A team in Japan demonstrated that by using white light imaging (WLI) and narrow-band imaging (NBI), an AI system could be trained to differentiate superficial and deep invasion of esophageal squamous cell carcinoma (ESCC) within several seconds and with an accuracy of more than 80%[22]. Besides the determination of invasion depth, another team found that AI could actually define the benign and malignant borderline and subsequently help guide endoscopic dissection[23]. Moreover, the ability to judge whether the dissection completely removed the suspected malignancy has contributed greatly to planning subsequent therapy. Therefore, if these technologies could be further validated and developed, AI-guided GI endoscopy could have greater application potential.

URGENT NEED FOR AI-GUIDED ESOPHAGOGASTRODUODENOSCOPY

With the popularization of esophagogastroduodenoscopy (EGD), it is now possible to detect stomach lesions at an early stage. However, as early-stage lesions are much more insidious in terms of size, morphology and biological activity, the efficiency varied with the competence of endoscopists as long-term specialized training is mandatory to gain the expertise and experience needed to detect insidious precursor lesions[24]. This was confirmed by a series of statistics reporting that the rate of mis-diagnosis of upper GI lesions was around 15% over the last 3 years mainly due to human factors[25,26]. To resolve this problem, AI-guided GI endoscopy was invented to reduce the possibility of human-related errors. However, since GI endoscopy carried more uncertainty and anatomical variations, the application of AI in GI endoscopy has been difficult[27].

AI-GUIDED EGD IN DEFINING GI MALIGNANCIES

One of the milestones of EGD is that it has made it possible to detect and resect precursor cancerous tissue and so prevent traditional surgical resection which would produce massive tissue damage. Thus, there was always an urgent need to increase the sensitivity, specificity and accuracy for the detection of precursor cancerous lesions under EGD. The first attempt to combine AI and EGD was by a Japanese scholar who trained his system with WLIs, NBIs and chromoendoscopy based on indigo carmine. Validation with 2296 images provided a sensitivity of 92.2% and a PPV of 30.6%[28,29]. Therefore, this indicated that despite a satisfactory detectable rate, it might also produce a large number of false positive results, thus aggravate the social medical burden. Another Japanese team evaluated a CNN-based model trained using an endoscopic video and reported a sensitivity of 94.1%[20,30]. A Japanese team attempted to diagnose *Helicobacter pylori* (*H. pylori*)-related gastritis based on WLIs, NBIs and chromoendoscopy images and videos, and demonstrated a sensitivity and specificity of 81.9% and 83.4%, respectively[31]. A study validated the performance of their AI-guided model using 100 defined gastric cancer examination videos and 100 non-gastric cancer examination videos and found a sensitivity of 94.0%, a specificity of 91.0% and an accuracy of 92.5%[32]. A multicenter study validated the capability of their AI-guided diagnosis system using 7 validation sets collected from over 10 different hospitals to detect upper and lower GI tract tumors. The reported accuracy was between 91.5% and 97.7% with regard to different validation subsets[33]. They also compared the performance of their AI-guided GI endoscopy to the results of senior experienced physicians and junior physicians working in minor hospitals, which indicated that the AI-guided system could achieve comparative sensitivity to that of the experts (94.2% *vs* 94.5%) and could exceed that of junior physicians (94.2% *vs* 72.2%). Considering that most patients would consult outside of advanced or national hospitals, the help provided by AI-guided systems is necessary in minor hospitals to ensure diagnostic accuracy. Kanesaka *et al*[34] trained an AI system with the help of NBIs and successfully achieved an accuracy of 96%. Besides the aforementioned studies, other studies have also reported high accuracy and sensitivity for the detection of early-stage lesions using AI systems trained using magnified NBIs, which seem to be the future direction[35]. According to some other reports, AI-guided GI endoscopy was not only able to detect early-stage lesions, but was also capable of characterizing their features, such as invasion depth or biological activities. For example, an AI-guided system was used to estimate the invasion depth and the accuracy was 89.16%, which was much higher than that by humans[36,37]. Our team also attempted to build an AI-assisted automated system for the diagnosis of precancerous lesions and ESCC by training the system using 6473 NBIs images and 47 video datasets. Our findings demonstrated that the AI system involving deep learning could achieve a sensitivity of 98.04% and a specificity of 95.03% when distinguishing between ESCC and non-cancerous lesions[38].

AI-GUIDED EDG IN DEFINING OTHER GI DISORDERS

Besides defining early GI tumors, AI is also able to determine other benign gastric disorders, such as chronic non-atrophic gastritis, gastric and duodenal ulcers, *etc*. Among these, the most well-known is the ability to recognize *H. pylori* gastritis, which has been widely discussed. In 2020, Lui *et al*[39] carried out a meta-analysis involving 23 studies including 969318 images. They pointed out that the AUC for AI detection of Barrett's esophagus, neoplastic lesions in the stomach, squamous esophagus and *H. pylori* infection state were 0.96 (95%CI: 0.93-0.99), 0.96 (95%CI: 0.93-0.99), 0.88 (95%CI: 0.82-0.96) and 0.92 (95%CI: 0.88-0.97), respectively[39,40]. They also pointed out that by using NBIs, the AI system was superior to white light with regard to the detection of neoplastic lesions of the esophagus (0.92 *vs* 0.83, $P < 0.001$). Moreover, they reported a superior performance of the AI system over the human eye in detecting neoplastic lesions in the stomach (AUC 0.98 *vs* 0.87, $P < 0.001$), Barrett's esophagus (AUC 0.96 *vs* 0.82, $P < 0.001$) and *H. pylori* state (AUC 0.90 *vs* 0.82, $P < 0.001$)[41,42]. Earlier this year, Xia *et al*[43] developed a new automatic lesion detection system using CNN and faster region-based CNN (Faster-RCNN) and a total of 1023955 MCE images were used to train the AI system and help validate it, including erosion, polyps, ulcers, submucosal tumors, xanthomas, normal mucosa, and invalid images. They found that their AI system could detect gastric lesions with a sensitivity of 96.2% (95%CI: 95.7%-96.5%), a specificity of 76.3% (95%CI: 75.97%-76.3%), a PPV of 16.0% (95%CI: 15.7%-16.3%), a

negative predictive value (NPV) of 99.7% (95%CI: 99.74%-99.79%). They also demonstrated the accuracy for each type of lesion, the accuracy for erosion was 77.1% (95%CI: 76.9%-77.3%), the accuracy for polyps was 96.5%, the accuracy for ulcers was 89.3%, the accuracy for submucosal tumors was 87.2%, the accuracy for xanthomas was 90.6%, the accuracy for normal tissues was 67.8% and the accuracy for invalid images was 96.1%[43,44]. Their study also showed that the AI system was likely to indicate problems during an endoscopy examination rather than determine that it was normal. Another team also performed a validation test using an AI model based on WLIs and reported a sensitivity of 86.7%[45,46]. In addition, they pointed out that AI-guided GI endoscopy met difficult problems when trying to define benign lesions compared with malignant lesions as the stomach is often inflamed and even eroded which could add to the difficulty in making a definite diagnosis. Another study also reported the diagnostic value of AI-guided GI endoscopy based on CNN technology with an accuracy of 92.9%detected[47]. Some scientists have started to optimize the AI system by introducing blue light imaging and linked color imaging techniques, and have compared their efficiencies with single WLI. The results showed that the AUCs of ROC analysis of blue light imaging, linked light imaging and WLI were 0.96, 0.95 and 0.66, respectively, which indicated that the newly introduced technologies could enhance the examination findings[45]. In addition to defining *H. pylori*-related gastritis, deep learning technology has also helped physicians to detect and evaluate gastric and duodenal ulcers and predict their prognosis[40,48]. With regard to polyps, contemporary AI technology is able to precisely detect polyps, make an accurate classification based on histology, predict the possibility of disease progression and guide subsequent treatment. In the past, older models of computer-aided diagnosis could not analyze polyps in real-time, which resulted in the diagnosis of polyps being challenging. A scientific team designed an AI model with the capability of analyzing nearly 100 images a second which greatly increased the speed of machine reading as the previous model was only able to process fewer than 10 images a second[49]. In addition, the technology they applied allowed their model to achieve an accuracy of up to 96.4% when detecting polyps among 8641 images of 2000 patients. Later, similar models were designed and used to compare the detection efficiency between experts only and experts with the help of AI systems. The results demonstrated that the AI system was able to detect all polyps, which were also identified by the experts with a 7% false positive rate. Moreover, the AI system extracted 9 other insidious polyps which were not detected by the naked eye[50]. In addition, scientists developed a more advanced model based on deep learning which could determine the histological features of polyps. This team found that with the help of NBIs, the AI diagnostic model could achieve an accuracy of 95% while restricting the NPV value within the limit set by the Preservation and Incorporation of Valuable Endoscopic Innovations for Adenoma Assessment of Diminutive Adenomas[51]. One of the major purposes of AI-guided GI endoscopy was to reduce human-related factors as much as possible, and to maintain a stable sensitivity, specificity and accuracy regardless of the expertise of the operator. One AI model presented by Mori *et al*[18] demonstrated that the application of AI systems for real-time histological classification based on NBI or staining and magnification with an integrated endoscopy lens provided NPV rates of > 92 for distal diminutive lesions, which was not related to the operators' expertise. In addition, full evaluation of the polyps could be done within a minute. The detailed information of some studies concerning the diagnosis of polyps and neoplasms in the GI tract published after 2018 is shown in Table 1.

DISCUSSION

From the studies we have researched and analyzed in depth so far, we have found that by incorporating several AI technologies, GI endoscopy has achieved higher accuracy, faster diagnostic speed, and fewer human-related errors, *etc*. Firstly, AI technology has made it possible to eliminate the errors caused by doctors' incompetence and lack of experience and has guided junior doctors and doctors working in less prestigious hospitals to gain the necessary expertise. Secondly, this technology improves the relevance rate and recall factor of less obvious and less typical lesions due to their size or atypical shape and helps to achieve "early discovery and early treatment". Thirdly, the present AI technology is able to assist judgement in a number of lesion types including polyps, precursor changes in tumors, all types of mucosal and submucosal abnormalities, and inflammation, *etc*., which almost covers the disease spectrum of the GI tract. Thus, it can be concluded that as a diagnostic tool, AI greatly contributes to

Table 1 Detailed information on the studies concerning the diagnosis of polyps and neoplasms in the gastrointestinal tract published after 2018

Ref.	Training	Validation	AUC	Sensitivity	Accuracy
Chen *et al*[51], 2018	1476 images of neoplasms; 681 images of *H. pylori*	188 images of neoplasms; 96 images of *H. pylori*	NA	96.3%	90.1%
Urban *et al*[16], 2018	8641 images; 9 videos	1330 images; 9 videos	0.974	NA	96.4%
Misawa *et al*[15], 2018	73 videos	Cross validation	NA	90%	76.5%
Yamada *et al*[56], 2019	4087 images of polyps; videos	705 images with polyps; 4135 images without polyps	0.975	97.3%	NA
Klare *et al*[57], 2019	NA	55 colonoscopy examination videos	NA	75.3%	NA
Wang *et al*[17], 2019	3634 images with polyps; 1911 images without polyps	5541 images with polyps and 21572 images without polyps	0.984	94.4%	NA
Song *et al*[58], 2020	12480 images	545 images	0.93	82.1%	81.3%
Zachariah *et al*[59], 2020	8246 images	634 images	NA	96%	94%

H. pylori: *Helicobacter pylori*; AUC: Area under curve; NA: Not applicable.

the work of clinical physicians.

However, studies concerning the guidance of AI during treatment under GI endoscopy have rarely been published and trials on training AI systems to gain the ability to direct the resection of malformations have seldom been discussed. One of the major advantages of GI endoscopy is that it allows the resection of abnormalities to be performed in a minimally invasive way, which results in less damage than traditional surgery or laparoscopic surgery, AI guided-treatment under GI endoscopy should be further developed and discussed. Moreover, an AI-guided robot physician may even be possible when AI is trained to guide such a process.

CONCLUSION

The last decade has witnessed a number of studies concerning the application of AI in modern medical procedures. However, due to specific reasons, there is an obvious lack of high-quality prospective clinical trials. In fact, despite the large number of clinical studies published so far, only 6 were prospective randomized controlled trials (RCTs) that were focused on the efficiency and effects of AI-guided models[17]. Far fewer RCTs have emphasized the comparison between machines and the human eye. Gastroenterology has always led RCTs concerning AI, and of the abovementioned 6 RCTs concerning AI in medical fields, 5 of them are related to gastroenterology. Therefore, more RCTs should be planned and carried out to gain more reliable data[52]. To perform effective RCTs, a series of protocols and rules should be strictly followed. For instance, the optimal study design approaches for clinical trials of AI have been put forward and these recommendations have significant implications for GI endoscopy. Clinically-related outcome measures should be prespecified according to the way the AI model is being investigated. Moreover, AI-assisted polyp detection studies should apply validated outcome parameters such as adenoma detection rate, adenomas per colonoscopy, or adenoma miss rate, *etc*[53-55].

The next couple of years will witness a tremendous change in the medical field with the ever-accelerating development of AI technologies, in which the field of gastroenterology will be the center of such unprecedented change. With the advancement of AI technology, more high-quality RCTs should be designed and carried out to assess the technologies being developed and to correct any errors. In addition, standardized methods that contribute to the storage, organization and labeling of clinical images should also be the focus of attention.

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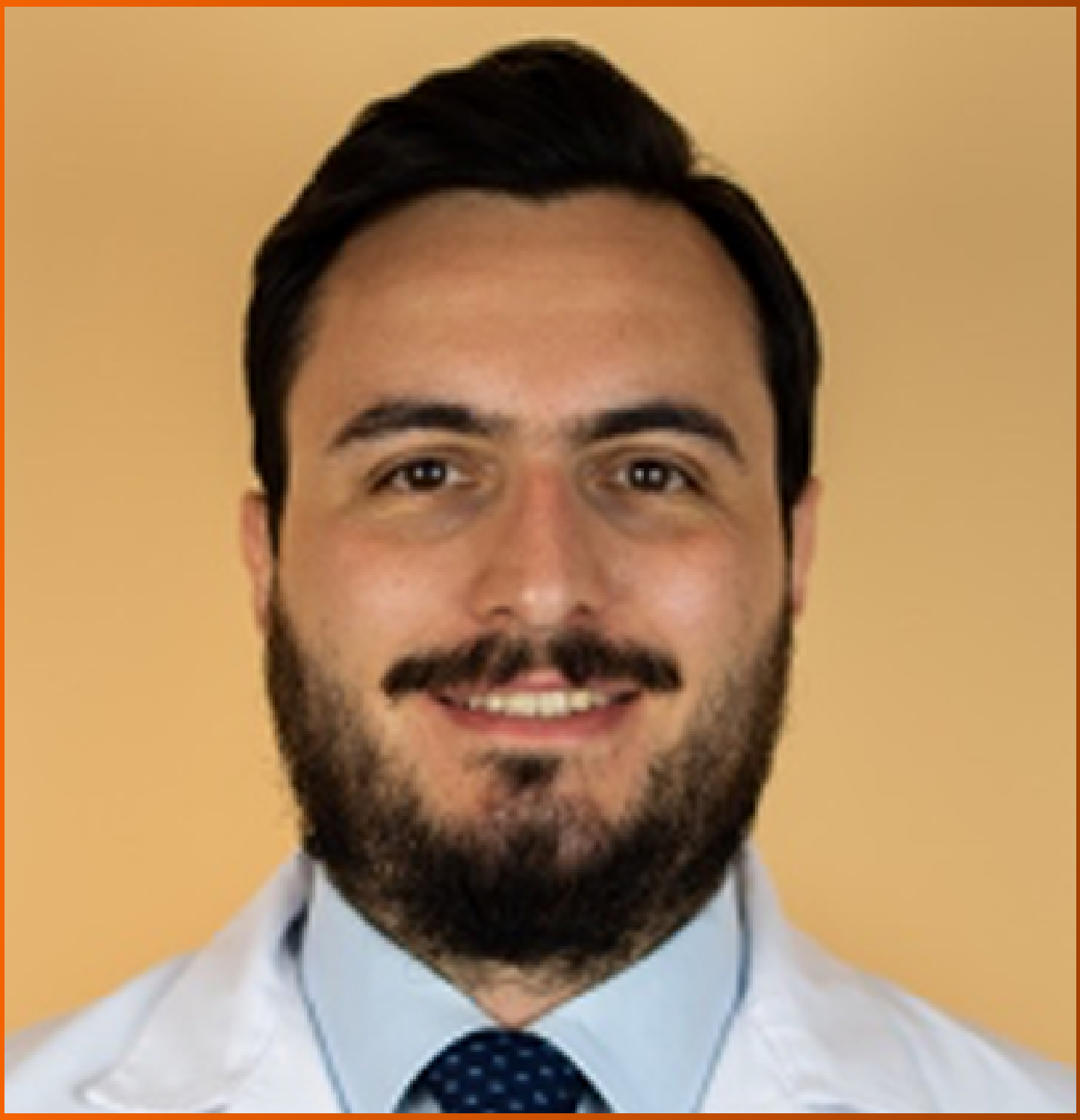

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ABOUT COVER

Editorial board member of *Artificial Intelligence in Gastrointestinal Endoscopy*, Dr. Marcello Maida received his medical degree in 2009, summa cum laude, at the University of Palermo (Italy), where he went on to perform his clinical training in gastroenterology. He is currently a consultant gastroenterologist at S. Elia - Raimondi Hospital in Caltanissetta (Italy), a member of the governing council of the Young Italian Gastroenterologists Association, and a manager of Gastrolearning, the Multimedia Educational Platform of Italian Medical Schools of Gastroenterology. Dr. Maida's research interests span several areas of gastroenterology, including endoscopy and liver diseases. He is author of several peer-reviewed publications indexed on PubMed, including some of the best referral journals in gastroenterology. (L-Editor: Filipodia)

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The primary aim of *Artificial Intelligence in Gastrointestinal Endoscopy* (*AIGE*, *Artif Intell Gastrointest Endosc*) is to provide scholars and readers from various fields of artificial intelligence in gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

AIGE mainly publishes articles reporting research results obtained in the field of artificial intelligence in gastrointestinal endoscopy and covering a wide range of topics, including artificial intelligence in capsule endoscopy, colonoscopy, double-balloon enteroscopy, duodenoscopy, endoscopic retrograde cholangiopancreatography, endosonography, esophagoscopy, gastrointestinal endoscopy, gastroscopy, laparoscopy, natural orifice endoscopic surgery, proctoscopy, and sigmoidoscopy.

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EDITORIAL

Artificial intelligence in Barrett's esophagus: A renaissance but not a reformation

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Abstract

Esophageal cancer remains as one of the top ten causes of cancer-related death in the United States. The primary risk factor for esophageal adenocarcinoma is the presence of Barrett's esophagus (BE). Currently, identification of early dysplasia in BE patients requires an experienced endoscopist performing a diagnostic endoscopy with random 4-quadrant biopsies taken every 1-2 cm using appropriate surveillance intervals. Currently, there is significant difficulty for endoscopists to distinguish different forms of dysplastic BE as well as early adenocarcinoma due to subtleties in mucosal texture and color. This obstacle makes taking multiple random biopsies necessary for appropriate surveillance and diagnosis. Recent advances in artificial intelligence (AI) can assist gastroenterologists in identifying areas of likely dysplasia within identified BE and perform targeted biopsies, thus decreasing procedure time, sedation time, and risk to the patient along with maximizing potential biopsy yield. Though using AI represents an exciting frontier in endoscopic medicine, recent studies are limited by selection bias, generalizability, and lack of robustness for universal use. Before AI can be reliably employed for BE in the future, these issues need to be fully addressed and tested in prospective, randomized trials. Only after that is achieved, will the benefit of AI in those with BE be fully realized.

Key Words: Barrett's esophagus; Artificial intelligence; Machine learning; Cognitive neural networks; Computer aided diagnosis; Endoscopy

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Core Tip: Screening and surveillance in patients with Barrett's esophagus (BE) remain problematic in regards to accuracy and adherence. This occurs in spite of recommendations and advances in endoscopic imaging. Artificial intelligence (AI) algorithms assist in endoscopic evaluation of BE by identifying potential targets for biopsy. This may occur by increasing endoscopic efficiency and diagnosing accuracy by decreasing procedure time. AI in BE has been developed by expert endoscopists and appear to perform similarly among them. At this point, the benefit of AI in BE may be for use by non-expert endoscopists and trainees to maximize BE endoscopic evaluation.

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INTRODUCTION

In 2020, the United States is estimated to record over 18000 new esophageal cancer cases and over 16000 deaths[1]. Furthermore, esophageal cancer remains in the top ten of cancers diagnosed and cause of cancer related death nationally. One common risk factor for esophageal adenocarcinoma (EAC) is the presence of Barrett's esophagus (BE). Currently, identification of early dysplasia requires an experienced endoscopist performing a diagnostic endoscopy consisting of random 4-quadrant biopsies to be taken every 1-2 cm within appropriate surveillance intervals based on absence or presence of dysplasia seen in the random biopsies[2-5]. Unfortunately, adherence to this recommendation remains inconsistent, particularly with low-grade dysplasia. Its subtle appearance and discontinuous nature can make it difficult to accurately biopsy areas for tissue pathology to confirm or rule out the diagnosis. In addition, there is significant difficulty for endoscopists to distinguish BE with low-grade dysplasiafrom high-grade dysplasia (HGD) or early adenocarcinoma. To combat this, high-definition white light, narrow band imaging (NBI), probe-based confocal endomicroscopy (pCLE), volumetric laser endomicroscopy (VLE) and optical computed tomography among others have all been tested and employed an in attempt to increase biopsy yield for accurate diagnosis[6-9]. However, early EAC is often flat and difficult to distinguish from the surrounding non-dysplastic Barrett's mucosa, even with these endoscopic advances. The rate-limiting step among of these technologies is that they are operator dependent, requiring hand-eye coordination to distinguish and biopsy suspicious areas, often-taking years to acquire the necessary skill set. Theoretically, artificial intelligence (AI) can assist in this by using methods of deep learning to identify and process - in real-time - endoscopic data that may not consciously appreciated by humans such as subtle changes in color and texture to aid in taking targeted biopsies rather than random biopsies.

There have been recent advances in the development and testing of AI and various machine learning (ML) algorithms to improve the ability to identify dysplastic and malignant mucosa. Previously, computer algorithms were trained to classify a patient's likelihood for EAC based on symptoms or compare patient biopsy cDNA microarrays to known EAC samples. These methods drew us closer to accurately diagnosing dysplasia and malignant mucosa, but their sensitivities/specificities could not match the parameters outlined in American Society for Gastrointestinal Endoscopy's Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) criteria for new technologies. PIVI criteria recommends that the sensitivity should be at least 0.90, specificity should be at least 0.80 and a negative predictive value of at least 0.98 for detecting HGD or BE[10]. AI makes use of several methods of ML. One commonly used method is the cognitive neural network (CNN). In CNN, each node (or "neuron") is connected to other nodes in a way that mimics real human neural networking. Several layers of neurons can exist to make a single decision to call a grouping of pixels on an image either normal tissue or dysplasia. Multiple recent studies have already experimented with the capabilities of such computer-aided diagnosis (CAD) (Table 1). The advantages that AI appears to confer per-endoscopy is a removal of the inter-observer or intra-observer variability in identification of non-

Table 1 Computer-aided diagnosis of Barrett's esophagus

Ref.	Year	Study design	Lesions	Imaging modality	Image qualification	Teaching dataset	Validation method	Outcomes	Compared to expert/current standard
van der Sommen *et al*[11]	2016	Retrospective	HGD, early EAC	WLI	High quality, clear visible/absence of lesions	100 images	LOO	Per-image SPEC/SENS: 83%/83%; Per-patient SPEC/SENS: 86%/87%	Inferior
de Groof *et al*[12]	2019	Retrospective	Non-dysplastic and dysplastic BE	WLI	1280 × 1024 pixels – HD	60 images	LOO	Accuracy: 0.92; SENS: 0.95; SPEC: 0.85	NA
Swager *et al*[13]	2017	Retrospective	HGD, early EAC	VLE	High quality image database	60 images	LOO	AUC: 0.95, 0.89, 0.91	Superior
Ebigbo *et al*[15]	2020	Prospective	Early EAC	WLI	1350 × 1080 pixels and 1600 × 1200 pixels – HD	129 images	LOO	Accuracy: 0.899; SENS: 0.837; SPEC: 1.00	NA

AUC: Area under the curve; BE: Barrett's esophagus; EAC: Esophageal adenocarcinoma; HD: High definition; HGD: High-grade dysplasia; LOO: LEAVE-one-out; NA: Not available; SENS: Sensitivity; SPEC: Specificity; VLE: Volumetric laser endomicroscopy; WLI: White light imaging.

normal lesions, combined with rapid, objective analysis of all visual inputs in such a way that is consistent and not subject to fatigue. CAD can allow endoscopists to take targeted, high-yield biopsies in real-time. Compared to taking random biopsies per the Seattle protocol or using enhanced imaging, CAD may increase efficiency and accuracy for making a diagnosis by limiting the chance of missing neoplastic mucosa. Moreover, CAD may decrease risk by decreasing sedation time secondary to decreased procedure length.

Recent studies would indicate that CAD can be successful in the detection of neoplastic lesions in BE. Von Der Sommen *et al*[11] developed a ML algorithm that used CAD to analyze texture and color in static images to detect early neoplastic lesions in BE. The sensitivity and specificity were between 0.90 to 1.00 and 0.65 to 0.91 respectively. In a study by Groof *et al*[12], six experts identified likely neoplastic tissue in the same image and used these expert-delineated images to train the computer algorithm to identify neoplastic BE and non-dysplastic BE in test cases. The resulting sensitivity and specificity of the computer algorithm was 0.95 and 0.85 respectively. Swager *et al*[13] used CAD on *ex vivo* VLE images to retrospectively detect non-dysplastic BE and HGD or early adenocarcinoma. They were able to achieve a sensitivity of 0.90 and specificity of 0.93 while using VLE as the reference images rather than high-definition white light endoscopy.

Though the data is promising, nearly all research has focused on training an algorithm on a set of retrospectively gathered images. Because of this, these studies are unfortunately subject to selection bias since the images are often curated for high definition and typically from a single endoscopy center. Therefore, the algorithms are usually overtrained on a relatively small sample set and not generalizable to other images of poorer quality or a population with different incidence and/or prevalence of BE. A sparing number of prospective or real-time studies currently exist and these are performed on a rather small number of samples. Furthermore, standardization of AI systems is proving difficult, given that the details of the algorithm are in a "black box" and inaccessible to critique and direct modifications. The struggles that have been encountered in using AI for identification of Barrett's mucosa have been encountered in identifying early esophageal cancers. Though promising, the thresholds to detect early esophageal cancer are below PIVI criteria which may be secondary to limited images and lack of ability to identify images in real time. Hashimoto *et al*[14] may have found a way to overcome previous difficulties by being able to create a faster algorithm which allowed for a real time video overlay using a large database of images. Using this technique, Hashimoto *et al*[14] were able to identify early esophageal neoplasms with high accuracy.

The process of standardization of ML algorithms poses a difficult challenge. The algorithm may be different for white light endoscopy compared to NBI, VLE or pCLE. It is possible that subtle differences such as the brand of endoscope, wavelength of

light or white balance could impact specificity or sensitivity of a tested algorithm. There is no guarantee that a single algorithm would work both in populations of high prevalence of BE and populations of low prevalence. Ideally, several algorithms should be tested prospectively and compared to the current gold standard of random biopsy in large, multicenter randomized clinical trials. Some of these studies are currently ongoing. User databases such as ImageNet or GastroNet contain samples of labeled images for use for training and testing of algorithms, but there is need for databases of patients with varying prevalence of risk factors for BE to determine if a single algorithm is robust enough to accurately diagnose BE nationwide.

To date, the ML platforms used have been developed by expert endoscopists. A recent study published by Ebigbo *et al*[15] used real-time AI to identify cancer in BE and found that the AI system performed in a similar fashion to the expert endoscopist. Such programs can also help train non-experts and gastroenterology fellows alike by giving real-time feedback, thus propagating more expert endoscopists in a shortened timeframe. Of course, endoscopists who are not BE experts can also benefit as well.

CONCLUSION

AI represents a renaissance in endoscopy, but not a reformation. The benefit may lie in the improvement in recognition of dysplastic and malignant tissue among non-expert endoscopists or gastroenterology fellows, since expert endoscopists have similar performance to AI. Generalizability, robustness of a single or few algorithms that can apply to either different imaging modalities or diverse populations, and the ability to easily modify an algorithm are current obstacles that need to be addressed before we can reliably use AI in endoscopic management of BE.

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MINIREVIEWS

Understanding deep learning in capsule endoscopy: Can artificial intelligence enhance clinical practice?

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Abstract

Wireless capsule endoscopy (WCE) enables physicians to examine the gastrointestinal tract by transmitting images wirelessly from a disposable capsule to a data recorder. Although WCE is the least invasive endoscopy technique for diagnosing gastrointestinal disorders, interpreting a WCE study requires significant time effort and training. Analysis of images by artificial intelligence, through advances such as machine or deep learning, has been increasingly applied to medical imaging. There has been substantial interest in using deep learning to detect various gastrointestinal disorders based on WCE images. This article discusses basic knowledge of deep learning, applications of deep learning in WCE, and the implementation of deep learning model in a clinical setting. We anticipate continued research investigating the use of deep learning in interpreting WCE studies to generate predictive algorithms and aid in the diagnosis of gastrointestinal disorders.

Key Words: Capsule endoscopy; Deep learning; Machine learning; Wireless capsule endoscopy; Small bowel capsule; Video capsule endoscopy

Core Tip: Wireless capsule endoscopy is the least invasive endoscopy technique for investigating the gastrointestinal tract. However, it takes a significant amount of time for interpreting the results. Deep learning has been increasingly applied to interpret capsule endoscopy images. We have summarized deep learning's framework, various

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characteristics in published literature, and application in the clinical setting.

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INTRODUCTION

Since 1868, endoscopy has been constantly evolving and improving to assess the lumen and mucosa of the gastrointestinal tract, including the esophagus, stomach, colon, and parts of the small bowel[1]. Despite its utility, endoscopic examination of the small intestine is limited by its length and distance from accessible orifices[2-4]. This limitation is a factor that contributed to the development of wireless capsule endoscopy (WCE).

Developed in the mid-1990s, WCE utilizes an ingestible miniature camera that can directly view the esophagus, stomach, entire small intestine, and colon without pain, sedation, or air insufflation[2,5-7]. An important clinical application of WCE is the evaluation of gastrointestinal bleeding after a high quality bidirectional conventional endoscopy and colonoscopy does not identify a source of bleeding[5]. A typical WCE study lasts 8 to 12 h and generates 50000-100000 images. Reviewing that quantity of images requires significant time effort and training. Additionally, abnormalities in the gastrointestinal tract may be present in only one or two frames of the video which may be missed due to oversight[2]. An automatic computer-aided diagnosis system may aid and support physicians in their analysis of images captured by WCE.

Artificial intelligence (AI), an aspect of computer-aided design, has been rapidly expanding and permeating in academia and industry[8]. AI involves computer programs that perform functions associated with human intelligence[9,10]. Specific features of AI include computer learning and problem solving. AI was first described as the development of computer systems to perform tasks that require human intelligence, which can include decision making and speech recognition[11]. Many techniques of AI have been proposed to facilitate the recognition and prediction of patterns[12].

Machine learning (ML) is an application of AI that provides systems with the ability to automatically learn and improve from experience without explicit programming[13]. ML can recognize patterns from datasets to create algorithms and make predictions[10,12]. A tremendous breakthrough in ML has been the development of deep neural networks (also known as deep learning)[13]. Deep learning consists of massive multilayer networks of artificial neurons that can automatically discover useful features. To put it simply, deep learning can extract more patterns from high dimensional data[5,12]. Several deep learning models have been reported in the literature and are differentiated by their application[12]. Convolutional neural network (CNN), a type of deep learning, is highly effective at performing image analysis[8,13,14]. Given CNN's utility in image analysis, applications for CNN have extended into the medical field, including gastroenterology[8,14]. The main drawback of deep learning is a long training time. Advances in graphic processing units, however, have drastically reduced the training time of deep learning from days or weeks to hours or days[15].

ML and CNN have been increasingly explored and applied to diagnostic images found in radiology, pathology, and dermatology[15-18]. Likewise, ML and CNN have utility in endoscopy and WCE through image-based interpretation without alteration of the existing procedures[8,11]. Current applications of ML and CNN in gastroenterology include polyp detection, esophageal cancer diagnosis, and ulcer detection through image-based interpretation from WCE. WCE is among the top interests of AI researchers in gastroenterology.

LITERATURE REVIEW

We conducted a literature review on December 15, 2019 and updated it on March 31, 2020 on PubMed/MEDLINE database and IEEE Xplore digital library. The search phrase used for query data in PubMed/MEDLINE database was ("Capsule Endoscopy") AND ("Deep Learning" OR "Neural Network" OR "Neural Networks"). Similarly, the search phrase used for query data in IEEE Xplore digital library was ("All Metadata":"Capsule Endoscopy") AND (("All Metadata":"Deep Learning") OR ("All Metadata":"Neural Network") OR ("All Metadata":"Neural Networks")). As presented in Figure 1, we found 50 records in PubMed/MEDLINE database and 71 records in IEEE Xplore digital library. After removing 14 duplicate records, the total number of distinct records were 107.

Only articles written in English language or available in English translation were considered. Conference abstracts, review articles, magazine articles, and unpublished studies were excluded to ensure quality. At this stage, two authors (AA and YE) independently reviewed whether the studies met the above inclusion criteria based on the title and abstract. Then, the articles that passed the initial screening were independently reviewed again based on the full-text articles to locate all included studies within a predefined scope of this article.

USE OF DEEP LEARNING FOR CLASSIFYING GASTROINTESTINAL DISORDERS

The most common indication for using WCE is the evaluation of small intestinal bleeding. WCE has also be used to diagnose other small intestinal disorders, such as celiac disease, Crohn's disease, polyps, and tumors, for the evaluation of esophageal pathology in non-cardiac chest pain, and for colon cancer screening. As shown in Table 1, previous studies have focused on the use of deep learning for classifying gastrointestinal diseases and lesions identified on WCE images. Unsurprisingly, a frequently investigated outcome in published literature is bleeding. Deep learning models have enhanced WCE's ability to detect bleeding lesions (including suspected blood content and angioectasia) with relatively high sensitivity and specificity[19-27]. In addition to bleeding, researchers have also used deep learning models in WCE to classify other gastrointestinal lesions such as ulcers[19-21,28-32], Crohn's disease[33], polyps[7,19-21,34], celiac disease[6], and hookworm[35].

Deep network architectures

The deep network architecture is the full arrangement of neural networks in deep learning models covering input layer, hidden layers, and output layer. Although there were some variations with the deep network architecture, 16 out of 17 studies in Table 1 used CNN-based architectures in their deep learning models. The choice of deep network architectures depends on the classification objectives and individual research group. Nevertheless, many research groups prefer to use the well-known CNN-based architectures when classifying WCE images or benchmarking the performance of their custom deep learning architectures. These prebuilt CNN-based architects include LeNet[25], AlexNet[25,27,31,32], GoogLeNet[6,25,31], VGG-Net[25], ResNet[20,22,30], RetinaNet[29], Single Shot MultiBox Detector[23,28,34], and Xception[33].

WCE devices

In addition to variations in the deep learning architect, researchers had some variation in WCE device. There were three brands of WCE devices mentioned in these deep learning studies: PillCam (Medtronics), NaviCam (Ankon Technologies), and MiroCam (IntroMedic). Deep learning models can be incorporated with each device. However, different devices have different sizes and qualities of raw images, brightness, and camera angles. Since these devices are not standardized, the application of a specific deep learning model may not perform at the same prediction accuracy when applied universally to the other WCE devices.

Image resolution

Although the size and quality of the original WCE images is dependent on the device, image resolution is dependent on training time, deep network architecture, and lesion types. Intuitively, physicians prefer a higher image resolution when making an image-based diagnosis. However, higher image resolutions can lead to an increase in

Table 1 Deep learning applications in wireless capsule endoscopy for classifying gastrointestinal disorders

Ref.	Class/outcome variable	Deep network architecture	Device/image resolution	Training and internal validation dataset	Testing/external validation dataset	Accuracy (%)/AUC	Sensitivity (%)/specificity (%)
Majid *et al*[19], 2020, NA	Multiple lesions (bleeding, esophagitis, ulcer, polyp)	CNN with classical features fusion and selection	NA/224 × 224 pixels	70% of 12889 images from multiple databases	30% of 12889 images from multiple databases	96.5/NA	96.5/NA
Ding *et al*[20], 2019, China	Multiple SB lesions[1]	CNN (ResNet 152)	SB-CE by Ankon Technologies/480 × 480 pixels	158235 images from 1970 patients	113268334 images from 5000 patients	NA/NA	99.88/100 (per patient); 99.90/100 (per lesion)
Iakovidis *et al*[21], 2018, NA	Multiple SB lesions[2]	CNN and iterative cluster unification	(1) NA/489 × 409 pixels; and (2) MiroCam CE/320 × 320 pixels	(1) 465 images from 1063 volunteers; and (2) 852 images	(1) 233 images from 1063 volunteers; and (2) 344 images	(1) 89.9/0.963; and (2) 77.5/0.814	(1) 90.7/88.2; and (2) 36.2/91.3
Aoki *et al*[22], 2020, Japan	Bleeding (blood content)	CNN (ResNet50)	Pillcam SB2 or SB3 CE / 224 × 224 pixels	27847 images from 41 patients	10208 images from 25 patients	99.89/0.9998	96.63/99.96
Tsuboi *et al*[23], 2019, Japan	Bleeding (SB angioectasia)	CNN (SSD)	Pillcam SB2 or SB3 CE/300 × 300 pixels	2237 images from 141 patients	10488 images from 28 patients	NA/0.998	98.8/98.4
Leenhardt *et al*[24], 2019, France	Bleeding (SB angioectasia)	CNN-based semantic segmentation	Pillcam SB3 CE / NA	600 images	600 images	NA/NA	96/100
Li *et al*[25], 2017, China	Bleeding (intestinal hemorrhage)	CNNs: (1) LeNet; (2) AlexNet; (3) GoogLeNet; and (4) VGG-Net	NA/NA	9672 images	2418 images	NA/NA	(1) 99.91/96.2; (2) 99.96/98.72; (3) 100/98.73; and (4) 99.96/98.72
Jia *et al*[26], 2017, Hong Kong, China	Bleeding (both active and inactive)	CNN	NA/240 × 240 pixels	1000 images	500 images	NA/NA	91.0/NA
Jia *et al*[27], 2016, Hong Kong, China	Bleeding (both active and inactive)	CNN (Inspired by AlexNet)	NA/240 × 240 pixels	8200 images	1800 images	NA/NA	99.2/NA
Aoki *et al*[28], 2019, Japan	Ulcer (erosion or ulceration)	CNN (SSD)	Pillcam SB2 or SB3 CE/300 × 300 pixels	5360 images from 115 patients	10440 images from 65 patients	90.8/0.958	88.2/90.9
Wang *et al*[29], 2019, China	Ulcer	CNN (RetinaNet)	Magnetic-guided CE by Ankon Technologies/480 × 480 pixels	37278 images from 1204 patient cases	9924 images from 300 patient cases	90.10/0.9469	89.71/90.48
Wang *et al*[30], 2019, China	Ulcer	CNN (based on ResNet 34)	Magnetic-guided CE by Ankon Technologies/480 × 480 pixels	80% of dataset from 1416 patients	20% of dataset from 1416 patients	92.05/0.9726	91.64/92.42
Alaskar *et al*[31], 2019, NA	Ulcer	CNN: (1) GoogLeNet; and (2) AlexNet	NA /(1) 224 × 224 pixels; and (2) 227 × 227 pixels	336 images	105 images	(1) 100/1; and (2) 100/1	(1) 100/100; and (2) 100/100
Fan *et al*[32],	(1) Ulcer; and (2) Erosion	CNN (AlexNet)	NA/511 × 511 pixels	(1) 5500 images; and (2) 7410	(1) 2750 images; and (2) 5500 images	(1) 95.16/0.9891; and (2)	(1) 96.80/94.79; and (2)

2018, China				images		95.34/0.9863	93.67/95.98
Zhou *et al*[6], 2017, USA	Celiac disease	CNN (GoogLeNet)	Pillcam SB2 CE/512 × 512 pixels	8800 images from 11 patients	8000 images from 10 patients	NA/NA	100/100
Klang *et al*[33], 2020, Israel	Crohn's disease	CNN (Xception)	Pillcam SB2 CE/299 × 299 pixels	Experiment 1: 80% of 17640 images from 49 patients; Experiment 2: Images from 48 patients	Experiment 1: 20% of 17,640 images from 49 patients; Experiment 2: Images from 1 individual patient	Experiment 1: 95.4-96.7/0.989-0.994; Experiment 2: 73.7–98.2/0.940-0.999	Experiment 1: 92.5-97.1/96.0-98.1; Experiment 2: 69.5-100/56.8-100
Saito *et al*[34], 2020, Japan	Polyp (protruding lesion)	CNN (SSD)	Pillcam SB2 or SB3 CE/300 × 300 pixels	30584 images from 292 patients	17507 images from 93 patients	84.5/0.911	90.7/79.8
Yuan *et al*[7], 2017, Hong Kong, China	Polyp	Deep neural network	Pillcam SB CE/64 × 64 pixels	Unknown proportion of 4000 images from 35 patients	Unknown proportion of 4000 images from 35 patients	98/NA	98/99
He *et al*[35], 2018, Israel	Hookworm	CNN	Pillcam SB CE/227 × 227 pixels	10 out of 11 patients (436796 images from 11 patients)	1 individual patient (11-fold cross-validation)	88.5/NA	84.6/88.6

[1]Abnormal classes include (1) inflammation; (2) ulcer; (3) polyps; (4) lymphangiectasia; (5) bleeding; (6) vascular disease; (7) protruding lesion; (8) lymphatic follicular hyperplasia; (9) diverticulum; and (10) parasite.
[2]Various lesions include gastritis, cancer, bleeding, ulcer, vascular anomalies, polypoid anomalies, and inflammation anomalies. AUC: Area under the receiver operating characteristic curve; CE: Capsule endoscopy; CNN: Convolutional neural networks; NA: Not available; SB: Small bowel; SSD: SingleShot Multi Box Detector.

trainable parameters, floating-point operations, memory requirements, and training time. To counteract this, original images are often modified (either cropped or resized) to lower image resolution. As illustrated in Table 1, image resolution can range from 64 × 64 pixels to 512 × 512 pixels. The typical range of resolution is 240 × 240 pixels to 320 × 320 pixels. It is worth noting that all studies using the images captured by NaviCam (Ankon Technologies) selected the original image resolution of 480 × 480 pixels[20,29,30].

Data partitioning

A collection of WCE images labeled by physicians is the main data source, which is commonly referred to as a dataset. As a part of data pre-processing, the dataset is typically divided into two groups. This creates two different datasets from the labeled WCE images. The first dataset is for training and internally validating the deep learning models. Once the final model is selected, the second dataset is used for testing the performance of the model with the data the model has not seen. Hence, data partitioning is one of the factors that could impact the predive performance of deep learning models[36].

There were two common approaches for dividing the initial dataset identified during the literature review. The first was to partition the data based on the aggregated images. The second was to partition the data per patient or video. The ratio of the two datasets varied dependent on the study, but common ratios included 50:50, 70:30 and 80:20[19,24,30,33]. The second approach to partition was often used when

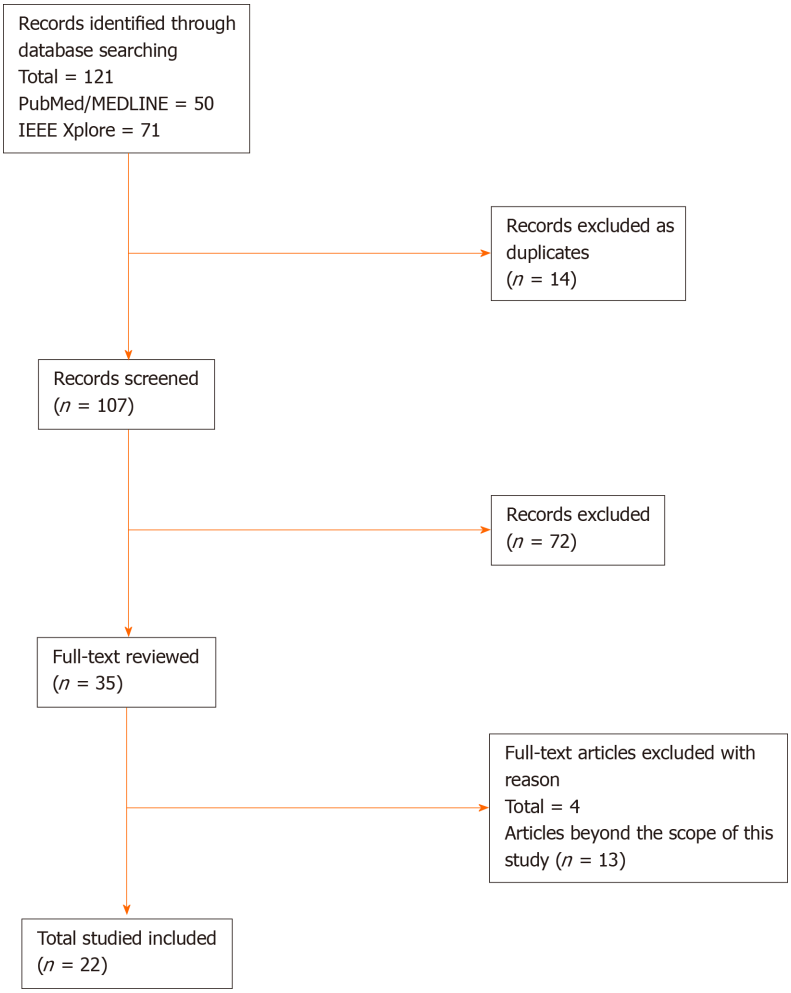

Figure 1 Study selection.

evaluating the predictive performance per patient[6,20,32,33]. Therefore, we can notice that the data partitioning approach in WCE images highly depends on the study design.

Performance metrics

In medical literature, the most popular performance metrics are accuracy, sensitivity, specificity, and area under the curve (AUC). In the case of WCE images, where few WCE images are true lesions, accuracy and specificity can be skewed by deep learning models correctly identifying normal mucosa. For this reason, in data science, the focus on performance evaluation is on true positive classification[37]. In other words, data scientists prefer their models correctly classify the small number of positive images (*e.g.*, angioectasia, tumor, or ulcer) rather than correctly classifying the normal mucosa images. Instead of accuracy and sensitivity, precision [true positive/(true positive + false positive)], recall [true positive/(true positive + false negative)], and F1 score (a harmonic mean of precision and recall) are the common performance metrics used by data scientists. It is worth noting that precision and recall are also known as positive predictive value and sensitivity respectively. Unfortunately, only a limited number of studies fully reported these set of performance metrics, especially F1 score[19,25-27]. In short, it is important to consider the performance metrics when determining or comparing the performance of deep learning models.

USE OF DEEP LEARNING FOR CLASSIFYING NON-DISEASE OBJECTS

The main goal when analyzing WCE images is to detect abnormalities in the gastrointestinal tract. However, it is also helpful to detect normal mucosa and anatomical landmarks. As shown in Table 2, only two studies were designed to classify non-disease objects. The first study used deep learning to classify the

Table 2 Deep learning applications in wireless capsule endoscopy for classifying non-disease objects

Ref.	Class/outcome variable	Deep network architecture	Device/image resolution	Training and internal validation dataset	Testing/external validation dataset	Accuracy (%)/AUC	Sensitivity (%)/specificity (%)
Seguí *et al*[38], 2016, Spain	Scenes (turbid, bubbles, clear blob, wrinkles, wall)	CNN	Pillcam SB2 CE/100 × 100 pixels	100000 images from 50 videos	20000 images from 50 videos	96/NA	NA/NA
Zou *et al*[5], 2015, NA	Organ locations (stomach, small intestine, and colon)	CNN (AlexNet)	NA/480 × 480 pixels	60000 images	15000 images	95.52/NA	NA/NA

AUC: Area under the receiver operating characteristic curve; CE: Capsule endoscopy; CNN: Convolutional neural networks; NA: Not available; SB: Small bowel.

complexities within the endoluminal scene, including turbid, bubbles, clear blob, wrinkles, and wall[38]. Although these images may not contribute to a final diagnosis, they can be used to characterize small intestine motility and to help rule out negative images. The second study created a predictive model for identifying organ locations such as the stomach, intestine, and colon[5]. Organ classification can be used to calculate the passage time of WCE in each organ and to determine if there are any motility disorders in the gastrointestinal tract. An important aspect of physician review of a WCE study is the identification of anatomical landmarks such as first images of the stomach, duodenum, and cecum which ultimately helps calculate capsule transit time through the small bowel. This transit time is vital to determining the location of lesion in the small bowel that may help guide treatment with deep enteroscopy techniques.

USEFULNESS OF DEEP LEARNING MODELS IN CLINICAL PRACTICE

An ideal goal for WCE would be the creation of a fully automated system for interpreting WCE images and generating accurate reports at least equivalent to conventional reading by physicians. Two retrospective studies compared the performance of conventional reading to the deep learning assisted reading (Table 3)[20,39]. The average reading times of deep learning assisted reading in both studies was less than 6 min. The average conventional reading time varied from 12 to 97 min depending on the expertise of the reader and the scope of WCE reading. In terms of overall lesion detection rate, there was a 3%-8% improvement of deep learning assisted reading over conventional reading. Interestingly, the accuracy of the deep learning model (as calculated during development) was higher than the actual detection rate. These findings may reflect the real-world challenges impacting human and deep learning model collaborations. An additional limitation was that there was no clear definition on how reading time was determined (*e.g.*, from data preprocessing to final report generation).

CHALLENGES

The goal when creating a deep learning model is to best fit your target function. Overfitting is a classic problem that can occur after creating the initial deep learning model. Overfitting occurs when a model learns the detail and noise of the training data too well to the extent that it negatively impacts the performance of the model on new data. Despite the standard methods for dividing datasets during training and testing, the detection rate in deep learning assisted trials are not as good when compared to the rates during the initial training and testing process[20,39]. The decreased performance could indicate that the model fits the training dataset too closely and does not perform well with an unseen dataset. Another explanation could be imperfect human and machine collaboration. Since the human physician is the one who makes the final diagnosis based on the information provided by the deep learning model, the misdetection could be derived from how human physicians use or trust the judgment

Table 3 Deep learning applications in wireless capsule endoscopy for improving the reading efficiency of wireless capsule endoscopy

Ref.	Experiment type	Scope of WCE reading /device	Conventional reading	Deep learning assisted reading	*P* value
Aoki *et al*[39], 2019, Japan	Retrospective study using anonymized data	SB section only/Pillcam SB3	mean reading time (min): Trainee: 20.7; Expert: 12.2	mean reading time (min): Trainee: 5.2; Expert: 3.1	< 0.001
			Overall lesion detection rate: Trainee: 47%; Expert: 84%	Overall lesion detection rate: Trainee: 55%; Expert: 87%	NS
Ding *et al*[20], 2019, China	Retrospective study by randomly selected videos	Small bowel abnormalities/SB-CE by Ankon Technologies	mean reading time ± standard deviation (min): 96.6 ± 22.53	mean reading time ± standard deviation (min): 5.9 ± 2.23	< 0.001
			Overall lesion detection rate: 41.43%	Overall lesion detection rate: 47.00%	NA[1]

[1]In per-patient analysis, deep learning assisted physician significantly outperformed conventional reading in detecting lymphangiectasia, lymphatic follicular, hyperplasia, inflammation, protruding lesion, and polyps. CE: Capsule endoscopy; NA: Not available; NS: Not significant; SB: Small bowel.

from deep learning models.

Traditionally, the risk stratification scores developed by one research team can be validated by another research team. Unfortunately, we have not seen the same level of transferability in deep learning research for WCE yet. As a result, the trials are very limited to their own research group and can be very difficult to have third party validation.

Each deep learning model is designed for a specific task that is based on the availability of positive lesions in their own dataset. Given this, it is questionable if it is even possible or effective to integrate these models. Integration can be even more complicated by the fact that each research group may use different devices, image resolutions, network architectures, and labeling practices.

One common barrier in medical device-related research is the use of proprietary file format. For example, the video file from PillCam device is stored in *.gvi and *.gvf file[40]. Thus, it may be difficult to extract data that is stored in the proprietary file format without help from the manufacturer. Such constraints may impact model integration and deployment. For example, it may take a longer time to prepare the files from deep learning models to use in a clinical setting. Also, there is no guarantee that the image resolution would be equivalent to the one seen in the proprietary reading software after extraction. For this reason, researchers should explore the pros and cons of each device available in their market to compare features and select the one that best aligns with their research goals.

Data preprocessing is the most time-consuming task in AI research. It is necessary to transform raw data into a ready-to-use and efficient format. Having a high-quality dataset is one of the key factors for creating a predictive model. By spending a lot of time extracting the data and labeling it, the dataset is a valuable asset to the research group. Ideally, high-quality datasets should be publicly available for researchers to use. However, there are a limited number of such datasets.

CONCLUSION

Since 2006, CNN-based architecture has proven to be an effective method for analyzing image data in various fields. Researchers have increasingly adopted CNN-based architecture for solving image classification problems. In our literature review, seventeen papers were identified that applied deep learning in WCE to classify gastrointestinal disorders. Our literature review demonstrated that the majority of CNN-based deep learning models were nearly perfect with regard to accuracy, sensitivity, specificity, and AUC[9].

There were only a few studies applying deep learning models to address non-disease objects, such as organ location and scenes in normal mucosa images (*e.g.*, turbid, bubbles, clear blob, wrinkles, and wall). These non-disease objects are important building blocks toward a fully automated system and can aid in the identification of "landmarks" such as the first images of each bowel segment.

Although there seems to be an increasing amount of deep learning research on classifying WCE images, we are still in the early stages of investigating the utility of

deep learning in enhancing clinical practice. The studies we identified often reflected the more standard view of WCE, as a means to view areas of the small bowel not accessible by upper and lower endoscopy. As the scope of WCE grows beyond the small bowel, we expect to see deep learning research on WCE expand accordingly. In addition, deep learning could enhance WCE capability to become highly effective in clinical practice and patient care by improving the speed and accuracy of WCE reading as well as predicting the location of abnormalities. Regardless of existing limitations and constraints, we expect the research and development in this area will continue to grow rapidly in the next decade.

The studies gathered in this literature review were indexed by PubMed. We also investigated publications concerning the utility of deep learning in computer science, medical image processing, mathematical modeling, and electrical engineering. Unfortunately, we cannot ensure that we identified every publication outside of PubMed.

In addition, it is difficult to compare one deep learning model to another based on their performance metrics alone. Most researchers have focused more on reporting traditional performance metrics without F1 score. The best practice for comparing these models would be to benchmark their performances on the same dataset that the models have never been trained on. To do so, researchers would need to make their trained models publicly available (*e.g.*, uploading them to GitHub). This would allow clinical trials on deep learning models to expand outside their research group.

The idea of using computational algorithms for analyzing WCE images is not entirely new. The earliest study identified was published in 2006[41]. Universal to all these studies was a central hypothesis investigating the ability of computational algorithms to improve the efficiency of reading WCE studies, specifically in terms of time and accuracy. The prospect of a fully automated system for interpreting WCE images would benefit patient care because of fast and accurate diagnoses of gastrointestinal medical conditions such as bleeding, polyps, Crohn's disease, and cancer.

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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *Artificial Intelligence in Gastrointestinal Endoscopy* (*AIGE*, *Artif Intell Gastrointest Endosc*) is to provide scholars and readers from various fields of artificial intelligence in gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

AIGE mainly publishes articles reporting research results obtained in the field of artificial intelligence in gastrointestinal endoscopy and covering a wide range of topics, including artificial intelligence in capsule endoscopy, colonoscopy, double-balloon enteroscopy, duodenoscopy, endoscopic retrograde cholangiopancreatography, endosonography, esophagoscopy, gastrointestinal endoscopy, gastroscopy, laparoscopy, natural orifice endoscopic surgery, proctoscopy, and sigmoidoscopy.

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MINIREVIEWS

Artificial intelligence assisted endocytoscopy: A novel eye in endoscopy

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Abstract

Over the past few years, emerging new approaches in endoscopic imaging technologies facilitate a high-quality assessment of lesions found in the gastrointestinal (GI) tract. Endocytoscopy (EC), as a novel tool in endoscopy, aids the more accurate evaluation of superficial mucosal surface. This review article aims to represent the most relevant information related to the latest EC technology and its clinical application in the lower GI tract diagnostic. We discuss EC-computer-aided diagnosis capability to differentiate between non-neoplastic and neoplastic lesion that offers a closer look to *in-vivo* assessment and diagnosis of cancerous tissue. Nevertheless, artificial-assisted EC diagnostics could also be employed with benefits in patients with inflammatory bowel disease (IBD) by accurately highlighting the presence of mucosal injury. In our review we included those studies comprising data about colonoscopy with narrow banding imaging and computer-aided diagnosis, as well as EC. Last but not least, artificial-assisted EC facilitates *in-vivo* diagnosis of the lower GI tract and may, in the future, remodel the field of *in-vivo* endoscopic diagnosis of colorectal lesions, representing another step towards the so-called optical biopsy.

Key Words: Endoscopic imaging; Endocytoscopy; Artificial intelligence; Artificial intelligence-assisted endoscopy; Colorectal cancer; Optical histology

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Core Tip: The possibility of obtaining "real-time histology" by endocytoscopy (EC) provides a time-saving and low-cost high-quality diagnosing process. It provides detailed detection and characterizations of gastrointestinal neoplasms, where EC defines the degree of neoplastic cellular transformation by visualizing variation in cell size, disorders of polarity, and nuclei deformity. Moreover, the EC system can evaluate the depth of cancer invasion and predict the therapeutic outcome. In line with this, one of the significant benefits from artificial intelligence (AI)-supported EC is avoiding unnecessary polypectomies and other pathological examinations and reducing redundant surgical procedures. Another major benefit of AI-assisted EC is to ensure enhanced delineation between benign and neoplastic colonic lesions. Furthermore, emerging EC-computer-aided diagnosis provides a novel endoscopic tool that contributes to the dramatic improvement of inflammatory bowel disease diagnosing and management.

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INTRODUCTION

In the last decade, the improvement in endoscopic detection of lower gastrointestinal (GI) lesions has dramatically improved. Advancement in endoscopic imaging technologies leads to a high-quality assessment of lesions found in the GI tract. One of the novel tools in endoscopy is endocytoscopy (EC), based on the principle of ultra-high magnification with intraprocedural stains[1]. This innovative endoscopic technique facilitates a more accurate evaluation of the superficial mucosal surface[2]. It allows real-time examination with the capability to distinguish normal from abnormal mucosa. EC allows evaluating the "*in vivo*" histological structure of colon epithelium by differentiation of colonic polyps and distinguishing invasive carcinoma from adenoma[3]. The aim of the "real-time" endoscopic diagnosis is time-saving and reduce medical patient costs. EC is a promising tool for the detection of GI abnormalities, which involves a contact light microscopy system with an ultra magnification capability (380-fold ultra-magnifying endoscopy), integrated into the distal tip of colonoscopy[4-7]. Using EC, we can perform "virtual histology" with high accuracy. It enables observation of cell stroma and nucleus, making it a perfect tool for diagnosing colorectal lesions[8].

In the last few years, with recent progress in artificial intelligence (AI), there is increasing interest in the application of computer-aided diagnosis (CAD) systems as a novel tool in improving the quality of EC[4]. The EC-CAD system's diagnostic algorithm includes three major steps: Nuclear segmentation, mucosal feature extraction, and output of predicted pathological classification. The major benefits of using EC-CAD systems are "real-time" high diagnostic ability during colonoscopy by expert and trainee endoscopists[9]. Many recent studies showed a correspondence between EC-CAD and pathological findings of lower GI lesions, which allowed this diagnostic endoscopic method to serves as a form of on-site "optical biopsy"[5,8].

The main goal of this review article is to represent the most relevant information related to the latest EC technology and its clinical use in the diagnostic of the lower GI tract. We included those studies comprising data about colonoscopy with narrow banding imaging (NBI) and CAD, as well as EC.

There are many directions in which this new endoscopic tool finds implications. We discussed the current situation of EC-CAD in the diagnostic process. EC observation could show not only cellular atypia with lumen observation and nuclei of the mucosal surface layer. Thus, differentiation between non-neoplastic and neoplastic lesion offers a closer look at *in-vivo* assessment and cancerous tissue diagnosis. Another critical point discussed concerns EC-CAD diagnostics in patients with inflammatory bowel disease (IBD), by highlighting the importance of accurate evaluation of mucosal injury.

FROM THE PAST TO THE PRESENT

First-generation EC was introduced in the clinical practice in 2003 (XEC120U; Olympus Medical Systems Corp., Tokyo, Japan). Afterward, the improved version of EC with double integrated-type lens was launched in 2005 (GIF-Y0001; Olympus Medical Systems Corp., Tokyo, Japan). Four years later, in 2009, the third generation of EC appeared with a single integrated-type lens and smaller outer diameter (GIF-Y0002; Olympus Medical Systems Corp., Tokyo, Japan). The latest version of EC arouses on the horizon in 2015 with the ability to provide high-quality colonoscopy (GIF-H290ECI; Olympus Medical Systems Corp., Tokyo, Japan). This latest model of EC comprises Magnified-NBI and EC observation with 520 × magnification[10]. Except for integrated EC, in the clinical practice exist a novel model of probe-based EC with higher magnification (1390×), providing simultaneously biopsy obtaining from the regions of interest[11].

In 2019, a new real-time interpretation of EC images, based on AI software, was introduced by Olympus. This new development is called "Endobrain" (EndoBRAIN; Cybernet Systems, Tokyo, Japan) and finds an application into ordinary colonoscopy as a helping tool for real-time diagnosis, allowing directly therapeutic decision[12].

PREPARATION AND STAINING OF THE COLONIC MUCOSA

EC requires good mucosal preparation to provide detailed images of colonic lesions. After intense washing of the mucosa with water, the second step of preparation is the application of simethicone and N-acetylcysteine[13]. The type of dye solution for mucosal staining is another crucial factor for informative imaging acquisition. Based on the literature data, three types of staining with different concentrations exist methylene blue (MB), toluidine blue, and crystal violet (CV). In 2006, Kodashima *et al*[14] published a protocol using 0.25% toluidine blue in the stomach and colon, with 60-sec time-exposure. According to Ichimasa *et al*[15], a mixture of 1% MB and 0.05% CV for colonic EC is superior to other staining combinations.

ROLE OF AI-ASSISTED EC IN COLORECTAL POLYPS

The possibility of obtaining "real-time histology" by EC provides time-saving and low-cost high-quality endoscopy. EC defines the degree of neoplastic cellular transformation by visualizing variation in cell size, disorders of polarity, and nuclei deformity[2]. Another significant EC system contribution is evaluating cancer invasion depth and predicting the therapeutic outcomes[16]. An interesting prospective study published by Kudo *et al*[5] in 2011 has demonstrated data about the feasibility of new EC classification in colorectal lesions. This classification was especially indicated to differentiate neoplastic from non-neoplastic colorectal lesions[5].

EC classification has five categories, which showed the glandular lumen changes and cellular nuclei of the target lesions. This evaluation system includes: EC1a, which indicates normal mucosa, EC1b show non-neoplasia (hyperplastic polyps), EC2 – adenoma with low-grade dysplasia; EC3a indicates adenoma with high-grade dysplasia (HGD), EC3b stands for invasive cancer (Figure 1)[5]. Histological findings have verified the abovementioned classification according to the Vienna classification (Figure 2).

Utsumi *et al*[17] conducted a study to differentiate neoplastic from non-neoplastic diminutive polyps (DP). They compared the results from EC in EC1b and EC2 DP with those obtained by histopathological results. The data showed that EC could be a potential tool for real-time histology in distinguishing benign from malignant colorectal lesions[17].

Over the past several years, a new understanding of colorectal carcinogenesis has emerged. In the past, lesions diagnosed as hyperplastic polyps (HPs) were thought to have no malignant potential. Nowadays, these allegations have changed. In this context, HPs may predispose to cancer because of their ability to transform into serrated lesions. These lesions could be found anywhere in the colon, but they are mostly placed in the distal colon (70%-80%). It was established that HPs, with right-side localization are more likely to have malignant potential.

Furthermore, although there are insufficient data on different microRNAs (miRNAs) expression profiles, they might play a role in serrated adenomas with different dysplasia grades. Compared to traditional colorectal carcinogenesis,

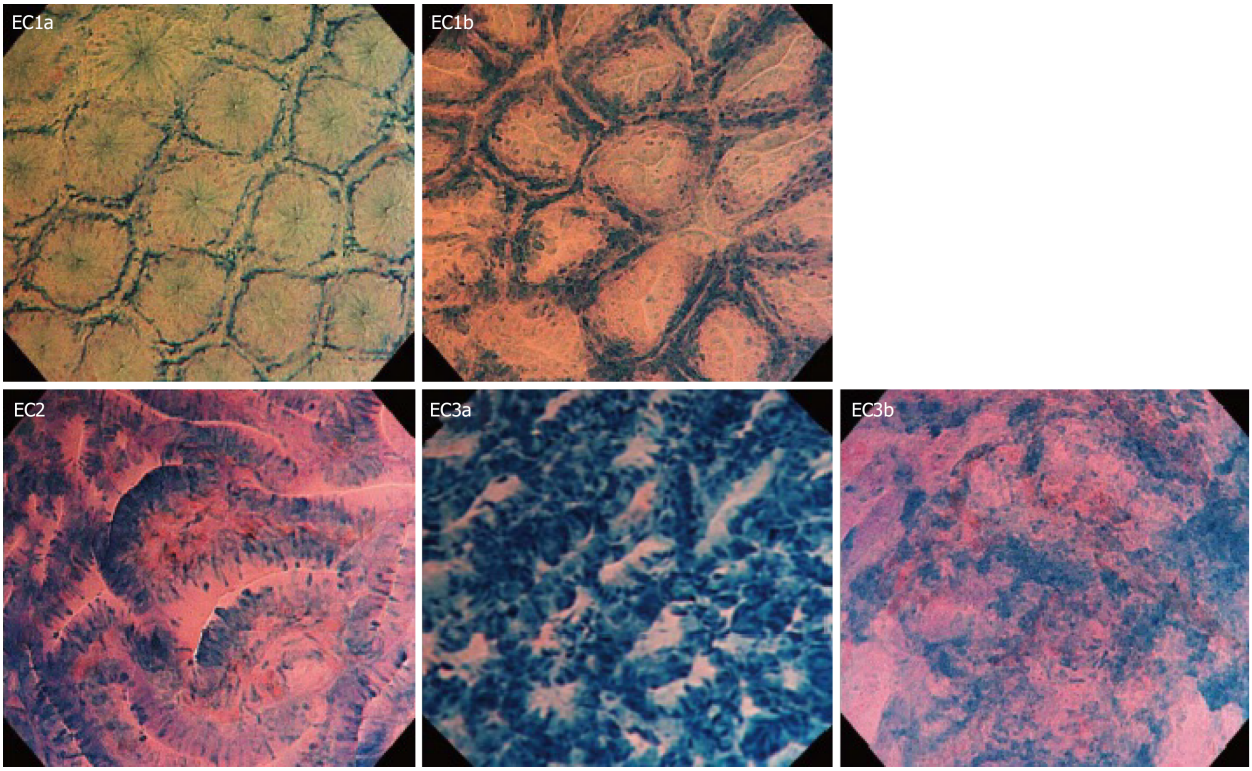


Figure 1 Endocytoscopy classification. This evaluation system includes endocytoscopy (EC) 1a, fusiform nuclei, and small round gland lumens - normal mucosa; EC1b, small granular nuclei and narrow, serrated gland lumens - non-neoplasia (hyperplastic polyps); EC2, slightly swollen fusiform nuclei or round nuclei and slit-like smooth gland lumens - adenoma with low-grade dysplasia; EC3a, plenty d swollen round nuclei and irregular gland lumens – adenoma with high-grade dysplasia, EC3b, plenty of highly distorted nuclei and unclear gland formation - invasive cancer. EC: endocytoscopy. This figure has been used with the permission of reference[5].

miRNAs' pivotal role and their related signaling mechanisms in the serrated pathway of carcinogenesis await to be elucidated[18]. In line with this, AI-assisted endoscopy could be an excellent complementary tool to provide the right and timely diagnosis.

According to the 5th edition of WHO classification of colorectal serrated lesions and polyps, they are classified into three histopathological subtypes: HPs, sessile serrated lesions (SSLs), and traditional serrated adenomas (TSAs)[19]. TSAs are extremely rare < 1% of all colorectal polyps, while HPs are the most common, comprising approximately 75% of all serrated polyps. SSLs (previously known as sessile serrated adenomas or sessile serrated polyps) cause nearly 25% of serrated polyps[20]. Thus, the management of serrated lesions depends on the accurate endoscopic diagnosis.

To provide a better understanding of serrated carcinogenesis and therapeutic strategies of these lesions, Kutsukawa *et al*[21] shed light on the accurate EC criteria for their proper diagnosis. In their study were included 785 SL, 712 were not observed with EC because of the smaller size (< 5 mm). The remaining 73 Lesions found out 12 mixed serrated polys, 3 of them with the carcinoma component, which led to their exclusion from the study. The remaining 58 polyps were divided into 27 HPs, 12 SSLs, and 19 TSAs. There were no polyps with HGD among the obtained specimens. The EC characteristic subdivided serrated polyps as follows: HP has star-like lumens and round nuclei; SSLs have oval lumens and round nuclei, and TSA has serrated or villous lumens fusiform nuclei. Their results pointed out that EC could be a feasible diagnostic tool in managing SL's therapeutic options. They concluded that SSLs and TSAs should be removed entirely. Indeed, many studies should be conducted regarding future therapeutic strategies related to SL[21].

Takeda's recent study evaluated the EC's diagnostic and therapeutic potential in juvenile polyps (JP). In the study, 154 JP were included, assessed by magnifying chromoendoscopy, 20 were analyzed by EC. The EC findings indicated that JP was characterized by dilatated ductal openings surrounded by normal glandular cells, greater distances between basal gland layers, and interstitial infiltration by inflammatory cells. This study showed that EC might be an additional diagnostic method for detecting JPs[22].

These findings indicate a tetralogy of magnifying chromoendoscopic findings characteristic of JPs: Reddish surfaces, surface erosion, open pits, and low pit density.

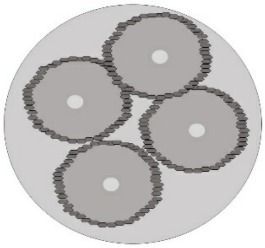
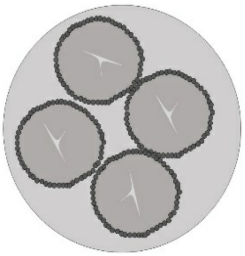
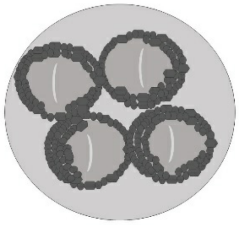
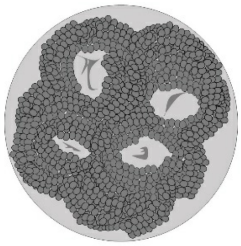
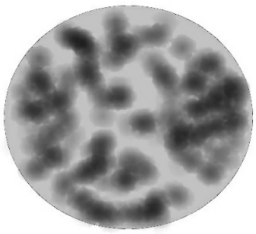
EC classification		Endoscopic findings	EC appearance	Histology report	Treatment
EC1	a		Fusiform nuclei Small round lumens	Normal mucosa	Observation
	b		Small granular nuclei Narrow and serrated lumens	Non-neoplasia (Hyperplastic polyp)	Observation
EC2			Slightly swollen fusiform nuclei or round nuclei Slit-like smooth lumens	Adenoma with LGD	Endoscopic resection
EC3	a		Plenty of swollen round nuclei Irregular lumens	Adenoma with HGD	Endoscopic resection
	b		Plenty of highly distorted nuclei Unclear gland formation	Invasive cancer	Surgical operation

Figure 2 Endocytoscopy classification with endoscopic findings. EC: Endocytoscopy; LGD: Low-grade dysplasia; HGD: High-grade dysplasia.

There is also a triad of EC findings characteristic of JPs, namely dilated ductal openings surrounded by normal glandular cells, greater distances between basal gland layers, and interstitial infiltration by inflammatory cells. The aforementioned magnifying chromoendoscopic and EC characteristics of JPs could be very useful in diagnosing JPs.

One of the GE field's critical issues is the ability of endoscopist to detect appropriately and characterize the different types of colon polyps. The combination of EC-CAD ameliorates the competence of endoscopists. Hence, the learning curve could be dramatically improved using EC-CAD as a diagnostic tool in lower GI endoscopy.

In line with this, an interesting study by Mori *et al*[23] revealed that EC-CAD could be a handy endoscopic device for the detection of DP as well as small polyps. The study was an international web-based trial, including 139 DPs and 205 small polyps (147 neoplastic and 58 non-neoplastic). The results showed 89% accuracy for detecting DPs

by EC-CAD compared to results obtained by experts. Additionally, they reported 89% sensitivity and 88% specificity for small polyps detection and differentiation[23].

For the first time in 2019, Kudo *et al*[24] performed an Endobrain analysis of images based on EC-NBI. Five academic centers in Japan participated in this study, where ten experts and 20 trainees made the endoscopic diagnosis. The endoscopists estimated images from 100 cases using white light endoscopy, EC with methylene blue, and EC-NBI images. Only EC images were assessed by the Endobrain system. The results showed 96.9% sensitivity and 100% specificity of Endobrain in distinguishing benign from malignant colorectal lesions compared with endoscopists and pathologists' findings[24].

On the other hand, Hassan *et al*[25], in 2020, published a comprehensive meta-analysis that aimed to summarize all reported information related to CAD system performance in colorectal dysplasia. The authors intended to emphasize the paramount importance of the CAD system in colorectal neoplasia detection because of the high percentage of missed lesions at screening colonoscopy.

The meta-analysis included 4354 randomizes patients (2163 in the CAD-group and 2191 in the control group). Five of them were performed in China and one in Italy from five studies. Their results give insight into how CAD could significantly increase the detection of colon polyps (DP, small and large adenomas), despite their location and their superficial morphology (flat and polypoid). Furthermore, they assumed that CAD significantly improved the detection rate of SSLs during colonoscopy. More interestingly, Hassan *et al*[25] reported nearly 2-fold enhanced diagnostics of advanced neoplasia. In detail, they concluded that CAD could lead to an increase in adenoma detection rate per colonoscopy, resp. 44% and 70%. The author emphasized that additional studies testing CAD in Western populations should be conducted to properly assess CAD's role in the polyp detection rate[25].

An interesting and significant publication by Mori *et al*[26] investigated the cost-effectiveness of AI in colonoscopy. The study investigated the performance of AI in the differentiation of colorectal polyps (neoplastic *vs* non-neoplastic). They included 207 patients with 250 rectosigmoid DP. The authors analyzed the colonoscopy's cost between two groups of patients with rectosigmoid polyps (≤ 5 mm). The first group included patients who underwent colonoscopy with a "diagnose and leave" strategy based on AI prediction. The second diagnostic and therapeutic strategy was "resect-all-polyps". Their results demonstrated that AI-assisted colonoscopy had 93.3% sensitivity, 95.2% specificity, and 95.2% negative predictive value in diagnostic colorectal neoplastic polyps. Moreover, they found out that the "diagnose and leave" strategy leads to a significant reduction in average colonoscopy costs. One of the study's significant benefits was that colonoscopy supported by AI can save a large amount of money spent on excessive polypectomies and pathological examinations[26].

ROLE OF AI-ASSISTED EC IN COLORECTAL CANCER

A massive breakthrough in technological developments in the last decade allowed performing *in vivo* real-time histology of the GI tract by simply pushing a button. Emerging EC-CAD provides enhanced delineation between benign and neoplastic colonic lesions. Furthermore, this novel diagnostic tool contributes to the detailed detection and characterizations of GI neoplasms.

With the emerging AI in endoscopy, therapeutic options for treating large colonic lesions become more accessible and accurate. AI technology provides "real-time" histology, thus determines whether a sizeable colonic lesion (> 2 cm) should be treated by endoscopic resection or surgery. AI endoscopy significantly shortens the process for making the final endoscopic and histological diagnosis of colonic lesions and avoids unnecessary tissue biopsy.

Lui *et al*[27]'s group has advocated a study that aimed to evaluate the application of AI-assisted image classifier to define the feasibility of curative endoscopic resection for large colonic lesions based on non-magnified endoscopic images. They trained the AI image classifier by 8000 endoscopic images of large colonic lesions. In comparison, the validation set comprises 567 endoscopic images from 76 patients. Histology findings of resected specimens have been used as a gold standard for validation in the study. Curative endoscopic resection was performed only in patients with well-differentiated adenocarcinoma, ≤ 1 mm submucosal invasion as well as without any lymphovascular invasion. The results obtained by the AI image classifier were compared with those taken by endoscopists (seniors and juniors). In patients with the lesions mentioned earlier, which are indicated for endoscopic curative resection, AI has excellent

accuracy (85.5%). This study highlights the clinical implication of AI in predicting endoscopic curative resection of large colonic lesions (> 2 cm)[27].

To the best of our knowledge, Ichimasa *et al* were the first to publish an article about the role of AI in predicting lymph node metastasis (LNM) in patients with T1 colorectal cancers (CRC). Their study aimed to point out that AI provides valuable information about the necessity for additional surgery after endoscopic resection for pT1 CRCs. One of the major key-points in deciding on additional surgery in patients who underwent endoscopic resection of T1 CRC is the presence of LNM. To minimize the necessity for additional surgery, the authors have used an AI model for predicting the possibility of LMN metastasis in patients with T1 CRC. The predicting LNM data were compared with those of the Japanese, European and American guidelines. The study results showed a 100% sensitivity of prediction LNM and a significant reduction of the unnecessary surgical procedure after endoscopic resection of T1 CRC without missing LNM positivity[28].

AI-ASSISTED EC IN INFLAMMATORY BOWEL DISEASES

With the implication of EC-CAD in clinical practice, the diagnostics of patients with inflammatory bowel disease (IBD) have dramatically improved. This novel endoscopic method allows for real-time histology diagnosis and predicts disease outcomes. Bessho *et al*[29] established an EC score system (ECSS) for assessment patients with IBD. ECSS assesses the shape, distance between crypts, and visibility of superficial microvessels. The system evaluated the severity of the disease according to the histological changes of the colonic mucosa. The authors also demonstrated a good correlation between this scoring system and Matt's histological grading[29]. ECSS was up-graded by Ueda *et al*[30] in 2018 by adding additional indicators: The mucosa pits' characteristics. Another benefit of this upgraded score system is the ability to predict disease relapse[30]. Using a probe-based EC with 1390× magnification, Neumann *et al*[31] shed light on EC's role in identifying mucosa's cellular structures in patients with IBD. This system allowed achieving a detailed analysis of ultrastructural patterns such as the nucleus - cytoplasm ratio and size and shape of the nucleus. The collected data provide the reliable distinction of different types of inflammatory cells in colonic mucosa[31]. In another study by Neumann *et al*[32], a concordance of 100% between standard histopathological grading and EC data was established. Another fascinating study by Nakazato *et al*[33], including 64 patients in clinical remission (Mayo 0 and Geboes score ≤ 2), revealed that ECSS has high accuracy for histological remission. In conclusion, they accept that ECSS could be a reliable assessment tool for histological healing evaluation[33].

A study by Maeda *et al*[34] reports about developing the EC-CAD system (520-fold ultra-magnifying endoscope), predicting persistent histological inflammation of colonic mucosa in patients with ulcerative colitis. The study's goal was to evaluate the colonic mucosa with the EC-CAD system to predict the onset of clinical exacerbation based on persistent inflammation of the mucosa. In their study, 187 patients with ulcerative colitis were included. They performed white light endoscopy to define the Mayo endoscopic score of colonic mucosa. After identifying the most severe inflamed area, they used EC with NBI mode. Their analyses showed that EC-CAD identified persistent histologic inflammation with 74% sensitivity and 97% specificity. Maeda *et al*[34] showed that EC-CAD has an incremental benefit for future therapeutic strategy. However, the authors considered more studies to be conducted because of the insufficient number of learning images[34].

CONCLUSION

Although the gold standard of histological observations of GI lesions based on a light microscopic analysis of hematoxylin and eosin-stained thin-slice specimens, a definition of optical biopsy has recently been introduced. Moreover, real-time EC evaluation can spare the histopathological diagnosis and allows the detection of cell-level lesions and the assessment of cellular and structural atypia *in vivo*. Both methods showed a significant correlation. Emerging novel AI-assisted EC is radically shifting our approach to treating gastrointestinal lesions. Indeed, not every lesion detected through colonoscopy needs to be excreted or sent for histopathological assessment.

However, before AI-assisted EC becomes a universal method, significant hurdles such as acceptance by patients or performing by less qualified endoscopists and

regulatory issues need to be carefully handled. The development of CAD and AI algorithms can promote, form, and improve decision-making in managing colorectal lesions. Overall, EC has shown an excellent diagnostic accuracy, offering to aid in the *in-vivo* diagnosis of lesions in the lower GI tract.

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