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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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OPINION REVIEW

Artificial intelligence assisted assessment of endoscopic disease activity in inflammatory bowel disease

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Abstract

Assessment of endoscopic disease activity can be difficult in patients with inflammatory bowel disease (IBD) [comprises Crohn's disease (CD) and ulcerative colitis (UC)]. Endoscopic assessment is currently the foundation of disease evaluation and the grading is pivotal for the initiation of certain treatments. Yet, disharmony is found among experts; even when reassessed by the same expert. Some studies have demonstrated that the evaluation is no better than flipping a coin. In UC, the greatest achieved consensus between physicians when assessing endoscopic disease activity only reached a Kappa value of 0.77 (or 77% agreement adjustment for chance/accident). This is unsatisfactory when dealing with patients at risk of surgery or disease progression without proper care. Lately, across all medical specialities, computer assistance has become increasingly interesting. Especially after the emanation of machine learning – colloquially referred to as artificial intelligence (AI). Compared to other data analysis methods, the strengths of AI lie in its capability to derive complex models from a relatively small dataset and its ability to learn and optimise its predictions from new inputs. It is therefore evident that with such a model, one hopes to be able to remove inconsistency among humans and standardise the results across educational levels, nationalities and resources. This has manifested in a handful of studies where AI is mainly applied to capsule endoscopy in CD and colonoscopy in UC. However, due to its recent place in IBD, there is a great inconsistency between the results, as well as the reporting of the same. In this opinion review, we will explore and evaluate the method and results of the published studies utilising AI within IBD (with examples), and discuss the future possibilities AI can offer within IBD.

Key Words: Inflammatory bowel disease; Artificial intelligence; Deep learning; Endoscopy; Disease severity; Machine learning

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Core Tip: Artificial intelligence (AI) is on the rise in inflammatory bowel diseases (IBD). Endoscopic evaluation is so far the most studied modality with promising results. Studies with others or the combination of several modalities have been carried out with moderate results leaving room for future research. Data availability and standardisation of the reporting of these new models seem to be the biggest challenges for AI's breakthrough within IBD. International consensus in the field is required to optimise research in AI.

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INTRODUCTION

The inflammatory bowel diseases (IBD), which mainly consist of Crohn's disease (CD) and ulcerative colitis (UC), are idiopathic immune-mediated diseases usually affecting young adults[1,2].

Currently, colonoscopy is considered the gold standard in the disease assessment of patients with UC as well as CD located in the terminal ileum and/or colon[3,4]. Disease activity of UC is assessed using scoring systems such as the Mayo Endoscopic Subscore (MES) or UC Endoscopic Index of Severity[5]. Despite their widespread use and being easy to use, both indices suffer from moderate to high inter-observer variation which reduces the credibility of the scores[6]. This has been demonstrated in clinical trials where up to one-third of patients deemed eligible for inclusion based on the MES did not live up to the inclusion criteria after reassessment[7]. Even central reading is associated with noteworthy inter-observer variation[7,8].

In CD, the CD Endoscopic Index of Severity and Simple Endoscopic Score for CD are currently the most used indices[4]. Both have demonstrated varying observer variance with central reading improving the inter-observer variation[9-11]. Capsule endoscopy (CE) for evaluating the small bowel can be scored using the Lewis score [12]. While widely used, the interobserver agreement between parameters in the index fluctuates widely (kappa 0.37-0.83)[13,14].

These interobserver variations and the risk of misclassification has led to the exploration of artificial intelligence (AI) assisted endoscopic assessment[15], especially in the field of colon cancer detection[16,17]. AI, depending on which method is used, mimics the human brain by having interconnected neurons that process the information given; however, in contrast to the human brain, AI can theoretically process an unlimited number of variables. In the field of IBD, the use of AI remains limited although it has received increasing attention. In the following review, we will discuss the use of AI-assisted assessment of endoscopic disease activity among CD and UC patients from a clinical perspective, the challenges the model faces and unexplored areas where AI has the potential to help patients and physicians.

CROHN'S DISEASE

CD can be examined using many modalities. Imaging has been an area of interest in terms of AI - especially CE[18]. A CE camera takes between 2-4 frames per second and has an approximate transit time of 250 min which can result in a total of approximately 60000 images[18]. One of the challenges CE entails is that it is a time-consuming process whereby a trained person must subsequently review all images. New AI has since assisted physicians and endoscopists in filtering out non-informative images, thereby leaving an image series where the computer believes there is an area of interest. Since the year 2000, AI has been used to identify polyps/tumours, ulcers, celiac disease, hookworms, angioectasia, and bleeding[18]. Among CD patients, special focus has been on small bowel lesions, erosions and ulceration[19]. The

majority of recent studies that have examined the listed parameters use a convolutional neural network - a deep learning method that has been shown to be effective in image recognition[18,20]. Overall, these studies have shown an accuracy of > 90% which must be considered close to perfect. However, the majority of these studies are conducted retrospectively and prospective results are wanted to demonstrate the models potential in clinical practice.

ULCERATIVE COLITIS

Due to UC only involving the colon it has been easier to categorise these patients than CD according to the extent and severity of inflammation[21]. Accordingly, most advances regarding AI in IBD has been done in UC and several clinical tools have been developed to assess the endoscopic disease severity. Such models have achieved an accuracy of 56%–77% in assessing the disease severity according to the MES or UC Endoscopic Index of Severity which was comparable to IBD experts[22-27]. The majority of studies have used methods such as the convolutional neural network to categorize images taken during a colonoscopy or sigmoidoscopy according to the MES. Recently, studies have also investigated the applicability of AI on videos; demonstrating a promising area under the receiver operating characteristic curve (AUROC or AUC) > 90%[24,26,27].

Currently, the available models are unable to distinguish between the different levels of the MES with sufficient accuracy. However, this is an area under great development and it is expected that within the coming years a model will be able to distinguish between the different MES levels with a satisfactory result and thereby eliminate the inter-observer variance, and standardize the clinical and academic evaluation of the endoscopic disease severity[28].

Few studies have further examined their model's MES score in relation to histological findings[29,30]. One study used endocytoscopy with a support vector machine and achieved an accuracy of approximately 90% in predicting histological findings which must be considered excellent results[29]. Endocytoscopy is, however, not an integral method in most clinics. Furthermore, although the study group utilized both a training and a test set, the training and optimizing process of the models is not described, leaving the reader with uncertainty with regard to *e.g.*, model selection and tuning of. Finally, samples were divided into active inflammation *vs* remission which might be too simplified a way of considering both the endoscopic and histological findings. Similar results were demonstrated by Takenaka *et al*[30] with white-light endoscopy, but with the same challenges. Ultimately, none of these studies validated the results on an independent cohort analyzed by independent experts, in order to test the performance of their model when compared to another population or to the point of view of different experts.

POTENTIAL AND DIFFICULTIES

As previously mentioned, AI has been shown to have great potential in the evaluation of endoscopic severity among patients with CD and UC. The models have shown to be at a level with or better than physicians to classify endoscopic disease severity; especially among UC patients[25]. Uniformity in the approach to the endoscopic procedure will make new clinical tools more credible and hopefully lead to less discrepancy between clinical and observational studies[31]. However, it is crucial that new models are developed for clinical purposes, which can be implemented more quickly, thereby reducing the gap between research and clinical practice.

Besides endoscopic evaluation, disease prediction in IBD has also been investigated using AI models. Waljee *et al*[32,33] used two clinical trial databases to predict C-reactive protein < 5 mg/L after 42 wk treatment with ustekinumab and steroid-free remission after 52 wk treatment with vedolizumab among CD patients, respectively. These studies used a combination of demographic, clinical, and biochemical data in a random forest model to predict patients' course after initiation of treatment. The models achieved an accuracy of 42% and 69%, respectively. Furthermore, the same study group investigated the treatment effect of vedolizumab in UC patients[34]. Using a random forest model, the model achieved an accuracy of 58% in predicting corticosteroid-free remission after 52 wk. When grouping UC and CD together, Biasci *et al*[35] used transcriptomics to identify a blood sample panel of 17 genes with sensitivity and specificity of approximately 73% to predict patients' risk of treatment

escalating within 1 year. A 5-year prediction study from Choi *et al*[36] demonstrated a sensitivity and specificity of 71% for predicting the risk of the use of biologics. In contrast to Biasci *et al*[35], this study utilized only demographical, clinical and common laboratory markers. Furthermore, Waljee *et al*[37,38] attempted twice to predict the treatment effect within 1 year, resulted in an AUC of 79% and 87% and accuracy of 72% and 80%, respectively. A limitation of these studies is that findings are only presented for IBD patients in total and not stratified according to the type of IBD. Despite these efforts, accuracies below at least 80% must be considered insufficient. Furthermore, even with accuracies above 80%, the results must be taken into perspective with the sensitivity, specificity and AUC to achieve an overall picture of the model's performance. Unfortunately, the majority of the studies have only reported some but not all measures of validity of which AUC is most commonly reported.

OTHER AREAS

It is not uncommon for some patients to undergo a lengthy diagnostic process before a definite diagnosis of CD or UC can be made[39]. This can be a challenge for both physicians and patients, and result in over or under treatments with major consequences for the patient. Recent studies using AI have attempted to use several modalities to better distinguish between these patients: endoscopy, histology, genetic markers, biochemical markers, clinical factors, omics, or a combination of one or more of these modalities[40-43]. These have shown acceptable results with AUC and accuracy of > 80%. It should be emphasized that these studies do not always report all results and many of the results are from validation data and not necessarily test data (unseen data) exposing the models to overfitting. However, to our knowledge, none of these models has been applied in clinical practice and real-life data are warranted to evaluate their efficacy.

To our knowledge, no other modalities explored in connection with AI have been published to date. In particular, the complexity of CD results in several challenges when developing new AI models. One area that remains untouched is the use of AI during colonoscopy in CD patients. This could be due to challenges in the endoscopic disease assessment of CD as the disease can be patchy and the severity varies between patches. Besides, indices for CD are difficult or time-consuming to use in clinical practice[4]. This could be accommodated by developing new scoring indices based on an evaluation from an AI model, allowing the possibility of assessing the gut as a whole rather than the segmented method currently being used.

In addition to endoscopies for both UC and CD, modalities such as ultrasound, magnetic resonance imaging, colon CE and computed tomography are obvious opportunities for the development of new clinical tools[44].

Unfortunately, this field is also challenged by several issues. First and foremost, a paradigm shift is needed; from a medical professional to a computer-aided assessment. This will first and foremost require doctors to accept the new technology [45] which can be difficult to understand as the latest AI architectures use deep learning where a black-box appears (the process between input and output)[46]. As it is not 100% possible to account for what happens in this black-box, mistrust might arise among the clinicians toward the models. Despite different ways of explaining the black-box, mathematically and illustratively, it is only possible to give an estimate of its process[46].

Secondly, medical education may need to be reorganized in the future to have more focus on interpretation and critical evaluation of the results of these new models. The medical field has experienced a similar paradigm shift before with the introduction of the World Wide Web[47]. This gave patients equal access to knowledge that physicians had and doctors went from being the ultimate definitive truth to now having to explain how the symptoms and the disease are connected and which diagnosis and disease courses are most likely[47]. However, a new organization of the medical education in connection with AI may require interdisciplinary involvement with, among others, bioinformatics and computer scientists to better equip doctors to interpret and critically evaluate the models' output.

Thirdly, larger amounts of data are needed – more than previously accustomed to developing these new models. However, the amount of data needed varies significantly in relation to the outcome and the methods used and no specific number of required data exists. As data is resource demanding, the estimate must be adjusted to what is clinically possible. In recent years, cross-border collaborations have been

Table 1 Recommendations for reporting of studies regarding artificial intelligence

Section	Requirements
Method	
	Origin of dataset and description of the acquisition process
	Pre-processing methods
	Definition of ground truth
	Split of data set and should include a training, validation and test set. A clear statement that the test set is not used to tune hyperparameters or in the selection of the model
	Method and architecture used, whether it is pretrained or not, and what dataset it is pretrained on
	Full technical detail should be included in supplementary files
	Statement of post-selection analyses and why these are conducted
Results	
	A complete report of all results including but not restricted to AUC, sensitivity, specificity, accuracy and kappa value for the overall model's performance and not for selected tasks
Discussion	
	Risks of overfitting and bias
	Generalisability and cautions to take
	Clinical implementation

AUC: Area under the receiver operating characteristic curve.

formed to make large amounts of data available. However, these are rarely freely available and the quality must also be critically evaluated when the workflow and equipment vary markedly between nations. We, therefore, encourage everyone to make their data at least partially accessible - a good example is The HyperKvasir dataset[48].

Finally, international reporting standards must be set within the field of IBD regarding AI studies. AI is still a relatively unexploited territory within IBD. This has led to great variation in the way the studies report both their methods and results, despite several calls for uniformity[49]. A good example is the endoscopic evaluation of disease severity in UC patients. Often, only AUC is reported, which can be misleading as sensitivity, specificity and accuracy may be only modest[25]. This is due to the fact that the AUC is a measure of how well the true positive can be separated from the rest, while measures of *e.g.*, accuracy hint at the actual performance of the models. Even when the studies report the wanted parameters, the reporting method can vary. For example, calculating the sensitivity, specificity and accuracy for each class rather than reporting the overall sensitivity, specificity and accuracy for the entire index. We, therefore, encourage that future articles as a minimum must report the information and parameters described in Table 1.

In addition, international journals should set standards for what is required of future AI studies within the field. The use of previous reporting methods, *e.g.*, STARD guidelines, seems outdated and should be updated to the new technological reality [50].

CONCLUSION

AI is on the rise in IBD. Endoscopic evaluation is so far the most studied modality with promising results. Studies with others or the combination of several modalities have been carried out with moderate results leaving room for future research. Data availability and standardization of the reporting of these new models seem to be the biggest challenges for the AI's breakthrough within IBD. International consensus in the field is required to optimize research in AI.

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OPINION REVIEW

Robotic pancreaticoduodenectomy: Where do we stand?

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Abstract

Pancreaticoduodenectomy (PD) is a complex operation accompanied by significant morbidity rates. Due to this complexity, the transition to minimally invasive PD has lagged behind other abdominal surgical operations. The safety, feasibility, favorable post-operative outcomes of robotic PD have been suggested by multiple studies. Compared to open surgery and other minimally invasive techniques such as laparoscopy, robotic PD offers satisfactory outcomes, with a non-inferior risk of adverse events. Trends of robotic PD have been on rise with centers substantially increasing the number the operation performed. Although promising, findings on robotic PD need to be corroborated in prospective trials.

Key Words: Pancreaticoduodenectomy; Whipple Procedure; Pancreas; Robotic; Surgery

Core Tip: The robotic Whipple procedure is a safe and technically feasible surgical operation. Robotic pancreaticoduodenectomy has shown favorable outcomes and is currently increasing in widespread implementation. Prospective trials are needed before this relatively new approach can be fully adopted as a standard of care in patients with pancreatic neoplasms.

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INTRODUCTION

Pancreaticoduodenectomy (PD) or Whipple surgery, is a complex procedure associated with significant morbidity rates[1]. Due to the complexity of this operation, PD's move to a more minimally invasive approach has lagged behind other general surgery procedures[2]. Gagner and Pomp[3], pioneered the laparoscopic PD (LPD) back in 1994, but LPD has not successfully transitioned into routine surgical care[3]. This is partly due to the difficulty associated with LPD in terms of expertise needed to perform the operation and the complexity of teaching the approach. In addition, the LEOPARD-2 trial demonstrated that LPD has a higher 90-d mortality as compared to the open PD (OPD). This eventually led to the discontinuation of the trial[4].

Robotic PD (RPD), which was first performed by Giulianotti *et al*[5], was originally described in 2001. Later in 2003, the same team published a series of 8 robotic-assisted cases[6]. The preliminary results established that RPD is both safe and feasible. Their reported mean operative time was around 8 h (490 min) in this case series.

Following these promising results, an increasing number of surgeons started utilizing the RPD approach. Different than initial reports of LPD, where some showed that LPD does not provide benefit as compared to the open approach, RPD benefits and advantages have been reported with increasing rate since its launch[7,8]. However, the "Miami International Guideline on Minimally Invasive Pancreas Resection" still does not assume minimally invasive PD is equal to OPD due to insufficient data[9].

WHAT IS THE ROBOTIC SURGICAL TECHNIQUE AND ITS CHALLENGES?

Robotic surgery is considered a direct advancement of laparoscopy. The most widely utilized surgical system to perform RPD in specific, as well as in other operations, is the DaVinci system developed by Intuitive Surgical Incorporated[10]. The robotic system provides surgeons increased dexterity employing endo-wristed instruction, three-dimensional stereoscopic views of the surgical field, filtering of user tremors, and it provides pancreatic surgeons the capability to perform extremely complex dissections, sutures, knots and reconstructions with unparalleled precision, magnification and accuracy[11,12].

Variations in robotic Whipple techniques exist between pancreatic surgeons. While some groups undergo the operation completely robotically, other choose to use a cross laparoscopic/robotic approach. Giulianotti *et al*[5] support a performing the operation entirely using the robotic approach, while other groups advocate the "hybrid" approach. The hybrid or cross method entails dissecting first using laparoscopy and then performing the reconstruction part using the robot[13,14]. At the University of Pittsburgh Medical Center, the surgeons employ a robotic exclusive approach, using four robotic ports, two assistant and one retractor port as shown in Figure 1. RPD follows the same steps as Whipple's 1935 description[15]. The gastrocolic ligament is first dissected to gain access to the lesser sac. Then, the ascending and transverse colon are mobilized. This is followed by a complete Kocher maneuver. Transection of the jejunum and the stomach (in classic Whipple) are then performed using stapling devices. Then, the porta is approached to transect the gastroduodenal artery and the hepatic duct. This is followed by transection of the pancreas at the neck and finally dissecting the uncinate of the mesenteric vessels. The reconstruction phase includes the creation of a pancreaticojejunostomy, followed by hepaticojejunostomy and finally a gastrojejunostomy. Finally, a drain is left behind and the port and extraction sites are closed.

The challenges facing the introduction of RPD are numerous. First, robotic operations are known to still have long operating time as compared to open ones. Second, due to the complexity of the robotic approach, there an increased need of training (higher learning curve) than the open and other minimally invasive techniques (laparoscopic). Third, robotic surgeries carry a high financial burden to patients, covering bodies and hospitals. This helps favor the open or laparoscopic approach for PD by insuring bodies and patients paying out-of-pocket. Fourth, RPDs require high-end infrastructure, which includes larger operating rooms, more technical staff present (in case any issues arise), and robotic certification by faculty and trainees. Finally, there is an increased difficulty in making prospective randomized trials in robotic operations. This issue arises with the decreased apparel/enrollment into robotic trials due to patient preference of open or laparoscopic approaches.

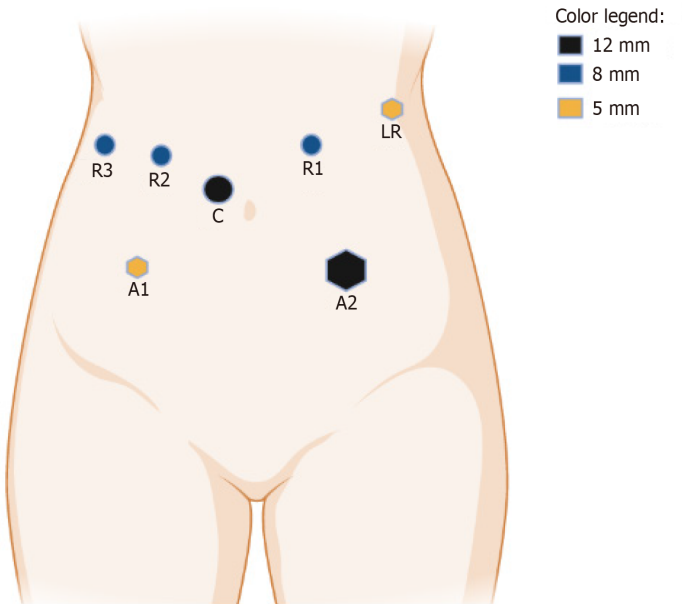

Figure 1 Port placement for robotic pancreaticoduodenectomy. R1: Robotic arm 1; R2: Robotic arm 2; R3: Robotic arm 3; C: Camera; A1: Assistant arm 1; A2: Assistant arm 2. Camera may be inserted through an 8 mm port in the Xi System. It may be inserted through a 12 mm port in the Si System.

WHAT ARE THE TRENDS AND OUTCOMES OF THE ROBOTIC WHIPPLE PROCEDURE?

A recent study exploring the trends of the RPD for pancreatic cancers demonstrated an increasing number of RPDs over the past decade. This was accompanied by a greater reach of RPD where it may be found in community centers across the US, after being present only in a few number of academic medical facilities[16]. Robotic procedures increased from 150 operations/year to around 450 operation/year from 2010-2016[16]. This is likely owing to an increase in the number of graduates from fellowship programs that include robotic pancreas surgery as part of their curriculum, as well as greater experience and "retraining" of experienced pancreatic surgeons in the robotic approach[17-20].

Overall, the robotic method appears to enhance short-term outcomes over time. Between 2010 and 2016, there was a substantial rise in the number of lymph nodes harvested (from 18 to 21), as well as a drop in postoperative mortality (from 6.7 percent to 1.8 percent)[16]. Yan *et al*[21] found that as compared to open PD, RPD had considerably longer operating time, less blood loss, shorter length of stay, and reduced infection rates in a recent meta-analysis comprising 2403 patients (788 robotic and 1615 open). There was no discernible change in lymph node harvesting, reoperation, readmission rate, or death rate[21]. Another meta-analysis by Kamarajah *et al*[22] found that RPD had substantially lower conversion and transfusion rates than LPD, with 3462 participants (1025 robotic and 2437 Laparoscopic]. RPD had a substantially shorter hospital stay after surgery, but there was no significant difference in postoperative outcomes or R0 resection rates. Zureikat *et al*[23] demonstrated that RPD was linked with decreased operating time, perioperative blood loss, and postoperative pancreatic fistula development in the largest series of RPD comprising 500 robot-assisted PD. These findings were described early in the group's experience and remained low despite growing complexity of cases. Less frequent conversion to open was also noted. As for long term outcomes, Nassour *et al*[24] identified 17831 PD from the National Cancer Database, of which 626 were RPDs. The median overall survival did not differ between the robotic (22 mo) and open (21.8 mo) approaches. Table 1 highlights RPD findings from a variety of research. In the hands of skilled surgeons, RPD is a relatively safe procedure with excellent perioperative and postoperative results.

Table 1 Outcomes of robotic pancreaticoduodenectomy in selected studies

Ref.	*n*	OR time (mean in min)	EBL (mean in mL)	Conversion (%)	R0 (%)	LN harvest (mean)	Fistula (%)	Morbidity (%)	Mortality (%)	LOS (mean in days)
Giulianotti *et al* [28], 2010	60	421	394	18.3	82	18	31.6	NR	3.3	22
Narula *et al*[29], 2010	5	420	NR	37.5	100	16	0	0	0	9.6
Zhou *et al*[30], 2011	8	718	153	0	100	NR	25	NR	0	16.4
Lai *et al*[31], 2012	20	491.5	247	5	73.3	10	35	50	0	13.7
Chalikonda *et al* [32], 2012	30	476	485	10	100	13.2	6.6	30	3	9.8
Bao *et al*[33], 2014	28	431	100	14	88	15	29	NR	2	7.4
Boone *et al*[34], 2015	200	483	250	6.5	92	22	17	67.5	3.3	9
Chen *et al*[26], 2015	60	410	400	1.7	97.8	13.6	13.3	35	1.7	20
Boggi *et al*[35], 2016	83	527	NR	1.5	NR	37	33.7	73.5	3	17
Nassour *et al*[36], 2017	193	399	NR	11.4	NR	NR	20.8	54.9	1	8
Jin *et al*[37], 2020	17	240	100	0	NR	4	59	66.4	NR	15
Mejia *et al*[38], 2020	102	352	321	12.7	73	24.2	3.9	31.3	2.9	7
Shi *et al*[39], 2020	187	279	297	3.7	94	16.6	10.2	35.6	2.1	22.4
Zureikat *et al*[23], 2021	500	415	250	5.2	85	28	20.2	68.8	1.8	8

EBL: Estimated blood loss; LN: Lymph node; LOS: Length of stay; NR: Not reported; OR: Operation; R0: Margin negative resection.

WHAT IS THE LEARNING CURVE AND FUTURE OF ROBOTIC WHIPPLE PROCEDURE?

The reported learning curves for RPD are currently variable among different institutions. The University of Pittsburgh Medical center reported that 80 RPDs would be required to optimize operative time, 40 cases for an optimal pancreatic fistula rate and 20 cases to improved blood loss and conversion[25]. This was due to the that fact the surgeons at the center had no prior training, mentorship, or guidance in the technique as the robotics program was implemented in 2008. According to Chen *et al* [26], a comparable result can be reached after 40 RPDs. At 40 patients, Zhang *et al*[27] found a comparable learning curve for RPD. The learning curve may be short if adequate training and guidance is performed in surgical formative years. A formal mastery-based curriculum which integrates complex robotic procedures into practice may help in shortening the learning curve.

The future directions of RPD will likely involve the use of robotics in borderline resectable or locally advanced pancreatic lesion cases i.e. more surgically complex cases. This also includes performing complex vasculature reconstructions using the robotic approach. However, in order to develop these surgical techniques, better infrastructure, increased training, and more prospective randomized clinical trials are required. The first step needed is to prove that RPD is noninferior to the open technique in PD with level 1 evidence. This entails increasing the number of prospective trials in order to perform meta-analyses and systematic reviews. Afterwards, increased funding and training can follow, which will allow for further developments of the RPD technique discussed. Additionally, robotic training will need to be introduced and integrated early into residency programs (possibly using simulation labs) to help with the learning curve of future robotic surgeons.

CONCLUSION

Current evidence indicates that RPD is a safe and feasible procedure. The robotic approach overcomes many of technical challenges associated with the laparoscopic Whipple procedure. RPD, in the proper hands, can help patients and surgeons with periampullary lesions achieve good results. More prospective clinical trials are still needed to verify previously published retrospective research on RPD.

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MINIREVIEWS

Robotic surgery in colon cancer: current evidence and future perspectives – narrative review

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Abstract

In the last 10 years, surgery has been developing towards minimal invasiveness; therefore, robotic surgery represents the consequent evolution of laparoscopic surgery. Worldwide, surgeons' performances have been upgraded by the ergonomic developments of robotic systems, leading to several benefits for patients. The introduction into the market of the new Da Vinci Xi system has made it possible to perform all types of surgery on the colon, an in selected cases, to combine interventions in other organs or viscera at the same time. Optimization of the suprapubic surgical approach may shorten the length of hospital stay for patients who undergo robotic colonic resection. From this perspective, single-port robotic colectomy, has reduced the number of robotic ports needed, allowing a better anesthetic outcome and faster recovery. The introduction on the market of new surgical robotic systems from multiple manufacturers is bound to change the landscape of robotic surgery and yield high-quality surgical outcomes.

Key Words: Colon cancer; Robotic surgery; Colectomy; Laparoscopy; Surgical outcomes: Robot system

Core Tip: Robotic surgery represents the natural evolution of laparoscopic surgery in the way to perform less-invasive operations. The robotic system Da Vinci Xi® with its technological innovations has made it possible to perform all types of interventions on the colon and has yielded large benefits to patients.

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INTRODUCTION

Cancer of the colon and rectum is one of the most common neoplastic diseases worldwide and is associated with high mortality rate[1]. Just as laparoscopic surgery has progressively replaced laparotomy, robotic surgery is becoming increasingly important in the treatment of this type of cancer. The advantages of robotic systems have been well known for years. Wrist flexibility, 3D vision and prevention of hand tremor enable surgeons to operate in reduced operative fields.

Many technological innovations have been introduced in recent years, such as a suprapubic approach, single port techniques and the use of tracers such as indocyanine green (used for the research of the sentinel lymph node and to verify tissues' vascularization).

The efficiency and effectiveness of robotic colonic resection have drawn the attention of many surgeons. Just as laparoscopic surgery in the late 1990s was compared to open surgery in terms of safety and effectiveness, nowadays robot-assisted surgery is often compared to the laparoscopic approach. From this point of view, robotic surgery seems to overcome the limits of laparoscopy. In fact, the proper value of the robot can be clearly appreciated in challenging tasks, such as performing intra-abdominal anastomoses in a restricted space, or in low pelvic dissection[2].

Although early results seem to encourage robot-assisted surgery, comparative studies investigating the effects of laparoscopic *versus* robotic colonic surgery are still ongoing and have not yet provided definitive data[3,4].

ROBOTIC VERSUS LAPAROSCOPY

The indications for robot-assisted and laparoscopic colorectal surgery are the same. Relative contraindications are emergency procedures, pneumoperitoneum intolerance and massive bleeding.

Comparison between robotic and laparoscopic surgery in terms of advantages and disadvantages has been considered a "hot topic" lately. Detractors of robotic surgery doubt its effective usefulness, citing the lack of definitive data demonstrating its superiority compared to the traditional laparoscopic approach[5] (many have stated that it is an "expensive toy" built to entertain surgeons). Nevertheless, increasing data about the effectiveness of robot-assisted surgery, in addition to its well-described technical advantages, have drawn the attention of surgeons all over the world.

Since the da Vinci System has been approved, an increasing number of robotic procedures has been registered worldwide. As a consequence, available data on robotics in colorectal surgery have increased greatly. In the international scientific literature, single- and multicenter studies, systemic reviews and meta-analyses can be easily found, focusing on the evaluation of robotic outcomes[6]. Two National Impatient Sample databases of laparoscopic and robotic colectomies[7,8] found no significant differences in overall complication rates and length of stay, while conversion rates were significantly lower in patients who underwent robotic resection (6.3% *vs* 10.5 %). One large study, based on the American College of Surgeons National Surgical Quality Improvement Program database, compared robotic and laparoscopic colorectal surgery in more than 11000 patients[9]. Focusing on pelvic surgery, the rate of conversion to open approach was lower in the robotic surgery group, while no significant differences in conversion rates were found in abdominal surgery. No differences were found in rates of wound infection, anastomotic leak, 30-day reoperation and 30-day readmission. When robot-assisted surgery was performed, mean hospital stay was significantly shorter but operating times were significantly longer. The reason for longer operating time is easily imagined. Robotic surgery needs longer preparation in terms of patient and arm positioning, moreover, being a new technique, the learning curve of the performing surgeon strongly affects the overall operating time. In our opinion, this highlights the importance of continued evaluation of the advances in robot-assisted surgery compared to more traditional minimally invasive techniques.

A retrospective cohort study of the Michigan Surgical Quality Collaborative registry compared robotic *versus* 2735 laparoscopy-assisted colorectal procedures in 2012–2014 [10]. Conversion rates were lower in robotic surgery, and this was significant for rectal resection. Also, hospital stay was significantly shorter in those operated upon with the robotic technique. No significant difference in rates of complications were found.

In our opinion, the most meaningful, largest and better-designed study was the Robotic Versus Laparoscopic Resection for Rectal Cancer (ROLARR) Trial[11] published in 2017. It was an international, multicenter, randomized controlled trial (RCT), involving 10 countries and 29 centers. Primary outcome was conversion to open procedure when performing total mesorectal excision (TME). Intra- and postoperative complications, circumferential resection margin, quality of life, bladder and sexual dysfunction and oncological outcomes were considered secondary outcomes. The results showed no differences in conversion rates or other secondary endpoints, demonstrating that, in expert hands, robotic colonic resection is safe and feasible. What deserves to be highlighted is that, once again, robotic surgery did result in longer operating time. Only experienced surgeons were included in the study (surgeons who performed at least 90 laparoscopic or at least 50 robotic procedures), excluding the influence of the learning curve on operating time. Therefore, we can conclude that, more likely, robotic operating time is more affected by its longer patient preparation, and instrument placement and changing. In our opinion, it is important to highlight that conversion rates were lower in the robotic *versus* laparoscopic surgery in men. This suggests that, when it comes to narrower pelvis, robotic surgery could be superior to the laparoscopic approach, bringing great benefits to patients. The authors concluded that robotic surgery does not confer an advantage in rectal cancer and has equivalent outcomes with increased costs (due to the price of robotic instruments and components).

A meta-analysis of five RCTs in 2018[12], including ROLARR, by Prete *et al*[12] compared laparoscopic *versus* robotic resection for rectal cancer. The results demonstrated no significant differences in circumferential radial margin positive rate, TME grade, postoperative leakage, number of lymph nodes harvested, mortality or complication rate. This meta-analysis highlighted that robotic procedures are connected to a decreased rate of conversion to open surgery but, at the same time, a significant increase in operating time.

Conversion rate is an important outcome that can influence other outcomes. The passage from minimally invasive to open surgery can influence postoperative complication rates. It can also be the cause of increased costs (due to longer hospital stay) and delays in chemotherapy, which can affect 5-year disease-free survival, leading to higher recurrence rates[9,13,14].

All the advantages and disadvantages of robotic surgery are summarized in the Table 1.

From the analysis of the literature, the following conclusions can be drawn regarding the different aspects taken into consideration.

Postoperative days until the first flatus and first oral diet

Robot-assisted colorectal surgery is associated with a shorter time to first flatus and to first oral intake[15-17].

Time of operation

The literature shows longer operating time for robotic surgery[15-20]. In most cases, the reason is probably related to the early learning phase of the surgeons. We believe that after an adequate learning curve, surgical times should be significantly reduced to be compared to laparoscopic surgery. Nevertheless, it is easy to imagine that overall operating time will be always slightly longer for robotic surgery due to longer time needed for patients' preparation and instrument placement and changing.

Length of hospital stay

The robotic approach had a shorter hospital stay in several studies[19-25].

Mortality (perioperative or 30 d after the operation)

A few studies have demonstrated that mortality rate is significantly reduced in robotic surgery[20-26], but, on the contrary, other systematic reviews and meta-analysis have not confirmed this result[16,21-23].

Conversion to open surgery

It has been demonstrated that, compared to laparoscopy, robotic surgery is associated

Table 1 Advantages and disadvantages of robotic surgery

Advantages	Disadvantages
High-resolution 3D view	Longer operating times due to patient preparation and positioning and docking time
Tool and wrist flexibility (seven degrees of freedom)	Lack of tactile sensation and stenic feedback
Elimination of hand tremors	High acquisition and maintenance cost
Ergonomic position which benefits the surgeon	
Faster learning curve	
Dual console and simulation software for training	
Integrated table motion	
Four trocars visualization with fluorescent/optical systems	
Robot-designed tools, like robotic stapler with smart-fire technology	

with a significantly lower rate of conversion to open surgery. This is more relevant in high-risk patients, such as men with a narrow pelvis, obese patients with lower rectal tumors, or those undergoing neoadjuvant therapy[13,16-23].

Intraoperative blood loss

In terms of blood loss, some studies have reported significantly lower rates in robotic surgery[17,18,20,24].

Anastomotic leakage

As far as we know, no significant differences regarding anastomotic leakage have been found in the literature. In our opinion, in the near future the introduction of new automatized stapling systems and new robotic technologies will reduce the rate of anastomotic leakage.

Resected lymph nodes

No differences have been reported in the number of lymph nodes resected using robotic *versus* laparoscopic surgery, although some studies have shown a higher number of harvested lymph nodes in the robotic approach[15].

Sexual and urological outcomes

Considering rectal cancer surgery, recovery of sexual and urological function is faster in patients who have undergone a robot-assisted approach compared to laparoscopic surgery. In one retrospective cohort study, rates of erectile dysfunction 1 mo after surgery were similar in both laparoscopic and robotic groups. However, 1 year after complete recovery, physiological functions were completely restored in all sexually active patients who underwent robotic resection and only in 43% of patients in the laparoscopic group[25-27].

Surgical wound infection

Review articles and clinical trials have not shown any significant difference between the robotic and laparoscopic groups for surgical wound infection. There is only one systematic review published in 2019 by Ng *et al*[16] that showed a significant difference in favor of the robotic approach. We believe that future technological innovation will allow an increasing number of full robotic procedures, and consequently, the size of the skin incisions will progressively reduce, therefore decreasing surgical wound infections.

Resection margins

Simillis *et al*[28] in a systematic review and network meta-analysis published in *Annals of Surgery* in 2019[28] demonstrated no significant differences regarding the involved resection margins. A study by Nixon *et al*[29] focusing on high-risk patients (preoperative chemoradiotherapy, male sex, tumor < 8 cm from the anal verge, body mass index > 30, and previous abdominal surgery) demonstrated that robotic surgery is related to higher rates of sphincter preservation, lower conversion rates, lower blood

loss and operating time, and consequently it is associated with shorter length of hospital stay.

THE PRESENT AND THE FUTURE

With advances in engineering and technology, surgical robots are constantly being improved. Exploration of new surgical approaches like the suprapubic approach or single port technique is of interest in the surgical field. The suprapubic surgical approach refers to a particular robotic technique in which ports used to perform colonic resection are placed in a horizontal line in the suprapubic area, and it is usually applied in robotic right colectomy. Recently, some authors have demonstrated[30,31] that the suprapubic approach has more advantages than the traditional port placement, with less console time and shorter hospital stay. Surgeons are attempting to reduce the number of ports used for robotic surgery. By reducing the number of surgical wounds, they aim to reduce the risk of postoperative wound infections. In this light, single port robotic surgery has begun to be performed more often. A systemic review[32] revealed that single port robotic surgery for colonic cancer is safe and feasible, with acceptable postoperative outcomes. These new changes have demonstrated promising potential in robotic surgery, in particular in colonic resection.

Until now, the surgical robot market has been monopolized, but it is easy to predict that the market for robotic platforms will rapidly grow in the near future as several manufactures are investing in the development of new robotic systems. For instance, MicroHand S is a robotic system produced in China and has recently entered clinical trials. Some studies have reported good performances and encouraging application prospects[33,34]. Senhance robotic system (TransEnterix Surgical Inc. Morrisville, NC, USA) has been recently introduced in Europe and approved for limited clinical use in the USA. Darwich *et al*[35] and Samalavicius *et al*[36] reported that procedures performed with this robotic system were safe and feasible and the robot could be used in general surgery. Versius from Cambridge Medical Robotics Ltd (Cambridge, UK), Hugo RAS from Medtronic Inc. (Dublin, Ireland), Meere Company (South Korea), Titan Medical (Toronto ON, Canada) and Virtual Incision (Pleasanton, CA, USA) have demonstrated potential in clinical applications. Competition between these new surgical robots from different manufacturers will surely change the market, leading to a reduction in costs with increased benefits for patients.

CONCLUSION

Robotic surgery offers a new minimally invasive approach in complex procedures or in anatomical areas that are difficult to reach. Robot-assisted procedures are not easier to perform, but robotic technology can make hard tasks feasible for less-experienced surgeons. In our opinion, robotic surgery could be considered the best option for rectal cancer surgical treatment, especially when compared to more traditional approaches (laparoscopic, open or transanal), since it offers the best combination of oncological, functional and patient recovery outcomes. Furthermore, the development of new approaches, like suprapubic and single port techniques, and the use of new devices, like the robotic stapler or vessels and lymph nodes tracers, will allow us to reach better results in oncological and clinical terms. The introduction of new surgical robots from multiple different suppliers will reduce their cost, leading to the widespread of the robot-assisted approach for colonic resection.

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MINIREVIEWS

Artificial intelligence in endoscopy: The challenges and future directions

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Abstract

Artificial intelligence based approaches, in particular deep learning, have achieved state-of-the-art performance in medical fields with increasing number of software systems being approved by both Europe and United States. This paper reviews their applications to early detection of oesophageal cancers with a focus on their advantages and pitfalls. The paper concludes with future recommendations towards the development of a real-time, clinical implementable, interpretable and robust diagnosis support systems.

Key Words: Deep learning; Oesophageal cancer; Early detection; Squamous cell cancer; Barrett's oesophagus

Core Tip: Precancerous changes in the lining of the oesophagus are easily missed during endoscopy as these lesions usually grow flat with only subtle change in colour, surface pattern and microvessel structure. Many factors impair the quality of endoscopy and subsequently the early detection of oesophageal cancer. Artificial intelligence (AI) solutions provide independence from the skills and experience of the operator in lesion recognition. Recent developments have introduced promising AI systems that will support the clinician in recognising, delineating and classifying precancerous and early cancerous changes during the endoscopy of the oesophagus in real-time.

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INTRODUCTION

AI is the artificial intelligence exhibited by computer machines, which is in opposition to the natural intelligence that is displayed by human being, including consciousness and emotionality. With the advances on both computer hardware and software technology, at present, we are able to model about 600 K neurons and their interlaced connections, leading to processing over 100 million parameters. Since the human brain contains about 100 billion neurons[1], there is still a long way to go to before AI models are close enough to a human brain. Hence machine learning (ML) techniques are developed to perform task specific modelling that is in part supervised by human. While this supervised ML process is transparent and understandable, the human's ability to comprehend large amounts of parameters, *e.g.*, in millions, is limited, from a calculation point of view. Hence the application areas are restricted by employing semi- or fully supervised ML approaches. More recently, propelled by the advances of computer hardware, including large memory and graphics processing unit (GPU), task specific learning by computer itself, *i.e.*, deep learning (DL), is realised, forming one of the most promising AI branches under the ML umbrella.

DL first made the headline when DL based computer program, AlphaGo, won the competition when playing board game Go with human players[2]. Since then, it has shown that nearly all winners in major competitions apply DL led methodologies, achieving state-of-the-art (SOTA) performance in nearly every domain, including natural language translation and image segmentation and classification. For example, the competition organised by Kaggle on detection of diabetics based on retinopathy has been won by DL based approach by a large margin in comparison with the other methods. While DL oriented methods have become a mainstream choice of methodology, there are advantaged and disadvantages, especially in the medical field. For example, a DL-based approach requires large amount of training datasets, better in millions, which is hardly met in medical domains. In addition, the training in deep layers demands higher computational power, leading to real-time processing a great challenge.

Hence this paper aims to review the latest development of application of AI to endoscopy realm and is organised below. Section 2 details the SOTA DL techniques and their application to medical domains. Section 3 explores the challenges facing early detection of oesophageal diseases from endoscopy and current solutions of computer aided systems. Section 4 points out future directions in achieving accurate diagnosis of oesophageal diseases with summaries provided in conclusion.

STATE OF THE ART DL TECHNIQUE AND ITS APPLICATION TO MEDICAL FIELD

DL neural networks refer to a class of computing algorithms that can learn a hierarchy of features by establishing high-level attributes from low-level ones. One of the most popular models remains the convolutional neural network (CNN)[3], which comprises several (deep) layers of processing involving learnable operators (both linear and non-linear), by automating the process of constructing discriminative information from learning hierarchies. In addition, recent advances in computer hardware technology (*e.g.*, the GPU) have propagated the implementation of CNNs in studying images. Usually, training a DL system to perform a task, *e.g.*, classification, employs an architecture in an end-to-end training fashion. As a result, by input of a raw datum, the trained system will output a classification label. The training activity takes place by processing the input data with known annotations (labels, or segmented regions) with a goal to establish a model to differentiate these annotated labels/region automatically by fine-tuning the relationship between parameters without the intervention of humans.

Conventionally, training a DL model requires large datasets and substantial training time. For example, the pre-trained CNN classifier, AlexNet[4], is built upon 7 Layers, simulating 500000 (K) neurons with 60 million (M) parameters and 630 M connections,

and trained on a subset (1.2 M with 1 K categories) of ImageNet with 15 M 2D images of 22 K categories, taking up 16 d on a CPU and 1.6 d on a GPU. Usually, more data will lead to more accurate systems. In the development of electric cars of Tesla's Autopilot, the training takes place with more than 780 million miles[5] whereas for playing AlphaGo[6] game using a computer, the training employed more than 100 million games.

DL-oriented approaches have recently been applied to medical images in a range of domains and achieved SOTA results. Although some doubt on DL has been casted on the 'black box' status while training without the embedding of human's knowledge in the middle stages (*e.g.,* hidden layers) apart from the initial input of labelled datasets, the performance of AI-led approached has been widely recognised, which is evidenced by the approval of medical devices by authorities. Between the year 2015 and 2020, 124 (about 15%) medical devices (mainly software) that are AL/ML/DL-based have been approved in Europe with *Conformité Européene* -marked and United States Food and Drug administration agency[7], highlighting the importance of AI/ML to the medical field, including an imaging system that uses algorithms to give diagnostic information for skin cancer and a smart electrocardiogram device that estimates the probability of a heart attack[8]. Table 1 summaries the recent achievements of DL-oriented approaches in medical domains.

Recently, AI or more specific DL-based approaches have won a number of competitions including the Kaggle competition on detection of diabetic retinopathy, segmentation of brain tumors from MRI images[9], analysis of severity of tuberculosis (TB) from high resolution 3D CT images in Image CLEFmed Competition[10] and detection of endoscopic artefacts from endoscopy video images in EAD2019[11] and EAD2020[12].

While applying AI/ML/DL approaches in medical domain, there are several challenges in need of responding. Firstly, in the medical domain, the number of datasets is limited, usually in hundreds whereas in other application, *e.g.,* self-driving cars, datasets are in millions. Secondly, images are in multiple dimensions ranging from 2D to 5D (*e.g.,* a moving heart at a specific location). And thirdly, perhaps the most outstanding obstacle is that medical data present subtle changes between normal and abnormal demanding the developed systems to be more precise.

Hence progress has been made to allow additional measures to be taken into account in order to apply DL techniques in medical fields. For example, for classification of 3D echocardiographic video images[13], a fused CNN architecture is established to incorporate both unsupervised CNN and hand-crafted features. For classification of 3D CT brain images[14], integration of both 2D and 3D CNN networks is in place. In addition, patch-based DL technique is designed to analyse 3D CT images for classification of TB types and analysis of multiple drug resistance[15,16] to overcome the sparse presence of diseased regions (< 10%). Another way to address small dataset issue is to employ transfer ML technique that is frequently implemented whereby a model developed built upon one dataset (*e.g.,* ImageNet) for a specific task is reused as a starting point for a model on a different task with completely different datasets [*e.g.,* coronavirus disease 2019 (COVID-19) computed tomography (CT) images]. Subsequently, most currently developed learning systems commence with a pre-trained model, such as VGG16[17] that is pre-trained on ImageNet datasets to extract initial feature maps that are then retrained to fit the new datasets and new tasks[18], capitalising on the accuracy a pre-trained model sustaining whilst saving considerable training times.

More recently, these AI techniques have been applied to predict COVID-19 virus and have demonstrated significant performance. With regard to medical images for diagnosis of COVID-19, CT and chest X-ray (CXR) represent the most common imaging tools. For 3D CT images, attention-based DL networks have shown effectiveness in classifying COVID-19 from normal subjects[19,20]. In relation to CXR, patch-based CNN is applied to study chest x-ray images[21] and to differentiate discriminatory features of COVID-19. In addition, COVID-Net[22], one of the pioneer studies, classifies COVID-19 from normal and pneumonia diseases through the application of a tailored DL network. To overcome the shortage of datasets, a number of researchers[23] apply generative adversarial neural network (GAN) to augment data first and subsequently to classify COVID-19.

In this paper, the application of AI/ML/DL techniques is exploited to endoscopy video images.

Table 1 Examples of deep learning-based approaches in application of medical tasks

Ref.	Medical domain	Tasks
Muehlematter *et al*[7]	Skin	Diagnosis of skin cancer
United States Food and Drug Administration[8]	Electrocardiogram	Detection of heart attack
Pereira *et al*[9]	Retinopathy	Detection of diabetics
Gao *et al*[10]	Pulmonary CT images	Detection of tuberculosis types and severity
Sharib *et al*[11], Ali *et al*[12]	Endoscopy	Detection of artefact.
Gao *et al*[14]	CT Brain images	Classification of Alzheimer's disease
Gao *et al*[15,16]	Pulmonary CT images	Analysis of multi-drug resistance
Gao *et al*[13]	Ultrasound	Classification of 3D echocardiographic video images
Wang *et al*[19], Ouyang *et al*[20]	Chest CT	Diagnosis of COVID-19
Oh *et al*[21], Wang *et al*[22], Waheed *et al*[23]	Chest X-Ray	Diagnosis of COVID-19
Everson *et al*[33], Horie *et al*[34], Ghatwary *et al*[35], Ohmori *et al*[38]	Endoscopy	Still image based cancer detection for 2 classes (normal vs abnormal)
de Groof *et al*[32], Everson *et al*[35], He *et al*[41], Guo *et al*[42]	Endoscopy	Video detection of SCC in real time
Gao *et al*[44], Tomita *et al*[45]	Endoscopy	Explainable AI for early detection of SCC

CT: Computed tomography; AI: Artificial intelligence; SCC: Squamous cell cancer; COVID-19: Coronavirus disease 2019.

ENDOSCOPY FOR DIAGNOSIS OF OESOPHAGEAL DISEASES

The oesophagus is the muscular tube that carries food and liquids from mouth to the stomach. The symptoms of oesophageal disorders include chest or back pain or having trouble swallowing. The most common problem with the oesophagus is gastroesophageal reflux disease which occurs when stomach contents frequently leak back, or reflux, into the oesophagus. The acidity of the fluids can irritate the lining of the oesophagus. Treatment of these disorders depends on the problem. Some problems get better with over-the-counter medicines or changes in diet. Others may need prescribed medicines or surgery.

As the 8th most common cancer worldwide[24], one of the most serious problems with regard to oesophagus is oesophageal cancer that constitutes the 6th leading cause of cancer-related death[25]. The main cancer types include adenocarcinoma and squamous cell carcinoma cancer (SCC). Globally, about 87% of all oesophageal cancers are in the form of SCC. The highest incidence rates often take place in Asia, the Middle East and Africa[26,27]. Early oesophageal cancer usually does not cause symptoms. At later stage, the symptoms might include swallowing difficulty, weight loss or continuous cough. Diagnosis of oesophageal cancer relies on imaging test, an upper endoscopy, and a biopsy.

Optical endoscopy or endoscopy is the primary diagnostic and therapeutic tool for management of gastrointestinal malignancies, in particular oesophagus cancers. As illustrated in Figure 1A, to perform an endoscopy procedure of monitoring oesophagus, an endoscopic camera along with a lighting inspection is inserted into the food pipe of the patient in concern, whereby the appearance inside the oesophageal tube in the form of video images can be visualised on a computer monitor that is linked to the camera image processing system, which is depicted in Figure 1B.

While Figure 1 presents the surface of oesophageal walls, it also shows the artefact in a number of frames. This is because the movements of the inserted camera is confined within the limited space of the food pipe. The most common artefacts include colour misalignment (C), burry (B), saturation (S), and device (D) as demonstrated in Figure 1B.

Challenges for detecting oesophageal squamous cancer

Commonly the five-year survival rate of oesophagus cancer is less than 20% as reported in[28]. However, this rate can be improved significantly to more than 90% if the cancer is detected in its early stages due to the fact that at this early stage,

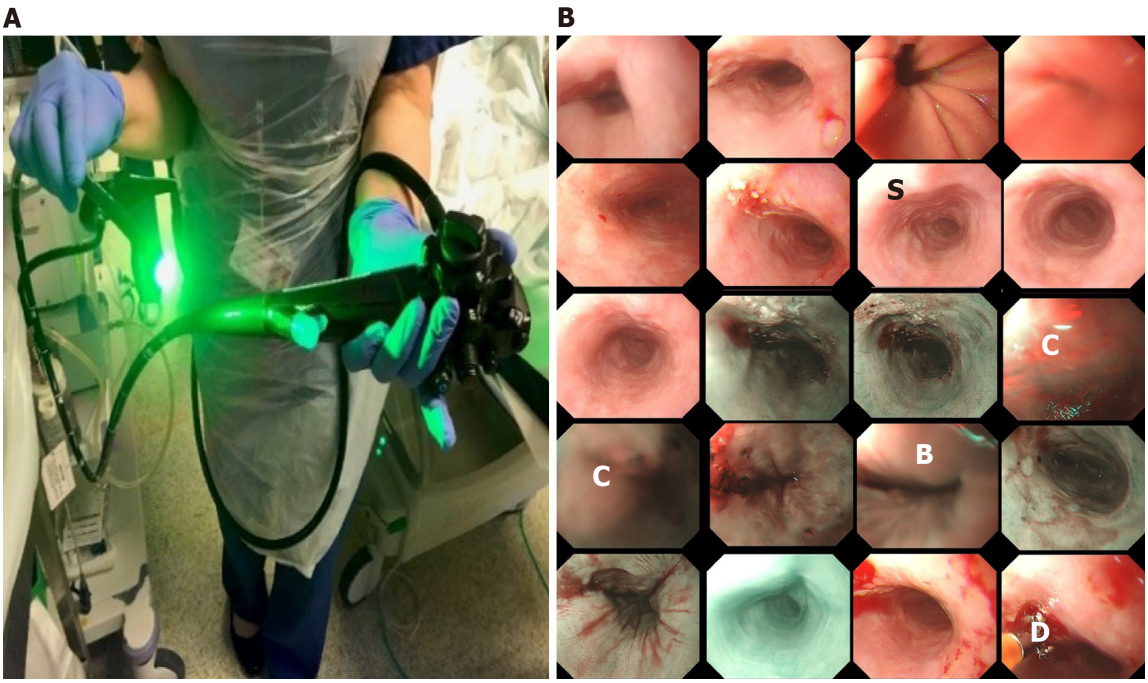

Figure 1 The endoscopy procedure. A: The oesophagus camera; B: A montage display of a clip of an endoscopic video including narrow-band imaging and conventional white light endoscopy (*e.g.*, top 2 rows). C: Colour misalignment; S: Saturation; B: Blurry; D: Device.

oesophageal cancer can be treated endoscopically[29], *e.g.*, by removing diseased tissues or administrating (spraying) treatment drugs. The challenge lies here is that precancerous stages (dysplasia in the oesophageal squamous epithelium) and early stages of SCC display subtle changes in appearance (*e.g.*, colour, surface structure) and in microvasculature, which therefore are easily missed at the time of conventional white light endoscopy (WLE) as illustrated in Figure 2A-D. To overcome this shortcoming while viewing WLE images, narrow-band imaging (NBI) can be turned on to display only two wavelengths [415 nm (blue) and 540 nm (green)] (Figure 2E-G) to improve the visibility of those suspected lesions by filtering out the rest of colour bands. Another approach is dye-based chromoendoscopy, *i.e.* Lugol's staining technique, which highlights dysplastic abnormalities by spraying iodine[30] (Figure 2H).

While NBI technique improves the visibility of the vascular network and surface structure, it mainly facilitates the detection of unique vascular and pit pattern morphology that are present in neoplastic lesions[31], whereas precancerous stages can take a variety of forms. With the Lugol's staining approach, many patients react uncomfortably to the spray.

It is therefore of clinical priority to have a computer assisted system to help clinicians to detect and highlight those potential suspected regions for further examinations. Currently, a number of promising results for computer-aided recognition of early neoplastic oesophageal lesions from endoscopic have been achieved based still images[32,33]. However, fewer less algorithms are applicable to real-time endoscopy to allow computer-aided decision-making during endoscopy at the point of examination. In addition, most of the existing studies focus mainly on the classification of endoscopic images between normal and abnormal stages with little work providing bounding boxes of the suspicious regions (detection) and delineating (segmentation).

Following challenges have been identified for the development of computerised algorithms for early detection of oesophageal cancers, which are inconspicuous changes on oesophageal surfaces artefacts of video images due to movement of endoscopic camera entering the food pipe limited time for patients undergoing each session of endoscopic procedure (about 20min) to minimise discomfort and invasiveness real time processing of video images to be in time to prompt endoscopist collecting biopsy samples while undertaking endoscopy limited datasets to train DL systems multiple modalities, including WLE, NBI and Lugol's multiple classes, including LD, GD, SCC, normal, and artefact.

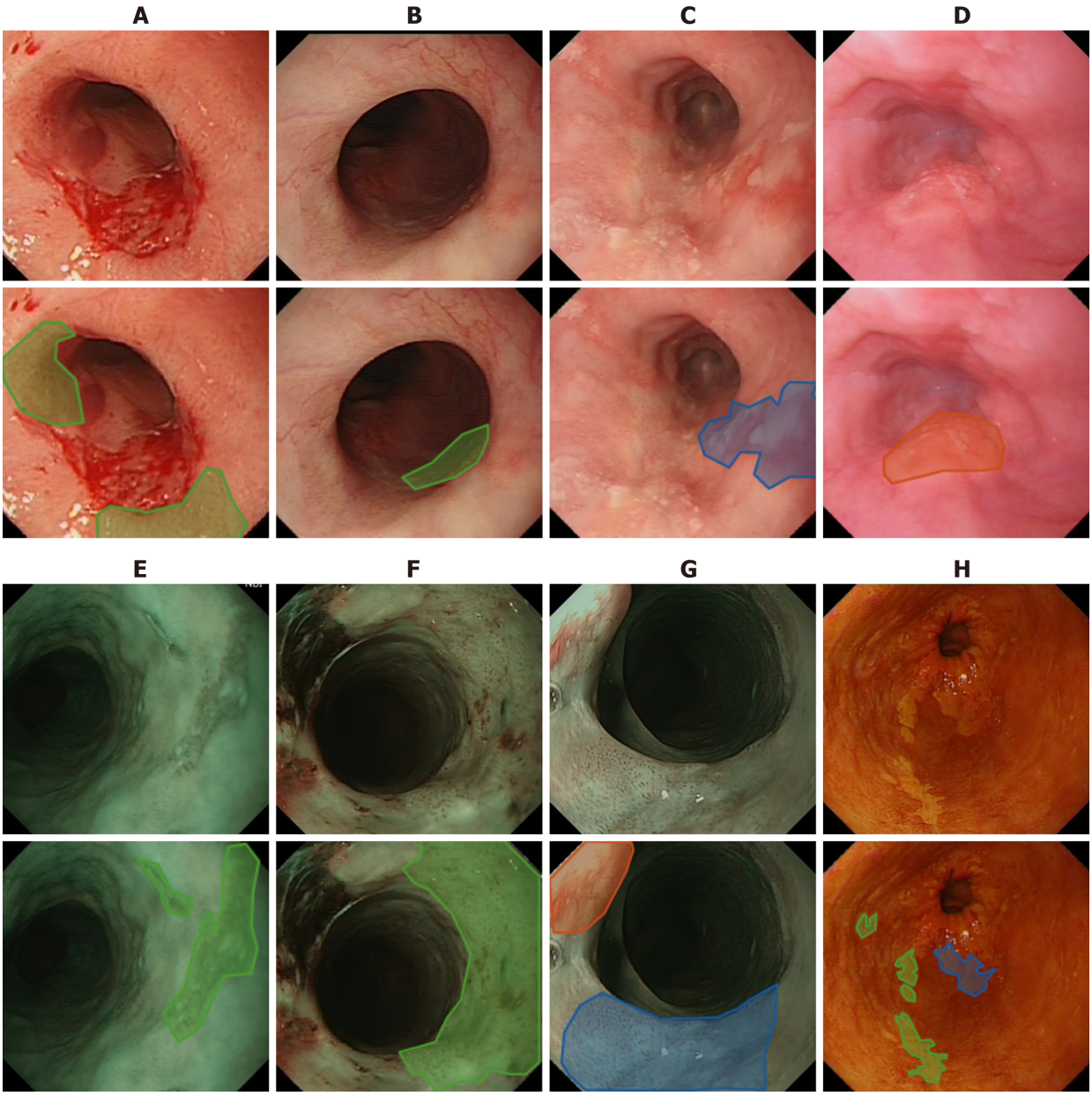

Figure 2 Examples of endoscopic images where green and blue masks refer to low and high grade dysplasia respectively and red for squamous cell cancer. A-D: White light endoscopy; E-G: Narrow band imaging; H: Lugol's. Mask colours: Green = low grade dysplasia; Blue = high grade dysplasia; Red = Squamous cell cancer.

Progress on the development of AI-based computer assisted supporting system for early detection of SCC

Progress on diagnosis of oesophageal cancer through the application of AI has been made by several research teams, mainly focusing on three directions, classification of abnormal from normal images, classification taking into consideration of processing speed, and detection of artefacts.

AI-based classification

Horie *et al*[34] conducted research to distinguish oesophageal cancers from non-cancer patients with an aim to reproduce diagnostic accuracy. While applying conventional CNN architecture to classify two classes, the researchers have achieved 98% sensitivity for cancer detection. In the study conducted by Ghatwary *et al*[35], researchers have evaluated several SOTA CNN approaches aiming to achieve early detection of SCC from high-definition WLE (HD-WLE) images and come to the conclusion that the approaches of single shot detection[36] and Faster R-CNN[37] perform better. They use one image modality of WLE. Again, two classes are investigated in their study, *i.e.*, cancerous and normal regions. While these studies demonstrate high accuracy of

classification, the main focus of those research remains on the binary classification distinguishing abnormal from normal. Similarly, in the study by Ohmori *et al*[38], while the authors studied oesophageal lesions on several imaging modes including blue-laser images, only two classes of either cancer or non-cancer are classified by employing a deep neural network. For detection of any potential suspected regions regardless how small they are, segmentation of abnormal regions also plays a key role in supporting clinical decisions.

Classification with near real-time processing

In addition, in order to assist clinicians in early diagnosis during endoscopic procedures, real-time processing of videos, *i.e.*, with processing speed of 24+ frames per second (fps) or at most 41 milliseconds (ms) per frame, should be realised. Everson *et al*[33] have achieved inference time between 26 to 37ms for an image of 696 × 308 pixels. The work conducted by de Groof *et al*[32] requires 240ms to process each frame (*i.e.*, 4.16 fps). For processing a video clip, frame processing and video playing back times all need to be considered to allow processed frames being played back seamlessly.

In order to ensure lesion detection takes place in time while patients undertaking endoscopy procedure, processing speed constitutes one of the key elements. Hence, comparisons are made to devalue the processing speed when detecting, classifying, and delineating multi-class (LD, HD, SCC) on multi-modality images (WLE, NBI, Lugol's)[39] employing DL architectures of YOLOv3[40] and mask-CNN[41]. In this study by applying YOLOv3, the average processing time is in the range of 0.064-0.101 s per frame, which leads to 10-15 frames per second while processing frames of endoscopic videos with a resolution of 1920 × 1080 pixels. This work was conducted under Windows 10 operating system with 1 GPU (GeForce GTX 1060). The averaged accuracies for classification and detection can be realised to 85% and 74% respectively. Since YOLOv3 only provides bounding boxes without masks, the approach of mask-RCNN is utilised to delineate lesioned regions, producing classification, segmentation (masks) and bounding boxes. As a result, mask-RCNN achieves better detection result (*i.e.*, bounding box) with 77% accuracy whereas the classification accuracy is similar to that obtained using YOLOYv3 with 84%. However, the processing speed applying mask-RCNN appears to be more than 10 times slower with an average of 1.2 s per frame, which is mainly stemmed from the time spent on the creation of masks. For the segmentation while employing mask-RCNN, the accuracy retains 63% measured on the overlapping regions between predicted and ground truth regions.

More recently, a research group by Guo *et al*[42] has developed a CAD system to aid decision making for early diagnosis of precancerous lesions. Their system can realise video processing time at 25 frames per second while applying narrow band images (NBI) that present clearer lesion structures than WLE. It appears that only one detection is identified for each frame, hence the study does not support localisation by bounding boxes.

Artefact detection

Due to the confined space to film the oesophageal tube, a number of artefacts are present, which not only hamper clinician's visual interpretation but also mislead training AI-based systems. Therefore, endoscopic artefact detection challenges were organised in 2019 (EAD2019)[11] and 2020 (EAD2020)[12] aiming to find solutions to these challenges. As expected, all top performant teams apply DL-based approaches to detect (bounding box), classify and segment artefacts including bubbles, saturation, blurry and artefacts[43].

FUTURE WORK

While significant progress has been made towards development of AI-enhanced systems to support clinicians' diagnosis, especially for early detection of oesophageal cancer, there is a still a considerable distance to go to benefit clinical diagnosis and to equip these assistant systems in an operative room. The following recommendations might shed light on future research directions.

Firstly, detection should be based on multi-classes, especially early onset lesions should be included. This is because most of the currently developed systems work on binary classifications between cancer and normal whereas cancers present most distinguishable visual features. At present, in 1 in 4 patients, the diagnosis of early stage oesophageal cancer is missed in their first visit[30]. Hence more work should emphasis

on the detection of early onset of SCC. Only in this way can patients' 5-year survival rates be increased to 90% from current 20%.

In addition, to circumvent data shortage, conventional data augmentation techniques appear to increase system accuracy by cropping, colour shifting, resizing and rotating. Due to the subtle change of early stages of SCC, data augmentation by inclusion of fake datasets generated by employing generative adversarial DL networks (GAN) appear to decrease the performance in this regard. Furthermore, when training with data that include samples with artefact, data augmentation with colour shifting also tend to hamper the system performance. Computational spectral imaging appears to benefit in this regard.

Secondly, to increase the wide acceptance by clinicians, the developed systems should be explainable and interpretable to a certain degree. For example, case-based reasoning[44] or attention-based modelling[45] are a way forward.

Lastly, real-time process should be achieved before the developed systems can make any real impact. This is because a collection of biopsy takes place only during the time of endoscopy. If those suspicious regions are overlooked, the patients in concern will miss the chances of correct diagnosis and appropriate treatment.

CONCLUSION

In conclusion, this paper overviews the current development of AI-based computer assisted systems for supporting early diagnosis of oesophageal cancers and proposes several future directions, expediting the clinical implementation and hence benefiting both patient and clinician communities.

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MINIREVIEWS

Deep learning applied to the imaging diagnosis of hepatocellular carcinoma

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Abstract

Each year, hepatocellular carcinoma is diagnosed in more than half a million people worldwide. It is the fifth most common cancer in men and the seventh most common cancer in women. Its diagnosis is currently made using imaging techniques, such as computed tomography and magnetic resonance imaging. For most cirrhotic patients, these methods are enough for diagnosis, foregoing the necessity of a liver biopsy. In order to improve outcomes and bypass obstacles, many companies and clinical centers have been trying to develop deep learning systems that could be able to diagnose and classify liver nodules in the cirrhotic liver, in which the neural networks are one of the most efficient approaches to accurately diagnose liver nodules. Despite the advances in deep learning systems for the diagnosis of imaging techniques, there are many issues that need better development in order to make such technologies more useful in daily practice.

Key Words: Hepatocellular carcinoma; Cirrhosis; Machine learning; Artificial intelligence

Core Tip: Hepatocellular carcinoma is diagnosed using imaging techniques, such as computed tomography and magnetic resonance imaging. In order to improve outcomes and bypass obstacles, many companies and clinical centers have been trying to develop deep learning systems that could be able to diagnose and classify liver nodules in the

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cirrhotic liver. Neural networks have become one of the most efficient approaches to accurately diagnose liver nodules using deep learning systems. Therefore, with the improvement of these techniques in the long term, they could be applicable in daily practice, modifying outcomes.

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INTRODUCTION

Each year, hepatocellular carcinoma (HCC) is diagnosed in more than half a million people worldwide, and it is the fifth most common cancer in men and the seventh most common cancer in women[1]. The greatest burden of this disease is in developing countries, such as Southeast Asia and Sub-Saharan Africa, where hepatitis B is endemic[2,3].

The incidence of HCC has been rising, unlike many other types of neoplasms[4]. This is expected to change, as the worldwide incidence of viral hepatitis B and C is expected to subdue in the next generation *via* vaccination and treatment, respectively. Nevertheless, the acute rise in the prevalence of nonalcoholic steatohepatitis in the last couple of decades might become a key risk factor for HCC and could become solely responsible for sustaining its incidence, both in the Western and Eastern population[5,6].

Therefore, understanding the diagnostic and therapeutic approaches to this disease is essential, especially if we keep in mind the quintessential basics of prevention and early detection to improve results[7,8].

DIAGNOSIS OF HCC

HCC diagnosis is currently made using imaging techniques, such as computed tomography and magnetic resonance imaging (MRI). For most cirrhotic patients, these methods are enough for diagnosis, foregoing the necessity of a liver biopsy[9-11]. Nevertheless, the precise diagnosis of a liver nodule *via* imaging techniques is a rather challenging task, requiring a highly trained and specialized multidisciplinary team of radiologists, hepatologists and oncologists.

In order to facilitate communication between professionals of such a team, a system for reporting imaging of liver nodules has been developed and adopted world-wide–the Liver Imaging Reporting And Data System (LI-RADS)[12]. The LI-RADS classification[13] can be found in Table 1. Although this was an attempt into standard-ization, a high discordance rate among radiologists has been described[14]. Inter-rater reliability has varied greatly in studies, with Cohen's kappa coefficients ranging from 0.35 to 0.73[15-19]. This is expected, since this classification requires high-quality imaging and radiologists with vast experience[19,20]. Another very important argument is that where HCC incidence is higher (developing countries), highly specialized radiologists are scarcest despite a high volume of patients[21]. In order to improve outcomes and bypass these obstacles, many companies and clinical centers have been trying to develop deep learning systems (DLS) intended to accurately diagnose liver nodules in the cirrhotic liver[22].

DLS AND HCC

There are many DLS approaches available in the literature, where neural networks are gaining much attention currently as one of the best approaches to accurately diagnose liver nodules. Particularly, a DLS based on convolutional neural networks (CNN) could achieve such capacities after machine learning (ML) by using examples of images with and without the disease in question[8]. Unlike other DLS, CNN does not

Table 1 Liver imaging reporting and data system classification[13]

Category	Description
LR-1	Definitely benign
LR-2	Probably benign
LR-3	Intermediate probability of HCC
LR-4	High probability of HCC, not 100%
LR-5	Definitely HCC
LR-5V	Definite venous invasion regardless of other imaging features
LR treated	LR-5 lesion status post-locoregional treatment
LR-M	Non-HCC malignancies that may occur in cirrhosis: metastases, lymphoma, cholangiocarcinoma, PTLD

HCC: Hepatocellular carcinoma; PTLD: Post-transplant lymphoproliferative disorder.

demand a clear definition of the lesion in order to interpret the images[23], which might lead to discovery of additional differential characteristics that are not currently known by radiologists[24]. Table 2 summarizes the main characteristics about the studies in diagnosis of liver tumors with images and clinical data using DLS.

There are several DLS applied in the recognition of image patterns[25,26], from which CNN-based approaches have achieved the highest performance[25]. While conventional deep learning algorithms require specific features to be extracted from images before the learning process, the application of CNNs requires rather a simpler feature representation based on the original image pixel intensities, also allowing to use all available image information in the learning process[27]. Moreover, CNNs can process extracted image features by several convolution filters, which allow analysis of the image at different granularities. Therefore, CNN is one of the most advanced techniques for artificial intelligence[25], which has been implemented with success for imaging and clinical interpretation in many medical fields. For example, CNN has been validated to identify liver tumors[28], the prognosis of esophageal variceal bleeding in cirrhotic patients[29], to predict the mortality of liver transplantation[30,31], to predict the prognosis of HCC[32-37] *Helicobacter pylori* infection[38], colonic polyps[39], to help classify mammary cancer, head and neck cancer and gliomas[36] and to focal liver disease detection[40].

In the topic of liver tumors, many studies have shown that CNNs performed the same or better when compared to experienced radiologists. Hamm *et al*[8] developed and validated a CNN that classified six types of common hepatic lesions on multiphasic MRI, achieving better sensitivity and specificity when compared to board-certified radiologists[8]. Nevertheless, this study was developed in only one center, using local and typical images, with no external validation. In a follow-up to this study, Wang *et al*[41] used a pre-trained CNN in a model-agonistic approach capable of distinguishing among several types of lesions and developed a post-hoc algorithm with the purpose of standardizing the lesion features used in the diagnosis. Such a tool could interact with other standardized scales, such as LI-RADS, validating auxiliary resources and improving clinical practicality[41]. This study found a sensitivity of 82.9% for adequate identification of imaging characteristics when analyzing lesions from a databank. It is expected that this type of DLS that can be transparent regarding its steps towards the diagnosis will have better clinical acceptance.

Yamashita *et al*[14] developed a DLS applied to diagnose liver carcinoma by using two CNNs: a pre-trained network with an input of triple-phase images (trained with transfer learning from other CNNs) and a custom-made network with an input of quadruple-phase images (trained from scratch from internal data)[14]. However, by using external data from other pre-trained CNNs, Zech *et al*[42] showed that the performance of the DLS worsened when compared to CNNs trained with internal data, showing that it is not still proved that CNNs trained on X-rays from one hospital or one group of hospitals will work equally well at different hospitals. This has also been demonstrated for the detection of pneumonia in chest X-rays, where CNN performed worse when exposed to external data with a wide range of diseases and radiological findings[42]. Besides, such CNNs could be used for the determination of LI-RADS category, which has been shown to be possible[14], even from a small data set. Nevertheless, external validation seems to be a major obstacle for the dissem-

Table 2 Main characteristics of the studies that evaluate deep learning for liver tumor diagnosis throughout images or clinical data

Ref.	Country	Deep learning method	Accuracy	Sensitivity	Specificity	AUROC	DLS performance compared	Multicenter validation	Conclusion
Hamm *et al*[8], 2019	United States	Proof-of-concept validation CNN	92%	92%	98%	0.992	Better than radiologists	Not done	DLS was feasibility for classifying lesions with typical imaging features from six common hepatic lesion types
Yamashita *et al*[14], 2020	United States	CNN architectures: custom-made network and transfer learning-based network	60.4%	NA	NA	LR-1/2: 0.85. LR-3: 0.90. LR-4: 0.63. LR-5: 0.82	Transfer learning model was better	Performed	There is a feasibility of CNN for assigning LI-RADS categories from a relatively small dataset but highlights the challenges of model development and validation
Shi *et al* [23], 2020	China	Three CDNs	Model-A: 83.3%, B: 81.1%, C: 85.6%	NA	NA	Model-A: 0.925; B: 0.862; C: 0.920	Three model compared, A and C with better results	Not done	Three-phase CT protocol without precontrast showed similar diagnosis accuracy as four-phase protocol in differentiating HCC. It can reduce the radiation dose
Yasaka *et al*[25], 2018	Japan	CNN	84%	Category[1]: A: 71%; B: 33%; C: 94%; D: 90%; E: 100%	NA	0.92	Not applicable	Not done	Deep learning with CNN showed high diagnostic performance in differentiation of liver masses at dynamic CT
Trivizakis *et al*[28], 2019	Greece	3D and 2D CNN	83%	93%	67%	0.80	Superior compared with 2D CNN model	Not done	3D CNN architecture can bring significant benefit in DW-MRI liver discrimination and potentially in numerous other tissue classification problems based on tomographic data, especially in size-limited, disease specific clinical datasets
Wang *et al* [41], 2019	United States	Proof-of-concept "interpretable" CNN	88%	82.9%	NA	NA	Not applicable	Not done	This interpretable deep learning system demonstrates proof of principle for illuminating portions of a pre-trained deep neural network's decision-making, by analyzing inner layers and automatically describing features contributing to predictions
Frid-Adar *et al*[45], 2018	Israel	GANs	Classic data: 78.6%. Synthetic data: 85.7%	Classic data: 78.6%. Synthetic data: 85.7%	Classic data: 88.4%. Synthetic data: 92.4%	NA	Synthetic data augmentation is better than classic data augmentation	Not done	This approach to synthetic data augmentation can generalize to other medical classification applications and thus support radiologists' efforts to improve diagnosis
Wang *et al*	Japan	CNN with	NA	NA	NA	Clinical	Combined	Not done	The AUC of the

[47], 2019		clinical data				model: 0.723. Model: A: 0.788; B: 0.805; C: 0825.	model C present with better results		combined model is about 0.825, which is much better than the models using clinical data only or CT image only
Sato *et al* [48], 2019	Japan	Fully connected neural network with 4 layers of neurons using only biomarkers, gradient boosting (non-linear model) and others	DLS: 83.54%. Gradient boosting: 87.34%	Gradient boosting: 93.27%	Gradient boosting: 75.93%	DLS: 0.884. Gradient boosting: 0.940	Deep learning was not the optimal classifier in the current study	Not done	The gradient boosting model reduced the misclassification rate by about half compared with a single tumor marker. The model can be applied to various kinds of data and thus could potentially become a translational mechanism between academic research and clinical practice
Naeem *et al*[49], 2020	Pakistan	MLP, SVM, RF, and J48 using ten-fold cross-validation	MLP: 99%	NA	NA	MLP: 0.983. SVM: 0.966. RF: 0.964. J48: 0.959	MLP model present with better results	Radiopaedia dataset	Our proposed system has the capability to verify the results on different MRI and CT scan databases, which could help radiologists to diagnose liver tumors

[1]Five categories: A: Classic hepatocellular carcinomas; B: Malignant liver tumors other than classic and early hepatocellular carcinomas; C: Indeterminate masses or mass like lesions (including early hepatocellular carcinomas and dysplastic nodules) and rare benign liver masses other than hemangiomas and cysts; D: Hemangiomas; E: Cysts. AUC: Area under the curve; AUROC: Area under the receiver operating characteristic curve; CDNs: Convolutional dense networks CNN: Convolutional neural network; CT: Computed tomography; DLS: Deep learning system; DW-MRI: Diffusion weighted magnetic resonance imaging; GANs: Generative adversarial networks; HCC: Hepatocellular carcinoma; LI-RADS: Liver Imaging Reporting and Data System; LR: LI-RADS; MLP: Multiplayer perceptron; MRI: Magnetic resonance imaging; NA: Not available; RF: Random forest; SVM: Support vector machine.

ination of ML tools. There are many devices that produce images, and there are many ways to store data from these exams.

When compared to other DLS, another advantage of the use of CNNs is that it can improve the diagnosis by using less images for ML, reducing the time of exam and the amount of exposure to radiation[23,43,44]. Moreover, by generating additional training samples through data augmentation, the liver lesion classification sensitivity and accuracy are enhanced whilst less images are required in the ML process[45]. Moreover, the sensitivity, specificity, and accuracy can be manually calculated with the confusion matrix. In Table 3, we compare the best ML algorithms for classification [46].

A DLS has been proposed for the prediction of HCC recurrence, using data from computed tomography combined with clinical information[47]. The triple layer model including imaging studies, clinical data and a filtering of this data has had the better performance, with an area under the receiver operating characteristic curve (AUROC) of 0.825. This is way more precise than the current tools are. Furthermore, Sato *et al*[48] proposed a ML model for predicting HCC using data obtained during clinical practice [48]. The AUROC of the optimal hyperparameter, gradient boosting model, involving multiple laboratories and tumor markets was 0.940. However, when compared with single tumor markers the AUROC to the prediction of HCC for alpha-fetoprotein, des-gamma-carboxy prothrombin and alpha-fetoprotein-L3 were 0.766, 0.644 and 0.683, respectively. Accordingly, a combination of multiple data can provide a reliable diagnostic tool.

A preliminary study has attempted to diagnose liver masses using a CNN without the aid of a radiologist, achieving a high accuracy to differentiate HCC from benign liver masses, achieving an AUROC of 0.92[25]. In another study, a CNN was designed to differentiate HCC from metastatic liver masses on MRI, but this time the DLS used a 3-D representation, with higher accuracy (83.0% of the 3-D model *vs* 65.2% of the 2-D model)[28]. Nevertheless, the authors stressed that more studies with larger databanks are needed to verify the accuracy of this method. Besides that, Naeem *et al*[49] performed a hybrid-feature analysis between computed tomography scans and MRI for differentiation of liver tumors using DLS. The accuracy of multilayer perceptron

Table 3 Best machine learning algorithms for classification[36]

Algorithm	Pros	Cons
Naïve Bayes Classifier	Simple, easy and fast. Not sensitive to irrelevant features. Works great in practice. Needs less training data. For both multi-class and binary classification. Works with continuous and discrete data	Accepts every feature as independent. This is not always the truth
Decision Trees	Easy to understand. Easy to generate rules. There are almost no hyperparameters to be tuned. Complex decision tree models can be significantly simplified by its visualizations	Might suffer from overfitting. Does not easily work with nonnumerical data. Low prediction accuracy for a dataset in comparison with other algorithms. When there are many class labels, calculations can be complex
Support Vector Machines	Fast algorithm. Effective in high dimensional spaces. Great accuracy. Power and flexibility from kernels. Works very well with a clear margin of separation. Many applications	Does not perform well with large data sets. Not so simple to program. Does not perform so well when the data comes with more noise *i.e.* target classes are overlapping
Random Forest Classifier	The overfitting problem does not exist. Can be used for feature engineering *i.e.* for identifying the most important features among all available features in the training dataset. Runs very well on large databases. Extremely flexible and have very high accuracy. No need for preparation of the input data	Complexity. Requires a lot of computational resources. Time-consuming. Need to choose the number of trees
KNN Algorithm	Simple to understand and easy to implement. Zero to little training time. Works easily with multi-class data sets. Has good predictive power. Does well in practice	Computationally expensive testing phase. Can have skewed class distributions. The accuracy can be decreased when it comes to high-dimension data. Needs to define a value for the parameter k

KNN: K-nearest neighbors.

model for hepatoblastoma, cyst, hemangioma, hepatocellular adenoma, HCC and metastasis were 99.67%, 99.33%, 98.33%, 99.67%, 97.33% and 99.67% respectively[49]. This method can be helpful to reduce human error.

Therefore, despite the advances in DLS for the diagnosis of imaging techniques, there are many points that need better development in order to become useful and common tools in daily practice. These techniques currently require comparison with trained radiologists and the application for many databanks with atypical images to achieve better results and the use of less radiation for HCC diagnosis.

We previously presented several DLS applied to liver nodule diagnosis; however, they are not able to segment the nodule from the liver in the analyzed images. Moreover, automatic nodule segmentation in an image is a challenging task since this kind of lesion may show a high variability in shape, appearance and localization and is dependent on the equipment, contrast, lesion type, lesion stage and so on[50].

There are some liver nodule segmentation methods available in the literature, and in one of them[50] a fully convolutional network architecture was adopted to determine an approximation for where the nodule was located on the image. This CNN works on four resolution levels, learning local and global image features. The final nodule segmentation is obtained by using post-processing techniques and a random forest classifier, achieving a quality comparable to a human expert.

However, this method uses hand-crafted features that need the supervision of an expert. There are also automatic approaches that can segment the nodule[51], where a CNN is used for ML. To refine the segmentation results, this method applies conditional random fields to eliminate the false segmentation points in the segmentation results, improving accuracy. However, liver nodule segmentation in general still needs improvements to achieve a better accuracy and practical applicability. Furthermore, it is necessary for more research effort in DLS to at the same time detect the tumor in the liver and segment it on the image.

CONCLUSION

In conclusion, the goal of statistical methods is to achieve conclusions about a population from data that are collected from a representative sample of that population, such as linear and logistic regression. Therefore, the objective is to comprehend the associations among variables. However, as reported by Sidey-Gibbons and Sidey-Gibbons[36], the primary concern about DLS is an accurate prediction. Moreover, explaining the relationship between predictors and outcomes when the relationship is non-linear is difficult. However, in several DLS as improving navigation, translating documents or recognizing objects in videos, understanding the relationship between features and outcomes is less important[46]. In summary,

enhancement of DLS features will allow more accurate diagnosis in the medical field. For future research, we recommend to test deep learning methods in other datasets (*e.g.*, other hospitals), develop an easy usable interface and introduce the tool in daily medical practice.

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MINIREVIEWS

Role of capsule endoscopy in inflammatory bowel disease: Anything new?

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Abstract

Capsule endoscopy (CE) is a recently developed diagnostic method for diseases of the small bowel that is non-invasive, safe, and highly tolerable. Its role in patients with inflammatory bowel disease has been widely validated in suspected and established Crohn's disease (CD) due to its ability to assess superficial lesions not detected by cross-sectional imaging and proximal lesions of the small bowel not evaluable by ileocolonoscopy. Because CE is a highly sensitive but less specific technique, differential diagnoses that can simulate CD must be considered, and its interpretation should be supported by other clinical and laboratory indicators. The use of validated scoring systems to characterize and estimate lesion severity (Lewis score, Capsule Endoscopy Crohn's Disease Activity Index), as well as the standardization of the language used to define the lesions (Delphi Consensus), have reduced the interobserver variability in CE reading observed in clinical practice, allowing for the optimization of diagnoses and clinical management strategies. The appearance of the panenteric CE, the incorporation of artificial intelligence, magnetically-guided capsules, and tissue biopsies are elements that contribute to CE being a promising, unique diagnostic tool in digestive tract diseases.

Key Words: Capsule endoscopy; Inflammatory bowel disease; Crohn's disease; Artificial intelligence; Capsule Endoscopy Crohn's Disease Activity Index; Lewis score

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Core Tip: Capsule endoscopy (CE) is the non-invasive diagnostic method of choice for visualizing the small bowel. Its utility is widely validated in both suspected and established Crohn's disease (CD) due to its high sensitivity for detecting early lesions and a high negative predictive value. CE enables estimating the activity and extent of disease, establishing prognosis, and evaluating the therapeutic response in patients with CD. New technologies, such as the panenteric CE and the recent incorporation of artificial intelligence to CE image analysis, render CE an attractive, unique diagnostic tool for diseases of the digestive tract in the future.

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INTRODUCTION

Capsule endoscopy (CE) is a non-invasive diagnostic method of increasing development in the study of small bowel diseases. Since its appearance in 2000[1], it has shown its greatest utility in studying obscure gastrointestinal bleeding, celiac disorder, polyposis syndromes, and Crohn's disease (CD). The role of CE in inflammatory bowel disease (IBD), especially in CD, has been extensively investigated in the diagnosis of suspected CD and the management of established CD for the evaluation of disease severity, extent, and response to treatment[2]. The main advantage of CE over ileocolonoscopy is its ability to visualize the mucosa of the proximal small bowel, and compared to imaging studies, its ability to detect superficial mucosal ulcerations missed on magnetic resonance enterography (MRE)[3] and computed tomography enterography[4]. This point is fundamental, considering that studies report that the involvement of the small bowel affects up to 66% of patients diagnosed with CD[5], corresponding to up to 90% of lesions located in the terminal ileum accessible by ileocolonoscopy[6]. Before CE development, the proximal small bowel was examined using indirect imaging methods such as radiography, cross-sectional imaging, and enteroscopy. Detection of lesions in the proximal small bowel is critical due to the implications for managing patients with CD. Jejunal lesions visualized by CE have been found in up to 56% of patients with CD, and these are associated with more severe disease and more rapid progression[7]. Moreover, the role of CE in ulcerative colitis (UC) is not well established because the evidence remains limited. In recent years, remarkable advances in CE technology and design, and the recent use of artificial intelligence, have improved its diagnostic yield in CD.

This review aims to assess the role of CE in IBD and discusses advances in the field and their implications for clinical practice going forward.

DIAGNOSTIC YIELD OF CE IN PATIENTS WITH CD

Studies comparing the diagnostic yield of CE with other diagnostic techniques in patients with CD conclude that CE has a high sensitivity[4,8] and a high negative predictive value (NPV)[9]. However, the diagnostic accuracy of CE has not been determined due to the lack of a gold standard for the diagnosis of CD. A meta-analysis [8] found that CE had a better diagnostic yield than small bowel radiography [52% *vs* 16%; incremental yield (IY) 32%, $P < 0.0001$, 95% confidence interval (CI) = 16%-48%], computed tomography enterography (68 *vs* 21%; IY 47%, w = 47%, $P < 0.00001$, 95%CI = 31%-63%), and ileocolonoscopy (47 *vs* 25%; IY 22%, $P = 0.009$, 95%CI = 5%-39%) in unsuspected CD patients. Similarly, in patients with established CD, CE also outperformed these diagnostic tests[8]. Furthermore, CE was superior to MRE in detecting small bowel lesions in patients with CD, mainly superficial and proximal lesions[10]. A subsequent meta-analysis of 13 studies[3] compared the diagnostic performance of CE with MRE and small bowel contrast ultrasound imaging for the evaluation of small bowel CD. These authors found that the diagnostic yield of CE was similar to MRE

[odds ratio (OR) 1.17; 95%CI: 0.83–1.67] and small bowel contrast ultrasound (OR 0.88; 95%CI: 0.51–1.53) when detecting lesions in the small bowel for both established and suspected CD. However, CE was superior to MRE in detecting proximal small bowel lesions (OR 2.79; 95%CI: 1.2–6.48).

In a recent study among the pediatric population, CE was as sensitive as MRE in identifying inflammatory activity in the terminal ileum and the proximal small bowel; however, the distribution of small bowel inflammation was more extensive when characterized by CE[11].

In summary, the diagnostic yield of CE is at least similar to MRE for established CD in the evaluation of the small bowel. However, the main advantage of CE is the detection of the most proximal and superficial lesions missed on MRE. In suspected CD, CE is more useful when the ileocolonoscopy results are negative.

DIAGNOSTIC SCORES IN CE

At the moment, there are no established diagnostic criteria for the diagnosis of CD by CE. Currently, the Lewis score (LS)[12,13] and Capsule Endoscopy Crohn's Disease Activity Index (CECDAI)[14] are the two validated diagnostic indexes for the evaluation of CE images. Their results must be interpreted in the patient's clinical setting because lesions are not pathognomonic for CD and can be found in other inflammatory conditions. The LS was the first and most widely used index for evaluating inflammatory changes in the mucosa of the small intestine, which is divided into three tertiles according to the transit time estimated using CE. Each characteristic CD finding (villous edema, ulceration, stenosis) is assigned a score for each tertile. The final result of the LS corresponds to the tertile with the highest score, in addition to the stenoses score. A score < 135 is considered normal or clinically insignificant inflammation; from 135 to 790 indicates mild inflammation; and > 790 moderate to severe inflammation[12]. The CECDAI evaluates the proximal and distal segments of the small bowel using an inflammation score (A; 0–5), an extent score (B; 0–3), and a stricture score (C; 0–3), which are combined using the formula A × B + C. The total score (from 0–26) results from adding both the proximal and distal segments. A higher CECDAI score reflects more severe mucosal inflammation[14]. Although there is a good correlation between the LS and CECDAI (Pearson's = 0.81, P = 0.0001) [15], a recent study of 102 patients with CD found that CECDAI was superior to LS in reflecting active intestinal inflammation[16]. Recently, Eliakim *et al*[17] published the Eliakim score, a quantitative measure for PillCam™ Crohn's with excellent reliability that significantly correlates with LS and fecal calprotectin (FC).

CE READING METHOD

So far, manual video review is the method of choice for the detection of lesions in CE. However, a fast-reading method is offered by TOP100, a new software tool in RAPID Reader version 9.0[18]. TOP100 automatically selects the 100 best images from the video with relevant findings, allowing the LS to be calculated quickly. An initial study that compared both reading techniques found agreement in 89.6% of cases calculated by TOP100 as having LS > 135 and those calculated by manual review of the video. Despite these encouraging results, TOP100 should not replace the traditional reading method but rather constitutes a complementary tool for quick LS calculation[18].

DESCRIPTION OF LESIONS WITH CE

Although studies have shown the usefulness of CE in identifying small bowel lesions, one of the difficulties in IBD studies was the lack of nomenclature and descriptions of small bowel lesions. The high interobserver variability in the interpretation and evaluation of the severity of the lesions has both clinical and research implications. Published in 2005, the Capsule Endoscopy Structured Terminology (CEST)[19] is an international consensus on standardized terminology for the findings or lesions detected by CE and also contains guidelines for reporting these findings (structure and content). However, the description of ulcerative and inflammatory lesions in the CEST is ambiguous and limited and, as such, fails to inform clinicians as to which type of lesion is most suspicious for the diagnosis of CD. Therefore, the international Delphi

consensus statement established seven definitions describing the ulcerative and inflammatory lesions seen in CD by CE: aphthoid erosion, deep ulceration, superficial ulceration, stenosis, edema, hyperemia, and denudation[20]. The use of a common language enables standardizing the results of clinical studies and improves patients' health care (Figure 1).

The use of virtual chromoendoscopy, such as flexible spectral color enhancement (FICE), can also be applied in the revision of CE images to improve the visualization of any lesions. FICE enhances mucosal surface patterns using software to convert white light images to certain ranges of wavelengths (red, blue, green). A systematic review and meta-analysis of 13 studies found that the use of FICE failed to significantly improve the injury detection rate in CE[21].

RETENTION OF CE

The CE retention rate (not passed in more than two weeks post-ingestion or less if endoscopic or surgical intervention is required)[22] in the general population ranges from 1.0% to 2.5%[23]. Due to the potential occurrence of stenosis in patients with CD, the retention rate in patients with suspected CD is 2.35%, and with established CD is up to 4.63%[24]. The risk of EC retention can be estimated with a patency capsule (Pillcam™), a capsule with a lactose body, and a barium section for follow-up by fluoroscopy. The disintegration that induces deformation of the capsule or non-expulsion after 30 h suggests small bowel stenosis[23]. The NPV of the patency capsule to predict CE retention ranges from 98% to 100%[25,26]. Given the high risk of CE retention in patients with established CD, and due to the impossibility of distinguishing high from low-risk retention in the clinic, the use of a patency capsule is recommended before CE[24].

CE IN IBD: CLINICAL SCENARIOS

The main clinical scenarios for the application of EC for IBD are both suspected and established CD. CE studies in UC are limited.

CE and suspected CD

The European Society of Gastrointestinal Endoscopy Clinical Guideline[23] and the Clinical practice guidelines for the use of CE[27] recommend the use of CE in patients with suspected CD and negative ileocolonoscopy[23,27] and imaging results[27] as a diagnostic method for the evaluation of the small bowel, in the absence of obstructive symptoms or known stricture.

In a study with 95 patients, CE excluded the diagnosis of CD if the result was negative (NPV of 96%). Only 3% of the cases with negative CEs were diagnosed with CD after 15 mo of follow-up[9]. Moreover, minor lesions detected by CE may be present in more than 10% of healthy subjects[28]. Non-steroidal anti-inflammatory drug (NSAID)-induced enteropathy is one of the main differential diagnoses of small bowel lesions. In this setting, lesions can appear as early as 2 wk from the onset of NSAID therapy[29,30]. Other differential diagnoses include radiation enteritis, ischemia, Bechet's disease, lymphoma, and gastrointestinal infections[30]. Then, the interpretation of the findings from CE against suspected CD must be supported for other clinical elements due to the impossibility of obtaining tissue samples by CE.

The use of biomarkers as a screening method for intestinal inflammation, such as FC, could be useful in patients with suspected CD. FC is a cytosolic protein present in neutrophils that is released during inflammation; as such, its elevation in stool samples is a good indicator of intestinal inflammation[31]. Although it is highly sensitive, it is not specific since its levels can increase in IBD, colon cancer, ischemic colitis, and NSAID-induced enteropathy, among others[31]. Although FC has shown higher sensitivity and a stronger correlation with inflammatory activity in UC[32], in CD, the usefulness of FC is less established[33,34], particularly in the small bowel. However, recent studies have shown that FC could be a useful tool for selecting which patients should undergo CE for suspected CD when the ileocolonoscopy results are negative due to its ability to predict inflammatory activity in CE in patients with suspected CD [35-37]. Monteiro *et al*[35] found a moderate positive correlation ($r = 0.56$, $P < 0.0019$) between FC and the LS. FC > 100 μg/g were correlated with LS > 135 in 89% of patients, showing a sensitivity of 78.6%, specificity of 87.9%, positive predictive value

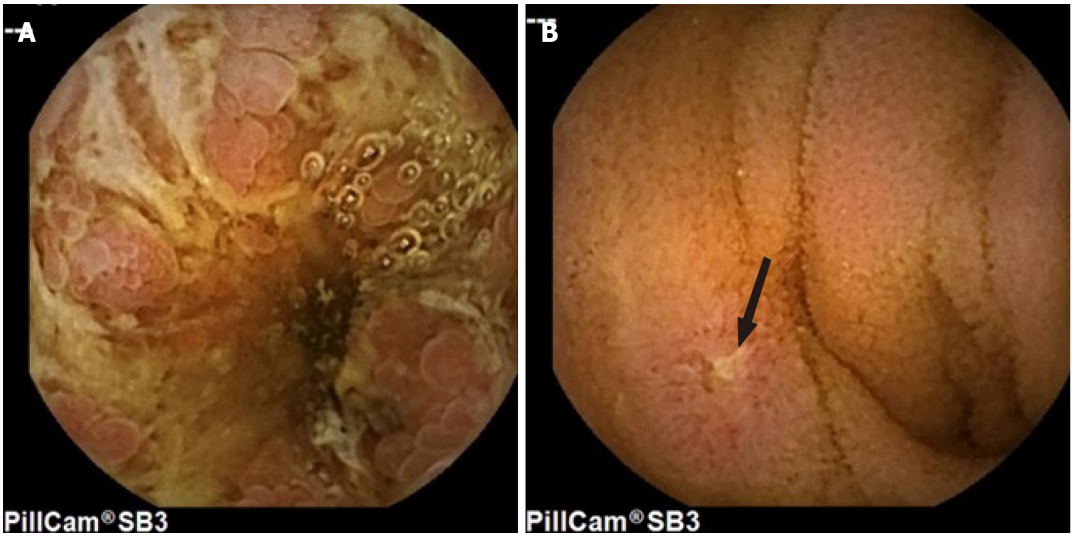

Figure 1 Capsule endoscopy findings in Crohn's disease. A: Deep ulceration; B: Aphthoid erosion (superficial lesion).

of 89.2%, and NPV of 76.3%[35]. Similar findings for FC[27,36,38] and, to a lesser degree, for CRP[36,38] were described by other authors. In a subsequent meta-analysis of 463 patients from seven studies, FC had a significant diagnostic accuracy in detecting small bowel CD, and with FC values < 50 μg/g, the probability of a positive diagnosis was very low[39].

Considering the available evidence and due to CE's ability to diagnose early disease, in patients with suspected CD (typical symptoms, elevated fecal and plasma biomarkers, anemia, or extraintestinal manifestations of CD), CE should be performed even if ileocolonoscopy results are positive due to the need to evaluate proximal lesions that could determine prognosis and treatment strategies (Figure 2).

CE in established CD

The American consensus guidelines for the use of CE recommends its use in patients with established CD when: (1) Clinical features unexplained by ileocolonoscopy or imaging studies are present; (2) The assessment of small bowel mucosal healing (not evaluable by ileocolonoscopy) is needed; and (3) Small bowel recurrence of CD after colectomy is suspected, undiagnosed by ileocolonoscopy or imaging studies[27]. Recently, the European Crohn's and Colitis Organisation and the European Society of Gastrointestinal and Abdominal Radiology guidelines recommend CE along with intestinal ultrasound and MRE for initial evaluation and follow-up of established CD [40] (Figure 3).

CE in patients with CD with unexplained clinical features

The persistence of irritable bowel disease-like symptoms in patients with IBD in remission can occur in almost one-third of patients[41,42], being more frequent in patients with CD[42]. In a scenario where traditional diagnostics tests (ileocolonoscopy and cross-sectional imaging) are normal, CE could play a role in evaluating the small bowel to rule out disease activity as the symptom origin. Another clinical scenario is the study of persistent anemia in patients with CD in remission.

CE in follow-up and prediction of relapse

Studies have shown that the clinical response to treatment does not correlate with mucosal healing in patients with CD of the small bowel evaluated by CE[43]. Therefore, objective monitoring of disease activity in the small bowel is necessary. Hall *et al*[43] conducted the first prospective study in 43 patients with CD evaluated with CE at baseline and after 52 wk of treatment. The authors found that 90% of the patients had an active CD in their small bowel at baseline, yet only 65% at week 52 of treatment, with 42% of the patients achieving complete mucosal healing at week 52 (P < 0.0001, 95%CI: 0.62-0.22). Stenosis detected by CE was a poor prognostic factor for the response to treatment in this study[43]. In a subsequent prospective study in 43 patients with CD in clinical remission, fecal biomarkers (FC, lactoferrin, and S100A12) were good predictors of mucosal healing assessed by CE, proving useful in monitoring the CD progression[44]. Finally, a recent prospective observational cohort study

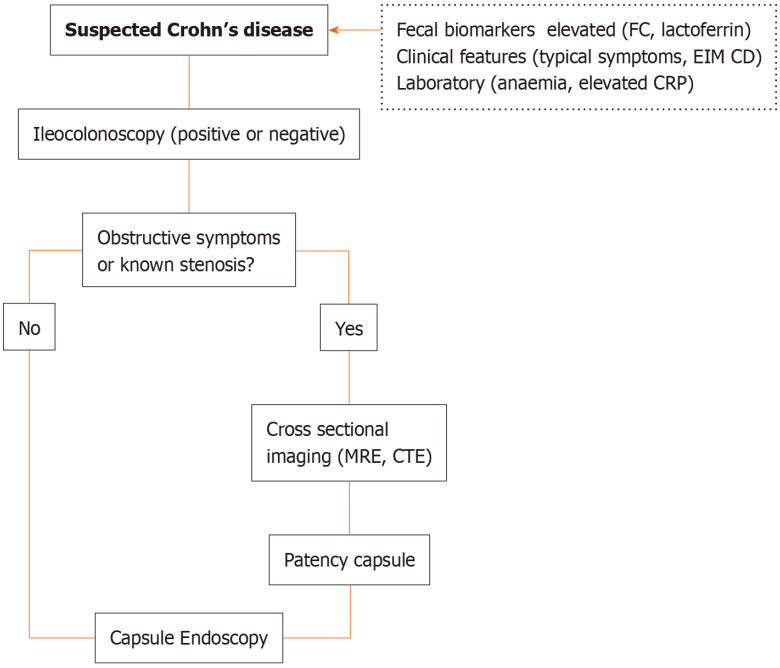

Figure 2 Diagnostic algorithm recommended for suspected Crohn's disease. MRE: Magnetic resonance enterography; CTE: Computed tomography enterography; FC: Fecal calprotectin; CRP: C-reactive protein; EIM: Extraintestinal manifestations.

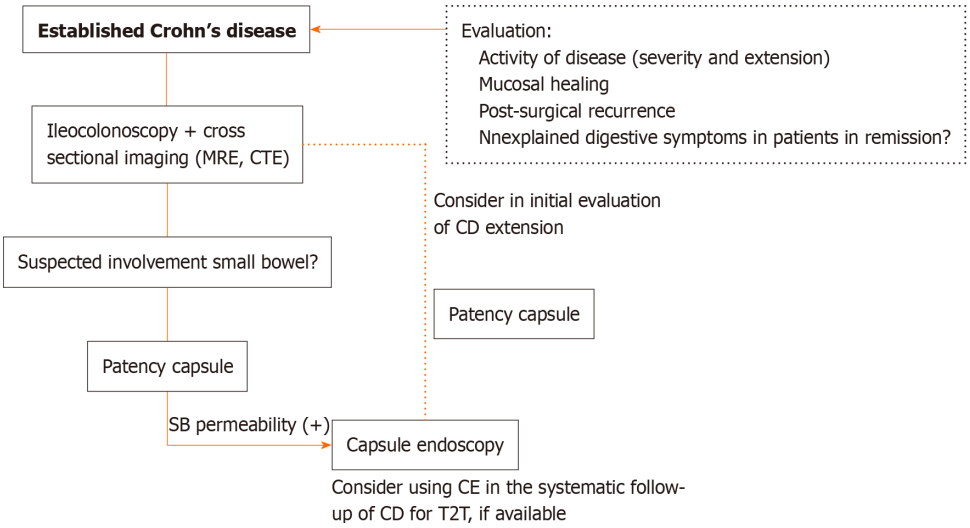

Figure 3 Diagnostic algorithm recommended for established Crohn's disease. T2T: Treat to target; MRE: Magnetic resonance enterography; CTE: Computed tomography enterography; CD: Crohn's disease; SB: Small bowel.

assessed the ability of MRE, FC, and CE to predict flare-ups in patients with quiescent CD. CE predicted both short-term (3 mo) and long-term [24 mo, area under curve (AUC) 0.79, 95%CI: 0.66–0.88; P = 0.0001] flares, while FC only predicted short-term flares within 3 mo (AUC 0.81, 95%CI: 0.76-0.85), and MRE correlated with 2-year flare risk (AUC 0.71, 95%CI: 0.58-0.82; P = 0.024)[45].

CE and post-surgical recurrence of CD

In a recent study, Shiga *et al*[46] compared the postoperative follow-up for CE in patients with CD who underwent intestinal resection with the appearance of clinical symptoms for treatment adjustment. In the CE group, 87% residual or recurrent lesions were found at the 3rd postoperative month. Adjusted treatment based on EC findings revealed a strong protective effect (0.30, 0.10–0.75)[46]. This study did not compare the use of CE with ileocolonoscopy in the postoperative follow-up. However, it included 37% of small bowel resections not evaluable by ileocolonoscopy. Previous studies have shown post-surgical recurrence by CE that was not detected by

ileocolonoscopy, which has allowed active treatment in this group of patients[47]. Although ileocolonoscopy continues to be the gold standard for the search for postoperative recurrence, CE is an excellent complementary tool, if available, that improves diagnostic performance in this clinical setting.

CE and "treat to target" in CD

The "treat to target" strategy in CD[48] is based on the regular assessment of disease activity by using validated outcome measures and the subsequent adjustment of treatment of disease activity, following targets, where the main target is mucosal healing. A recent systematic review that included 47 studies highlighted CE as an objective method of evaluating CD activity that enables reclassifying patients with CD, monitoring the effect of medical treatment through the evaluation of mucosal healing, and detecting postoperative recurrence[49]. Owing to its diagnostic accuracy, CE could be incorporated into the "treat to target" management of patients with CD[49]. However, larger, randomized, controlled trials are necessary to confirm these findings.

CE and IBD – undefined

CE allows the classification of patients with a diagnosis of IBD-undefined (IBD-U)[50-53], where the inflammatory involvement of the colon cannot differentiate between UC and CD. IBD-U occurs in up to 10% to 15% of patients[54], and at least 15% to 30% of patients will be reclassified as having CD during their disease[50,55]. Establishing this difference is important from a surgical point of view regarding the selection of the type of surgery and which complications to expect in patients with CD and, from the medical point of view, in the selection of the type of biological therapies.

CE and UC

The role of CE in the evaluation of the colonic mucosa in UC is unclear. Colon CE (CCE and later CCE-2 or second-generation) was developed in 2006 and was designed for non-invasive visualization of the colon[56]. A systematic review showed that the diagnostic accuracy of CCE in the colon is comparable with ileocolonoscopy in assessing the severity and extent of the disease[57]. However, some studies with a small number of patients have found a weak correlation between the findings from CCE and colonoscopy, which supports the latter for the evaluation of the mucosa in UC[58,59].

Regarding the evaluation of the small intestine in UC, a prospective observational study (capcolitis) on CE in 127 patients with known UC found that only 4% of the diagnoses changed to CD upon evaluating the small bowel with CE[60].

PANENTERIC CE

Panenteric CE (PCE) is a new type of CE similar to PillCam™ COLON 2 (CCE-2) and is currently known as PillCam™ Crohn's System (Medtronic, Dublin, Ireland)[61]. PillCam™ Crohn's System is designed for the evaluation of the mucosa of patients with CD. This capsule has a field of view that allows for a 344° view between both capsule heads to provide a pan-intestinal panoramic visualization. The rate frame of PillCam™ Crohn's System ranges from 4–35 frames per second depending on the speed of the capsule into the gut and has an operating time of more than 12 h[61]. PCE was first described in a multicenter prospective study where it demonstrated a better diagnostic yield of PCE than ileocolonoscopy in 66 patients with active CD who underwent both modalities[62]. The authors found that the per-subject diagnostic yield rate for active CD lesions was 83.3% for PCE and 69.7% for ileocolonoscopy (yield difference 13.6%; 95%CI: 2.6%–24.7%), and the per-segment diagnostic yield rate was 40.6% for PCE and 32.7% for ileocolonoscopy (yield difference 7.9%; 95%CI: 3.3%–12.4%)[62].

In an observational cohort study performed on 93 patients (established CD: 71 and suspected CD: 22), the use of PCE allowed to change the treatment in 38.7% of patients [63]. Moreover, Montreal classification was up-staged in 33.8% of patients with established CD, and identifying proximal small bowel disease in 12.7% predicted treatment intensification[63]. A recent prospective, multicenter study in patients with established CD found that sensitivity of PCE was superior to MRE for proximal small bowel inflammation (97% *vs* 71%, $P = 0.021$) and similar to MRE and/or ileocolonoscopy in the terminal ileum and colon[64]. However, the overall sensitivity for active enteric inflammation for CE *vs* MRE and/or ileocolonoscopy was similar (94% *vs* 100%, $P = 0.125$), but the specificity was 74% *vs* 22%, respectively ($P = 0.001$)

[64]. In the pediatric population, a prospective study in 48 children with CD found that PCE led to a change in therapy for 71% of patients at baseline and 23% at 24 wk. A "treat to target" strategy in these children led to increased mucosal healing and deep remission from 21% at baseline to 54% at week 24 and 58% at week 52[65]. A recent multicenter study[66] compared the 344° panoramic-view recorded by PillCam™ Crohn's System (lesions detected by cameras A and B) with the standard 172°-view (lesions detected by one camera only) in 41 patients who underwent CE for suspected or established CD. The study found that the panoramic 344°-view increased small bowel CE accuracy *vs* the standard 172°-view, detecting a greater number of relevant lesions (56.1% *vs* 39.0%; $P = 0.023$), resulting in higher LS (222.8 *vs* 185.7; $P = 0.031$), and improved clinical management (48.8% *vs* 31.7%, $P = 0.023$)[66].

PCE, as the only study modality, could reduce costs associated with the evaluation of patients with CD, considering the need for MRE and ileocolonoscopy for the complete evaluation of the intestine in these patients. Furthermore, PCE is a safe method preferred by patients[64] that does not require sedation, representing advantages for the pediatric population[65].

Table 1 presents the main characteristics of the capsules used in IBD.

In summary, based on the available literature, CE is essential in evaluating patients with CD. The finding of lesions in the small bowel detected by CE and not observed in conventional studies (cross-sectional imaging, ileo-colonoscopy) determines changes in the Montreal classification in patients with CD[10]. This leads to a modification of the therapeutic strategies, with the earlier introduction of immunomodulators and/or biological therapy, improving the prognosis of these patients[67].

ARTIFICIAL INTELLIGENCE IN CE AND ITS APPLICATION IN IBD

In recent years, the development of artificial intelligence (AI) in medicine has made it possible to apply this technology to the automated identification of images on CE. AI, through deep learning artificial neural network (ANN) algorithms[68], facilitates image recognition according to which characteristics the algorithm chooses for itself based on what it considers best for that task, which requires much less time than conventional readings by endoscopists (5.9 min *vs* 96.6 min)[69]. Convolutional neural network (CNN), a type of ANN[68] applied to CE, has shown excellent performance for the detection of ulcers, polyps, celiac disease, and bleeding[69].

A recent study by Klang *et al*[70] evaluated the accuracy of CNN for the detection of ulcers in CD on CE for image sets from 49 patients. They reported an AUC of 0.99 for split images and accuracies ranging from 95.4% to 96.7%. The AUC for individual patients was 0.94 to 0.99[69]. Also, the use of CNN enabled characterizing the severity of ulcers on CE images in patients with CD with high accuracy in the detection of severe CD ulcerations and better differentiation between mild and severe ulceration (accuracy 0.91, 95%CI: 0.867-0.954) but a less accurate separation of moderate from severe: (Accuracy 0.78, 95%CI: 0.716–0.844) and mild *vs* moderate (accuracy 0.624, 95%CI: 0.547–0.701)[71]. Undoubtedly, this technology provides accurate and rapid detection of ulcers from CE images, thereby decreasing reading times. Moreover, deep neural networks are highly accurate in detecting stenosis in CE images (accuracy 93.5%) and differentiating between stenosis and healthy mucosa (AUC 0.989), stenosis, and all ulcers (AUC 0.942), and stenosis and different degrees of ulcer severity[72]. In another area, recent studies suggest that CNN would allow for the automatic evaluation of the degree of intestinal cleansing in CE studies, which could serve as a means of comparing different intestinal preparation methods and thus design recommendations[73].

Despite the encouraging results on the use of AI on CE in IBD, prospective studies are necessary to evaluate its usefulness in the diagnosis and follow-up in CD.

OTHER NEWS IN CE

Because CE passage is passive and dependent on the peristalsis of the intestine, only 80 to 90% of patients have their entire intestine visualized. Thus, up to 30% of minor injuries may not be seen during the study[23]**.** One of the new challenges is the possibility of directing the navigation of the CE in the intestine. Magnetically-assisted CE (MACE) has been tested as a screening tool in gastric cancer[74], Barrett's esophagus, and esophageal varix[75]. MACE has generated results comparable with esophagogastroduodenoscopy in detecting focal lesions[76] and the study of iron

Table 1 Characteristics of available capsule endoscopy systems for the study of inflammatory bowel disease

	SB CE (Pillcam SB3Ò)	Colon CE	PillCam CrohnÒ
Dimensions	26 mm × 11 mm	32 mm × 11 mm	32.3 mm ± 0.5 mm × 11.6 mm
Weight	3.0 g	2.9 g	2.9 g
Camera	One	2-one at each end	2-one at each end
Field of view	156º ISO-8600-3	344º: 172° ISO-8600-3 per camera	344º: 172° ISO-8600-3 per camera
Frame rate	2-6 fps (2-6)	4-35 fps (AFR)	4-35 fps (AFR)
operating time	≥ 8 or longer (max.15)	10 h	Minimum of 10 hr
Operating temperature	20-40 ºC	20-40 ºC	20-40 ºC

SB: Small bowel; CE: Capsule endoscopy; AFR: Adaptative frame rate; fps: Frames per second.

deficiency anemia[77]; however, it has not been evaluated in patients with IBD.

Other CE prototypes in development include biopsy[78] and drug delivery[79] capabilities, which could be clinically relevant for patients with IBD in the future.

CONCLUSION

The use of CE has played a fundamental role in evaluating the small bowel of patients with IBD, mainly in those with suspected CD and established CD. The development of new types of capsules, such as the panenteric capsule, and the integration of AI into CE image analysis, have improved the visualization and automated the identification of lesions in the digestive tract using a non-invasive, safe, highly tolerated method. Treatment optimization for patients with CD, thanks to CE findings, has improved the course of the disease. More studies are needed to support the use of CE in the evaluation of all patients with CD.

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MINIREVIEWS

Role of optical coherence tomography in Barrett's esophagus

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Abstract

Traditional endoscopic techniques for Barrett's esophagus (BE) surveillance relied on factor of probability as endoscopists performed cumbersome random biopsies of low yield. Optical coherence tomography (OCT) is a novel technique based on tissue light interference and is set to break conventional barriers. OCT was initially introduced in ophthalmology but was soon adopted by other areas of medicine. When applied to endoscopy, OCT can render images of the superficial layers of the gastrointestinal tract and is highly sensitive in detecting dysplasia in BE. Volumetric laser endomicroscopy is a second generation OCT endoscope device which is able to identify buried glands after ablation. Addition of artificial intelligence to OCT has rendered it more productive. The newer additions to OCT such as angiogram and laser marking will increase the accuracy of investigation. In spite of the few inevitable drawbacks associated with the technology, it presently outperforms all newer endoscopic techniques for the surveillance of BE.

Key Words: Optical coherence tomography; Volume laser endomicroscopy; Esophageal adenocarcinoma; Endoscopy; Gastroesophageal reflux disease

Core Tip: Surveillance of Barrett's esophagus for dysplasia is a long-debated and intensively researched topic. Optical coherence tomography (OCT) is a breakthrough technology in the medical field that enables the visualization of the layers of a structure in an office setting. The application of artificial intelligence (AI) to OCT endoscopy is the latest addition to the armamentarium of endoscopists. AI-based diagnostic algorithm scores are proven to be better than clinical scores. The accuracy of AI-based

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system is enhanced further by using color coding software and convolutional neural networks. Multi-center randomized control trials validating these technologies is the need of the hour.

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INTRODUCTION

Barrett's esophagus (BE) is defined as columnar metaplasia (or intestinal metaplasia, as some authorities prefer to call it) of the stratified squamous epithelium, lining the lower end of the esophagus[1]. It occurs due to chronic exposure of the distal esophagus to acidic contents as a part of gastroesophageal reflux disease. The prevalence of BE is around 1.6% in general population[2]. It varies in different regions of the world with increased prevalence in the western population. Apart from the gastroesophageal reflux disease, other risk factors for BE include advancing age, male gender, obesity, tobacco consumption, and Caucasian race[3].

Once the diagnosis of BE is made based on endoscopy, the endoscopist evaluates its extent as *per* the Prague C and M classification. All cases of BE should be biopsied at multiple levels as *per* the Seattle biopsy protocol to identify the presence of dysplasia or adenocarcinoma, which is the main concern. Traditional endoscopic techniques relied on the chance factor as endoscopists performed random cumbersome biopsies of low yield. The early diagnosis of esophageal neoplasia is important because it helps to initiate curative therapies for cancer. This has directed the path of research to identify newer techniques and technologies to increase the accuracy of biopsies during endoscopy[4]. Optical coherence tomography (OCT) is one of such techniques which is set to break conventional barriers.

Humans are prone to do errors due to fatigue, increased workload and working environment. The use of artificial intelligence (AI) has grown rapidly in the past few decades from using technology to perform simple household tasks to piloting aircraft. AI is also adopted into the medical field in the form of surgical robots in the last decade. The application of AI to endoscopy is widely researched as newer technologies of endoscopy are being developed. The purpose of this narrative review is to enlighten the readers about the principles of OCT and its application to BE and the use of AI in the OCT endoscopy.

OCT

OCT is an imaging modality based on light interference. It is used to produce cross-sectional images of a structure based on the differential properties of various layers with respect to light refraction[5]. The basic setup of OCT consists of a light source which is a low-coherence semiconductor super-luminescent diode. The light is split into two beams by an optical splitter: A reference beam and a sample beam. The reference beam is reflected back by a mirror, while the sample beam is focused onto the tissue to be imaged. Based on the refractory properties of the layers of the tissue, the sample beam is variably reflected back. The reflected light from the reference and sample beams are coupled in a coupler, producing interference patterns which are analyzed, after which a cross-sectional image is created (Figure 1). The axial resolution of OCT will depend on the spectral band of the light source with large spectral bands having better resolution[5]. The transverse resolution is independent of axial resolution and will depend on the numerical aperture of the lens through which the light beam passes[5].

The conventional OCT technology is based on the time-domain (TD-OCT) concept in which variations in the time of the travelled beams of light are analyzed to form an image with the help of moving mirrors. The technology has now evolved into the Fourier-domain (FD-OCT) which uses static mirrors so an image is formed based on the modulations in the source spectrum. The FD-OCT has higher image acquisition

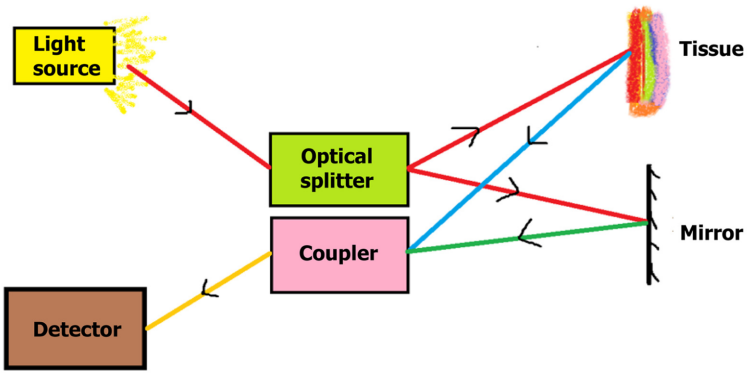

Figure 1 Basic schematic representation of the principle of optical coherence tomography.

speeds than TD-OCT. The resolution of FD-OCT is 1-3 μm, which is far better than the 10 μm resolution of TD-OCT. The FD-OCT is based on either charge-coupled device-based image acquisition (spectral-domain OCT) or photodetector-based image detection with longer wavelengths of the light source (swept-source OCT)[6]. The swept-source OCT has better resolution and twice the image acquisition speed compared to spectral-domain OCT[6].

OCT was initially introduced in ophthalmology as a method to visualize the layers of the retina but it was soon adopted into other areas of medicine. Nevertheless, the utility of OCT is still only the "tip of the iceberg" with its vast potential yet to be unleashed. When applied to endoscopy, OCT is able to render images of the superficial layers of the gastrointestinal tract. OCT can be combined with either a forward-viewing endoscope or a side-viewing endoscope, with the forward-viewing endoscope enabling the sampling of the desired tissue[7]. There are two main types of OCT endoscopes: The proximal scanning rotating endoscope, which is less expensive but has lower capture speed, and the distal scanning endoscope, which comes with a micromotor, acquires images at a much higher speed but comes at a cost higher than the proximal scanning endoscope[7].

Volumetric laser endomicroscopy (VLE) is a second generation OCT endoscope device presently used for imaging[8] (Figure 2). It uses balloon centered imaging probes for imaging with a high axial resolution of 7 μm and a depth of 3 mm, which is 10 times greater compared to the standard endoscopic ultrasound[9]. It images the esophagus in six-centimeter intervals and is quite fast in image acquisition compared to the conventional OCT. It images about 1200 cross-sectional areas in the six cm span which are reconstructed. The application of VLE in BE is mainly to diagnose suspicious areas of mucosal abnormalities and in the post-treatment surveillance of BE and early neoplastic lesions.

PREDICTIVE FEATURES OF DYSPLASIA IN BE USING OCT/VLE AND THE USE OF AI

The absence of layering, surface maturation, and gland maturation are the three independent predictive factors for dysplasia in OCT imaging. The surface maturation is assessed in terms of the surface OCT signal, which if equal or stronger than the sub-surface signal, is predictive of dysplasia. Gland maturation is assessed in terms of the number of abnormal glands identified in imaging with more than five glands predictive of dysplasia.

AI is based on computer algorithms which provide result based on the received input. The algorithms are created based on previous OCT images which are correlated with histological diagnosis. The AI system has been automated to evolve with time, based on its previous results just as a human brain which is known as machine learning. Machine learning may be supervised, semi-supervised or unsupervised. Hence, AI is said to as good as a human brain and sometimes even better. Swager *et al* [10] created an AI-based VLE prediction score using multivariable logistic regression analysis of 60 VLE images[10]. The components of the score were: the lack of layering of superficial layers, higher surface intensity than sub-surface intensity, and the number of abnormal glands (Table 1). A cut-off score of ≥ 8 was predicative of dysplasia with a sensitivity and specificity of 83% and 71% respectively[10]. This VLE

Table 1 Volumetric laser endomicroscopy prediction score and diagnostic algorithm[9]

VLE prediction score		
Parameter		Score
Layering	Layering present-more than 50%	0
	Layering present–less than 50%	8
Surface signal	Surface signal < subsurface signal	0
	Surface signal = subsurface signal	6
	Surface signal > subsurface signal	8
Abnormal glands	0-5	0
	> 5	5
VLE-diagnostic algorithm		
Mucosal layer partial effacement	Abnormal glands > 5	Dysplasia
	Abnormal glands ≤ 5	Non-dysplasia
Mucosal layer complete effacement	Surface intensity > subsurface intensity	Dysplasia
	Surface intensity ≤ subsurface intensity	Non-dysplasia

VLE: Volumetric laser endomicroscopy.

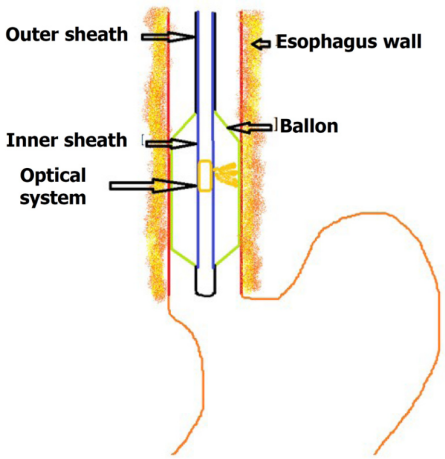

Figure 2 Parts of the volumetric laser endomicroscopy device.

prediction score based on computer-based VLE diagnostic algorithm (VLE-DA) was more sensitive (86%) and specific (88%) than the clinical VLE predication score[10-12]. The components of VLE-DA are listed in Table 1.

Outcomes of first generation OCT

The traditional OCT criteria were found to be 97% sensitive and 93% specific when applied to BE surveillance prospectively in a study by Poneros *et al*[13] in 2001. The accuracy of OCT in diagnosing dysplasia in BE was about 78% in a double-blinded study by Isenberg *et al*[14] in 2005. The utility of OCT in diagnosing dysplasia was also confirmed in a study by Evans *et al*[15] using the dysplasia index which was 83% sensitive and 75% specific[15]. Chen *et al*[16] used ultra-high-resolution OCT for diagnosing dysplasia and adenocarcinoma with an accuracy of 83.3% and 100% respectively[16]. The utility of ultra-high-resolution OCT was also confirmed in the study by Cobb *et al*[17].

OUTCOMES OF SECOND-GENERATION OCT

The imaging capability of three-dimensional OCT is faster than conventional OCT. Its utility was proved in the study by Adler *et al*[18]. VLE has been found to be more sensitive and specific than random blind biopsies as *per* Seattle protocol. The role of VLE was initially proved in a study by Vakoc *et al*[19], while in a study by Trindade *et al*[20] five out of six patients were upstaged due to the diagnosis of dysplasia which was missed by conventional endoscopy and narrow band imaging[19,20]. The sensitivity and specificity of VLE in diagnosing dysplasia was 86% and 88% in a study by Leggett *et al*[11]. In a study by Jain *et al*[21], VLE was compared with histology; the sensitivity in diagnosing BE-related dysplasia was 50% and specificity was 47.1%[21]. The false negative rate was 2.9%. Even though the specificity was low in the study, it is far better than the random biopsies. In a systematic review by Kohli *et al*[22], the sensitivity and specificity of OCT in diagnosing dysplasia and early malignancy was in the ranges of 68%-83% and 75%-82% respectively[22].

POST-ABLATION BE SURVEILLANCE USING OCT

A variety of ablation therapies such as radiofrequency ablation, cryoablation, laser ablation, photodynamic therapy, *etc.* are used for the treatment of high-grade BE dysplasia and insitu carcinoma. One of the main disadvantages of these procedures is the occurrence of buried glands or subsquamous glandular structures[23,24]. These glands, present beneath the epithelium, may undergo dysplastic changes and turn malignant, but are not visualized on routine endoscopy as the surface epithelium appears normal. OCT is one of the few techniques able to diagnose buried glands[25]. The sensitivity and specificity in identifying buried glands in post-treatment BE using VLE was shown to be 92.3% and 23.8% in a study by Jain *et al*[21]. However, in the study by Swager *et al*[26], most of the subsquamous glandular structures identified on OCT were histologically normal[26]. The role of OCT in post-ablative surveillance was also proved in a study by Benjamin *et al*[27].

Doppler-OCT is useful in detecting the changes in the sub-mucosal micro-vascular network, which further improves the accuracy of OCT. Doppler-OCT is also used to detect the change in the vascular pattern during post-photodynamic therapy for BE. Doppler-OCT helps to monitor the dose of photodynamic therapy[28,29].

NEWER ADDITIONS TO OCT

As neoplasia is associated with neovascularization, this is one of the features used to distinguish benign epithelium form malignancy. OCT angiography is used to image the subsurface vasculature without the need for any contrast and is useful in diagnosing neoplasia[30]. The changes in the OCT signal caused by the movement of erythrocytes are quantified by calculating the decorrelation. However, this makes the OCT signal susceptible to artifacts due to respiratory and cardiac movements.

As a balloon is used to augment the scanning speed in VLE, simultaneous sampling of mucosa is not possible. The biopsy taken from the mucosa may not be the original mucosa intended on imaging. This disadvantage is overcome by using laser marking along with VLE. The laser fiber is used for creating point coagulation spots which act as markers for biopsy after the scan[31,32]. Simultaneous laser coagulation along with OCT is also possible[32].

The addition of deep learning to AI-based OCT systems further improved the accuracy of prediction of BE related dysplasia. Deep learning is one kind of machine learning where multiple diagnostic algorithms are layered to form a convolutional neural network just as a human brain. The output from one layer is fed to the next layer which further processes it and feeds it to the next layer to produce a refined output[33]. Deep learning also increases the speed of processing the images.

Trindade *et al*[34] used an AI-based new software termed intelligent real-time image segmentation for BE surveillance. The software provided color codes based on the degree of dysplasia using the previously mentioned VLE prediction features[34]. A multi-center randomized control trial with trial number NCT03814824 is going on, validating the above software, the results of which are awaited.

OCT IN COMPARISON TO OTHER ADVANCED ENDOSCOPIC IMAGING

VLE has been proved to be better than confocal laser endomicroscopy (CLE), which is one of the emerging endoscopic imaging techniques for BE and associated dysplasia. The sensitivity and specificity of VLE using VLE-DA were higher than CLE in a study by Leggett *et al*[11]. CLE is also disadvantageous as it requires injection of contrast into the blood and a limited field of view and imaging depth[35]. Endoscopic ultrasound is an excellent imaging modality for assessing the depth of tumor involvement. However, its accuracy is lower in differentiating early invasive carcinoma (T1 and T2). In a study by Kahn *et al*[36], VLE showed good results in differentiating T1a lesions from T1b lesions[36].

DRAWBACKS OF OCT

All technologies have one or more drawbacks and OCT is no exception. The main drawback of OCT is the absence of real-time imaging, as it is the case with other imaging modalities. Even the fastest OCT technology and probes require seconds to process the reflected waves. VLE requires balloon apposition and although perfect apposition is theoretically possible, it is rare in reality. The mucous layer on the surface epithelium, the contractions of the esophagus, and the presence of blood interfere with the close approximation resulting in artifacts. Simultaneous biopsy is not possible during imaging in VLE probes, which may pose a difficulty in biopsying the originally identified area. Movement artifacts are common in Doppler-OCT and OCT angiography. Unlike endoscopic ultrasound, OCT cannot be used to image the deeper tissues. Finally, cost is one of the main limiting factors for the widespread usage in all institutes.

The application of AI to OCT requires inputs from a large number of experts with expertise in this new technology who are fewer at present. The accuracy of the AI systems is based on the data fed which requires advanced imaging techniques and higher quality images. As AI and machine learning require input from humans it may be the victim of human errors during data input. Much of the knowledge of AI in OCT is based on pilot studies and case series. The number of randomized control trials and multi-center trials are very less due to concerns raised by ethical committees.

CONCLUSION

Surveillance of BE for dysplasia is a long-debated and intensively researched topic. OCT is a breakthrough technology in the medical field that enables the visualization of the layers of a structure in an office setting. The application of OCT to endoscopy is the latest addition to the armamentarium of endoscopists. Even though earlier OCT instruments were slow to image tissues, the newer AI-based technologies are fast enough to add only a few minutes to the conventional endoscopy time and are highly accurate compared to clinical diagnosis. OCT is highly sensitive in detecting dysplasia in BE. Even though the specificity in diagnosing dysplasia is lower, it is far more efficient than the conventional blind biopsy protocol. An especially important feature is the ability of VLE to identify buried glands after ablation. The newer additions to OCT, such as angiogram and laser marking, will help to increase the accuracy of the investigation. The AI software systems and deep learning systems are evolving over time. However, the utility of AI to BE surveillance is still at its bud stage. In spite of the few unavoidable drawbacks associated with the technology, AI-based OCT system is presently the most promising of all newer endoscopic techniques for the surveillance of BE.

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MINIREVIEWS

Artificial intelligence and colonoscopy − enhancements and improvements

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Abstract

Artificial intelligence is a technology that processes and analyzes information with reproducibility and accuracy. Its application in medicine, especially in the field of gastroenterology, has great potential to facilitate in diagnosis of various disease states. Currently, the role of artificial intelligence as it pertains to colonoscopy revolves around enhanced polyp detection and characterization. The aim of this article is to review the current and potential future applications of artificial intelligence for enhanced quality of detection for colorectal neoplasia.

Key Words: Artificial intelligence; Colon polyp; Adenoma detection rate; Dysplasia; Inflammatory bowel disease; Colon preparation

Core Tip: The application of artificial intelligence (AI) in medicine and gastroenterology has demonstrated to date, broad utility in both disease diagnostics and management. The utility of AI in colonoscopy has recently demonstrated enhanced polyp detection and characterization, assessment for mucosal healing and identification of dysplasia associated with inflammatory bowel disease, as well as assessment of the quality of bowel preparation for colonoscopy.

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INTRODUCTION

Although artificial intelligence (AI) was first conceptually presented as a means for machines to mechanize human actions and cognitive thinking approximately 70 years ago, the current applications are exponentially broad[1,2]. This technology is predicated on the fact that AI is able to exhibit certain facets of human intelligence which is derived from techniques known as machine learning (ML) and deep learning (DL)[3]. Machine learning involves automatically building mathematical algorithms from data sets and forming decisions with or without human supervision[3,4]. When an algorithm is able to learn predictive models, it can use new inputs to form outputs [3,5,6]. These models can be combined to form artificial neural networks (ANN) which mimic the neural network of a brain. Each algorithm assumes the role of a neuron and when grouped together form a network that interacts with different neurons[5,6]. ANN have pathways from inputs to outputs with hidden layers in between to help make the inner nodes more efficient and improve the overall network[3]. DL is a domain in which AI process a vast amount of data and self-creates algorithms that interconnect the nodes of ANN with interplay in the hidden neural layers[3,6]. Researchers have been using DL to form computer aided diagnosis systems (CADS) to aid in polyp detection and characterization[7]. Two major CAD systems have been developed so far: CADe (termed for computer-aided detection) and CADx (termed for computer-aided characterization). CADe uses white-light endoscopy for image analysis with the ultimate goal to increase the number of adenomas found in each colonoscopy thereby increasing adenoma detection rate (ADR) and reducing the rate of missed polyps[8]. CADx is designed to characterize polyps found during colonoscopy, thereby improving the accuracy of optical biopsies and reducing unnecessary polypectomy for non-neoplastic lesions[8]. It predominantly uses magnifying narrow band imaging (mNBI) but could also incorporate a variety of other techniques including white-light endoscopy, magnifying chromoendoscopy, confocal laser endomicroscopy, spectroscopy, and autofluorescence endoscopy[8]. In addition, AI technology is being applied to evaluate the quality of bowel preparation for colonoscopy. In this review, we outline the role of AI in polyp detection and characterization of dysplastic and/or neoplastic lesions. We also provide the current data on utility of AI in evaluation of bowel preparation and future directions of AI in colonoscopy.

POLYP DETECTION AND CADS

Polyps are abnormal tissue growths that arise in the colon that carry malignant potential[9]. Polyps are detected during colonoscopy but can sometimes be missed due to a variety of factors *e.g.*, age of patient, diminutive polyp size, failure to reach cecum, quality of bowel preparation, and experience of endoscopist[10,11]. The ADR is the frequency to detect one or more adenomatous polyps during screening colonoscopy and is a universal quality metric with the strongest association to the development of interval cancers[11-13]. Owing to growing concerns of increasing rates of colon cancer in adults, CADS have been developed and utilized to aid in polyp detection and ultimately increase ADR[9,14-18].

Multiple research groups have created automated computer vision methods to help analyze and detect polyps during colonoscopy[15-19] (Figure 1). One of the first groups to use CADe to help detect polyps relied mainly on still images from videos for analysis and polyp detection[20]. Their CADe used 24 videos containing a total of 31 polyps which were detectable in at least 1 frame[20]. The study demonstrated a sensitivity and specificity for polyp detection of 70.4% and 72.4%, respectively[20]. Another group created a model using DL which used 546 short videos and 73 full length videos to create the software and train it with positive and negative polyp containing videos[21]. The sensitivity and specificity were 90% and 63.3% respectively, showing that the model could potentially be used in a clinical setting to help minimize polyp miss rates during colonoscopy[21]. A recent, prospective multicenter trial

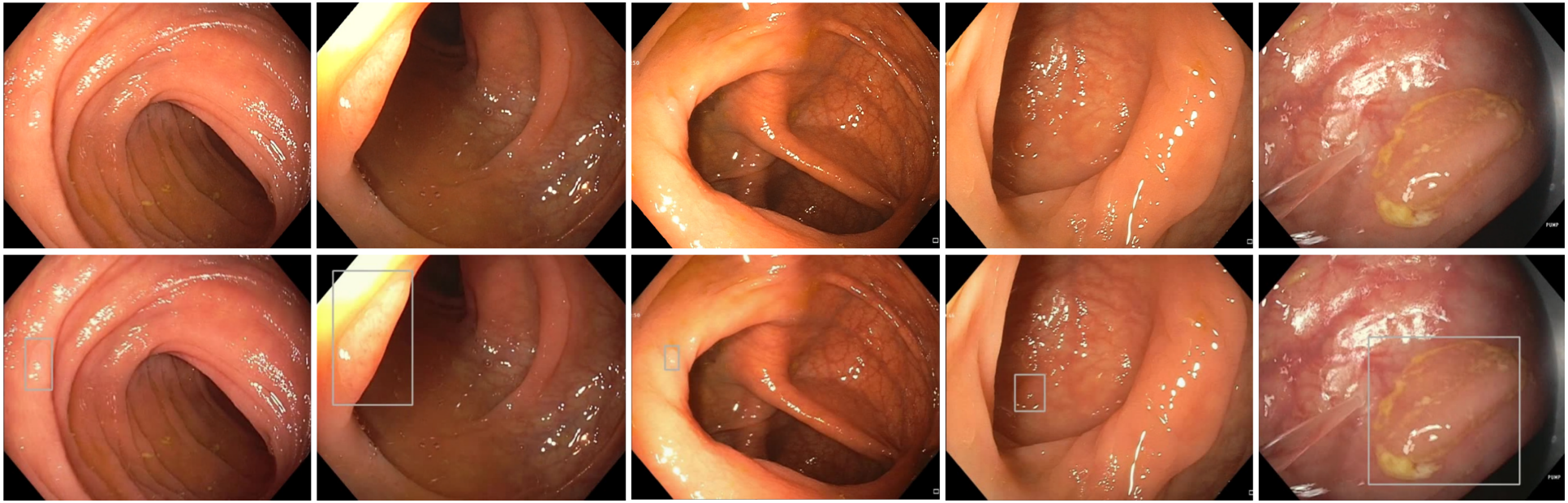

Figure 1 Polyp detection without artificial intelligence (top) and with artificial intelligence (bottom).

comparing a CADe system to trained endoscopists and found that endoscopists (with a baseline ADR ≥ 35%) and CADe had a diagnostic accuracy of 98.2% and 96.5% respectively[22]. This led the authors to conclude that CADe was non-inferior to expert endoscopists[22].

As CADe systems proved to enhance polyp detection, researchers then focused on the role of AI on improving ADR. A prospective, randomized, controlled study evaluated 1058 patients undergoing colonoscopy with or without an automatic polyp detection system (APDS) found a relative ADR increase of 43.3% (29.1% *vs* 20.3%) using the APDS compared to standard colonoscopy[23]. This increase was most prevalent amongst diminutive adenomas which suggests that smaller adenomas are more likely to be missed compared to larger adenomas[23]. To expand upon the previous study, a double-blinded, randomized, controlled trial was performed with a sham group to control for operational bias[24]. There was a 21.4% relative increase of ADR in the CADe group (34% *vs* 28%) when compared to controls[24]. They found the delta to be higher amongst endoscopists with lower baseline ADR than compared to those with a higher baseline ADR[24]. A recent meta-analysis which included 6 randomized controlled trials comparing AI-assisted-colonoscopy to non-AI-assisted-colonoscopy totaling 5058 patients showed a significantly higher ADR within the AI group compared to the control (33.7% *vs* 22.9%, respectively)[25]. The study also

showed an overall increase in detecting proximal colon adenomas with the AI-assisted-group compared to the control group (23.4% *vs* 14.5%, respectively)[25]. This is important because currently colorectal cancer (CRC) screening with colonoscopy alone is not effective at reducing proximal colon cancers and their mortality[25,26]. Thus while improving ADR is vital to preventing CRC, particularly in the proximal colon, the use of AI alongside endoscopists can be an ideal starting point. The CADe systems could be used as second observers, as second observers have been shown to increase ADR[27].

POLYP CHARACTERIZATION AND AI

Worldwide, CRC is the third most common cancer diagnosed in men and second in women[28]. Overall incidence of CRC in the United States has decreased due to lower smoking rates, early colonoscopy screenings, and early identification of patient-specific risk factors, but recent studies have reported a global increase in incidence of CRC in the younger population[29,30]. Thus, the latest endoscopic research is aimed towards techniques to better identify polyps and allow for real-time polyp histologic characterization which provides vital information for early intervention through endoscopic or surgical resection[31].

Studies evaluating AI and histologic assessment with optical biopsy have been a targeted focus- in particular for a "resect and discard" strategy for diminutive polyps < 6 mm, thereby avoiding the costs of pathology for low risk lesions[32] (Figure 2) top.

Several studies have found the range of sensitivity and specificity for polyp detection and characterization to be 70%-98% and 63%-98%, respectively[33]. An optical biopsy allows for differentiation of polyp type based on certain features. For example, NBI is an image-enhanced type of endoscopy that is used to identify microstructures and capillaries of the mucosal epithelium and allow for prediction of histologic features of colorectal polyps. Use of this advanced imaging technique often requires expertise to differentiate hyperplastic polyps from neoplastic polyps with high accuracy. AI systems offer a standardization of polyp characterization that overcomes the expertise or training differences across endoscopists[34]. Analysis of a CAD system with a deep neural network for analyzing NBI of diminutive polyps found that the AI system could identify neoplastic or hyperplastic polyps with 96.3% sensitivity and 78.1% specificity[34]. The system was compared to both novice (in-training) and expert endoscopists and it was notable that over half of the novice endoscopists classified polyps with a negative-predictive value of ranging from 73%-84%, compared to 91.5% of the system. The system also had a shorter time-to-classification compared to both expert and novice endoscopists ($P < 0.05$)[34]. Other groups have had similar results showing promise for AI-identification. One study compared images of 225 polyps as evaluated by a CAD system compared to diagnosis by endoscopists[35]. The polyps were classified using the Kudo and NBI international colorectal endoscopic classifications which found of the 225 polyps, 142 were dysplastic and 83 were non-dysplastic after endoscopy. The results of the CAD system correctly classified 205 polyps (91.1% of the total) and correctly delineated 131/142 (92%) as dysplastic and 74/83 (89%) as non-dysplastic[35]. There were no statistically significant differences in histologic prediction between the CAD system and endoscopic assessment, thus they concluded that a computer vision system based on characterization of the polyp surface could accurately predict polyp histology[35].

AI IN INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory gastrointestinal tract disorder that remains a global concern as incidence in developing countries continues to grow[36]. Studies with AI and large datasets of endoscopic images have shown that AI can improve the way to diagnose IBD, evaluate the severity of disease, and follow-up treatments and provide follow-up[37]. Initial diagnosis of IBD through endoscopic evaluation remains a challenge due to wide ranging clinical manifestations of IBD and overlap across subtypes. Key endoscopic features of IBD include ulceration or erosions, and AI has shown its role in better predicting the need for further evaluation [38]. Aoki *et al*[38] have demonstrated that a deep convolutional neural network (DCNN) can be trained to detect erosions and ulcerations seen on wireless capsule endoscopy. Their system evaluated 10440 images in 233 s and demonstrated an area

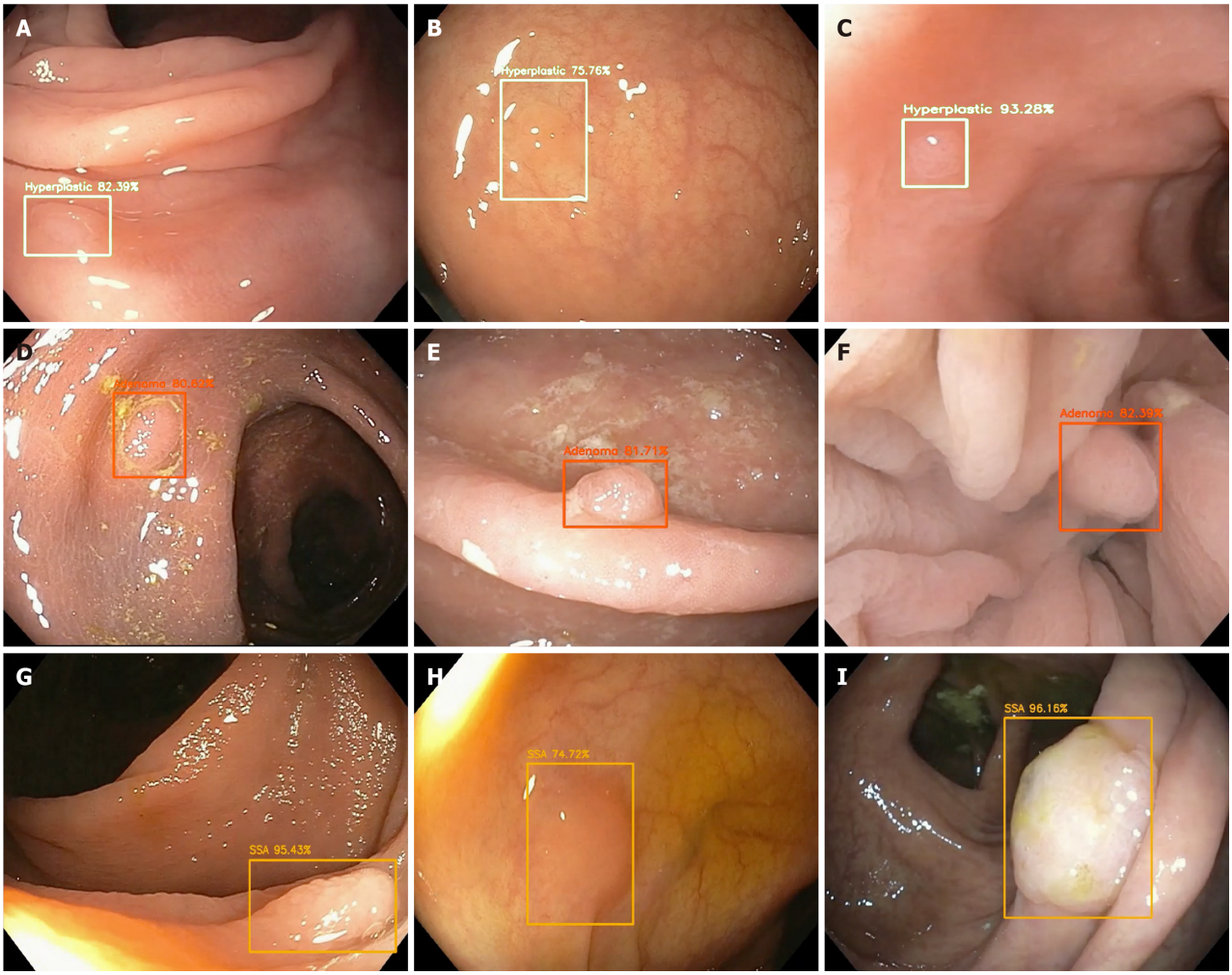

Figure 2 Optical pathology of detected polyps with associated probability utilizing artificial intelligence. A-C: Hyperplastic polyps; D-F: Adenomas; G-I: Sessile serrated adenomas.

under the curve for detection of erosions and ulcerations at 0.958 (95% confidence interval: 0.947-0.968) and sensitivity, specificity and accuracy of 88%, 90% and 90%, respectively[38]. Tong *et al*[39] studied 6399 patients with UC, CD, or intestinal tuberculosis (ITB) who underwent colonoscopies. The colonoscopic images were then translated in the form of free texts and Random Forest (RF) and CNN were utilized to distinguish the three diseases. Diagnostic sensitivity and specificity of RF in UC/CD/ITB were 0.89/0.84, 0.83/0.82, and 0.72/0.77, respectively and that of CNN were 0.99/0.97, 0.87/0.83, and 0.52/0.81, respectively[39]. The studies showed that AI can be employed to discern and diagnose IBD although real-time diagnostic utility remains an area to develop[39].

Determining disease severity and activity in IBD can be done using endoscopic inflammation indices, and histologic scores. However, there can be certain flaws to using these methodologies such as intra-observer and inter-observer variability[40]. Studies using AI have been done to help control some of these factors. Bossuyt *et al*[41] developed a red density (RD) system, which was specific for endoscopic and histologic disease activity in UC patients, to help mitigate the observer bias by endoscopists. The study had 29 UC patients compared against 6 control patients using the RD score gained during colonoscopy[41]. The RD score was linked to the Robart's Histologic Index in a multiple regression analysis and was found to be correlated with the RHI (r = 0.65, P < 0.00002) from the patients with UC[41]. The RD score from the control patients was also correlated with the RHI, Mayo endoscopic subscores (r = 0.76, P < 0.0001) and UC Endoscopic Index of Severity scores (r = 0.74, P < 0.0001), showing it correlated well with the validated tests[41]. A study done by Takenaka *et al*[40] used their algorithm, the deep neural network for evaluation of UC (DNUC), in 875 UC patients. The DNUC was developed using 40785 images from colonoscopies and 6885 biopsy results from 2012 UC patients[40]. The DNUC was able to identify patients in endoscopic remission with 90.1% accuracy and a kappa coefficient of 0.798 and

identify patients in histologic remission with 92.2% accuracy and a kappa coefficient of 0.895 between the biopsy result and the DNUC[40]. The researchers concluded that it could be used to identify patients in remission and potentially avoid mucosal biopsy and analysis[40]. Stidham *et al*[42] created a 159-layer CNN using 16514 images from 3082 UC patients to help categorize patients groups in remission (Mayo subscore 0 or 1) to moderate to severe (Mayo subscore 2 or 3). The CNN had a positive predictive value of 0.87, sensitivity 83% and specificity of 96%[42]. The CNN was compared against human reviewers when assigned the Mayo scores, with a kappa coefficient of 0.84 for the CNN *vs* 0.86 for the human reviewers[42]. This shows that the AI is effectively able to help categorize patients into their respective severity stages[42].

Patients with IBD are at increased risk for CRC and it is important for these patients to undergo frequent surveillance. Guidelines differ depending on the medical society, but overall recommended intervals are from 1-5 years[43]. IBD surveillance guidelines and whether AI has a role in CRC detection has yet to be directly studied. A large reason for the lack of studies of AI and IBD has been due to IBD being an exclusion criterion for many of the early colonoscopic AI studies. A single study by Uttam *et al*[44] was one of the first to look at IBD and cancer risk, utilizing a three-dimensional nanoscale nuclear architecture mapping (nanoNAM). By analyzing 103 patients with IBD that were undergoing colonoscopy, their system measured for submicroscopic alterations in the intrinsic nuclear structure within epithelial cells and compared findings to histologic biopsies after 3 years. They found that their nanoNAM could identify colonic neoplasia with an AUC of 0.87, sensitivity of .81, and specificity of 0.82[44]. Additional studies on AI in IBD surveillance could help personalize surveillance strategies or guidelines for patients.

AI SYSTEMS IN PRACTICE

The most recent developments in clinical practice have been with the approval of several different devices: EndoBRAIN (Olympus Corporation, Tokyo, Japan), GI Genius (Cosmo Pharmaceuticals N.V., Dublin, Ireland), and WavSTAT4 (SpectraScience, Inc., San Diego, CA)[33,45,46]. EndoBRAIN is an AI-based system that is able to analyze pathologic features present on endoscopic imaging, and was developed and approved as a class II medical device[33]. In a multi-center study to determine the diagnostic accuracy of EndoBRAIN, their system was trained using 69142 endocytoscopic images taken from patients that had undergone endoscopy and the EndoBRAIN was compared against 30 endoscopists (20 trainees, 10 experts) with primary outcome of assessing neoplastic *vs* non-neoplastic lesions. Their results found that EndoBRAIN distinguished neoplastic from non-neoplastic lesions with 96.9% sensitivity, 94.3% specificity, which was higher than trainees and comparable to experts[33].

GI Genius has been approved by the FDA as an AI device to detect colonic lesions. GI Genius was compared to experienced endoscopists for colorectal polyp detection[45]. This system was trained on a data-set using white-light endoscopy videos in a randomized controlled trial and primarily looked at reaction time on a lesion as the primary endpoint. Results demonstrated that the AI system held a faster reaction time when compared with endoscopists in 82% of cases[45].

Lastly, laser-induced fluorescence spectroscopy using a WavSTAT4 optical biopsy system was evaluated for efficacy in accurately assessing the histology of colorectal polyps with the end goal of reducing time, costs, and risks of resecting diminutive colorectal polyps[46]. The overall accuracy of predicting polyp histology was 84.7%, sensitivity of 81.8%, specificity of 85.2%, and negative predictive value of 96.1%. This suggests that the system is accurate enough to allow distal colorectal polyps to be left in place and nearly reaches the American Society for Gastrointestinal Endoscopy threshold for resecting and discarding without pathologic assessment[46].

REAL-TIME EVALUATION FOR INVASIVE CANCER

AI prediction of invasive cancers through the utilization of real-time identification of colorectal polyps has the potential to improve CRC screening by limiting misses and improving outcomes, especially in geographic regions with less access to highly trained endoscopists.

Advanced imaging techniques during endoscopy (without AI) to provide a real-time prediction of lesion pathology and depth of invasion has been widely used. For example, a study assessed white-light endoscopy, mNBI, magnifying chromoen-

doscopy, and probe-based confocal laser endomicroscopy in real-time, in order to evaluate and classify the depth of invasion for colorectal lesions[31]. Of the 22 colorectal lesions, 7 were adenomas, 10 were intramucosal cancers, and 5 had deep submucosal invasion or deeper involvement. Sensitivity and specificity of white light endoscopy and mNBI were both 60% and 94%, respectively. Magnifying chromoendoscopy and probe-based confocal laser endomicroscopy were both 80 and 94%, respectively[31].

With data showing reliability of advanced imaging techniques in real-time for information to establish a diagnosis and drive intervention pursuits, integration of AI systems with these advanced imaging techniques has been a growing research focus. A recent review assessed 5 retrospective studies with wide ranging sensitivities ranging from 67.5%-88.2% sensitivity and 77.9%-98.9% specificity in finding invasive cancers[47]. The prediction of cancer invasion was made using magnified NBI, confocal laser endomicroscopy, white light endoscopy, or endocytoscopy. As the numbers reflect, more studies are needed to better evaluate how AI can provide more stable reliability in evaluation for invasive cancers[47].

COLON PREPARATION AND AI

Bowel preparation significantly impacts the diagnostic accuracy of colonoscopies. Inadequate colon preparation impairs visualization of the mucosa, thus causing missed lesions, extended operative time, and increased need for repeat colonoscopies [48,49]. Approximately 10%-25% of all colonoscopies are inadequately prepared[50-52]. In addition, studies have shown that suboptimal bowel preparation can result in an adenoma miss rate ranging from 35%-42%[51]. A recent prospective study discovered that variable bowel preparation quality did not have a measurable effect on their AI algorithm's ability to accurately identify colonic polyps. However, the applicability of these findings is limited by the study's small sample size of 50[50]. Therefore, the ability of AI to accurately identify polyps in suboptimal conditions remains unknown.

Currently several scales, the most validated and reliable of which is the Boston Preparation Scale (BBPS), are used to assess bowel preparation quality[52]. Scores ranging from 0-3 are individually given to the right, transverse, and left colon during colonoscope withdrawal. A bowel preparation that fails to have a total BPPS score of ≥ 2 would mandate a repeat colonoscopy before the recommended 10-year interval (assuming a normal colon)[48,52]. Despite BBPS being deemed the most reliable scale, it cannot accurately account for variability in bowel preparation throughout the entire colon or gradients in adequacy of cleansing. Although BBPS takes into consideration the 3 colonic segments, regions of the same segment can be variably cleansed[49,52]. Therefore, 1 score cannot accurately represent one-third of the colon. This limitation is further exacerbated by the scale's susceptibility to subjectivity, as individual experiences can shape how physicians interpret data[49].

Most studies indicating the efficacy of AI in detecting colonic polyps utilized still images and videos of ideally prepared colons to train and test their AI software[53]. A DCNN known as ENDOANGEL (Wuhan EndoAngel Medical Technology Company, Wuhan, China) provided real-time and objective BPPS scores during the colonoscopy. ENDOANGEL circumvents subjective bias *via* DL using thousands of images scored by different endoscopists[49]. Additionally, the DCNN simultaneously calculates a real-time BPPS score every 30 s throughout the colonoscopy and provides a cumulative ratio of the different stages, thus providing an accurate assessment of preparation quality throughout the colon[49,52]. Through DL and frequent scoring, ENDOANGEL proved to be far more effective than endoscopists at accurate BPPS scoring (93.33% *vs* 75.91%)[49].

Overall, poor bowel preparation quality significantly increases ADR[51]. Although previous applications of CADe and CADx have been used to optimize endoscopic image quality and mucosal visualization, ENDOANGEL, is the first utilization of AI to provide objective, real-time assessments of bowel preparation quality throughout the entire colon[49,54,55]. Another laboratory group has since independently released promising results regarding use of their AI to assess bowel preparation, indicating AI's potential to improve the preparatory-phase of colonoscopy[56].

FUTURE DIRECTIONS

A significant problem in the advanced imaging trials is that these are done by experts and accordingly, there is good inter-observer performance characteristics. These results are not the same when evaluated by lesser experienced providers[57]. Application of AI as a formidable tool seems logical and promising to mitigate the costs and learning curves for application of these newer techniques across the broad and variable ranges of providers.

Although the current CADS provide promising results, a larger data sets for training the systems can provide improvements in sensitivity and specificity in addition to minimizing false positives and false negatives. The larger training data also increases the burden of annotations, however, this can be overcome by an annotation software which incorporates a DL module. The precise effects of AI once it is widely available in clinical practices are yet to be determined, but the evidence based on EndoBRAIN, GI Genius, and WavSTAT4 are hopeful that significant benefits in training gastroenterologist and diagnosing a polyp can be expected.

Additional areas of future study include better detection of various polyps (adenomatous, non-adenomatous, dysplastic), evaluation of lesion size and morphology, and distinguishing invasive involvement. Additionally, further study is necessary to evaluate the adequacy of large polyp resection (*i.e.*, margins free of adenomatous change). Much of the early data to date have used AI systems which are based on algorithms using still-images and videos[58]. Larger-scale studies can help us better understand real-time use of AI to show how it compares to endoscopists. Due to the novelty of AI systems in the clinical setting, study methods utilizing AI have also largely been done in a non-blinded manner, which may interfere with how the endoscopists perform the procedure, leading to a component of observation bias.

Finally, the future of AI lies in simplifying the tool for utilization by many endoscopists as well as achieving the goal of treatment. One way to overcome the complexity is incorporating the CADS into the colonoscope and display instead of existing as a separate entity that needs to be installed. In addition, an improved model for distinguishing polyps and invasion can further facilitate treatment process for patients.

CONCLUSION

AI is widely applied and utilized in endoscopy and continues to be researched to augment the accuracy of screening and differentiation of neoplastic *vs* non-neoplastic lesions. Although this wide applicability and active investigations are encouraging, further work is needed to solidify the integration of AI into everyday practice. Real-time diagnosis using AI remains technically challenging, however, these recent studies exemplify promising advancements for enhanced quality assessment and management of colonic disease.

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MINIREVIEWS

Impact of endoscopic ultrasound elastography in pancreatic lesion evaluation

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Abstract

Pancreatic malignancy still becomes a major global problem and is considered as one of the most lethal cancers in the field of gastroenterology. Most patients come in the late stage of the disease due to organ's location, and until now the treatment result is still far away from satisfaction. Early detection is still the main key for good, prolonged survival. However, discerning from other types of tumor sometimes is not easy. Endoscopic ultrasound (EUS) is still the best tool for pancreatic assessment, whereas fine-needle aspiration biopsy (FNAB) is considered as the cornerstone for further management of pancreatic malignancy. Several conditions have become a concern for EUS-FNAB procedure, such as risk of bleeding, pancreatitis, and even needle track-seeding. Recently, an artificial intelligence innovation, such as EUS elastography has been developed to improve diagnostic accuracy in pancreatic lesions evaluation. Studies have shown the promising results of EUS elastography in improving diagnostic accuracy, as well as discerning from other tumor types. However, more studies are still needed with further considerations, such as adequate operator training, expertise, availability, and its cost-effectiveness in comparison to other imaging options.

Key Words: Pancreatic malignancy; Pancreatic lesion; Endoscopic ultrasound; Fine needle aspiration biopsy; Elastography

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Core Tip: The application of endoscopic ultrasound (EUS) elastography is one of the most potential roles of artificial intelligence in pancreaticobiliary disorders. EUS elastography becomes a promising method to evaluate pancreatic lesions by providing information of tissue elasticity, which may correlate with malignant characteristics. Incomplete elastographic delineation, especially in large tumor size, as well as compelling intra-/inter-observer variability also still become limitations in performing adequate EUS elastography examination on pancreatic lesions.

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INTRODUCTION

Pancreatic malignancy is still considered as the most lethal cancer in the field of gastroenterology. Based on Global Cancer Observatory database 2020, it is still holding the 12th rank of the most common malignancies all over the world. The mortality rate related to pancreatic cancer has increased more than double within 27 years. The survival rate has also been considered far from satisfaction with regards to the standard treatment development. In Asian population, the incidence and mortality related to pancreatic cancer are also quite high (47.1% and 48.1%, respectively)[1]. Most of the patients are diagnosed at the late stage due to organ's location, non-specific clinical manifestation in early stages, and the absence of simple screening test with high accuracy for early stages of the disease.

In the evaluation of pancreatic cancer, imaging has been proven to play a central and critical role. Imaging modalities are expected to be able to detect and characterize the tumor mass, evaluate local and vascular involvement, evaluate lymphatic and perineural invasion, and find any metastases. Evolution of diagnostic imaging examination such as abdominal computed tomography (CT) scan and magnetic resonance imaging (MRI) have shown good accuracy for detecting pancreatic lesion. A single-center retrospective study in 140 subjects showed higher sensitivity (89.5% *vs* 81.4%) and specificity (63.4% *vs* 43%) in MRI compared to CT-scan for evaluating pancreatic adenocarcinoma. This study also showed that only 14% of the patients were diagnosed in the early stage at the time of diagnosis. Nevertheless, in the setting of small size of tumor mass, uncooperative patients for MRI evaluation, availability of MRI, lack of clinicians' familiarity with the device, and high cost of performing MRI still become the limitations in clinical practice. Additionally, from the same study, the highest diagnostic accuracy was shown by endoscopic ultrasound (EUS) (sensitivity 97.5%, specificity 90.3%). In the new era of the old instrument development, EUS has become the cornerstone in pancreatic malignancy, as it has a high sensitivity for small tumor size (< 2 cm), evaluation of staging (including the presence of lymph nodes, ascites, liver metastasis, and vascular involvement), and to perform direct tissue sampling[2,3]. However, in the conditions of uncertain malignant condition, normal tumor markers level, and possibility of needle tract seeding, a dilemmatic condition on whether the lesion should be punctured or not may arise[3-5]. Learning from the non-invasive tool development, such as elasticity evaluation, has opened a better insight for utilizing EUS, not only for diagnostic purpose, but also for therapeutic purpose.

PRINCIPLE OF ENDOSCOPIC ULTRASOUND ELASTOGRAPHY

The concept of utilizing combination of elastography (EG) and ultrasonography in diagnosing pancreatic disorders has been proposed as a way to overcome the diagnostic problem of solid pancreatic lesions (Figure 1). A prospective study conducted by Uchida *et al*[6] showed that real-time tissue EG and transcutaneous ultrasonography can provide real-time visualization and information of pancreatic tissue elasticity. Combination of sonic and ultrasound waves will cause less compression in fibrotic and stiff tissue, in comparison to softer and healthy tissue. This characteristic may overcome the limitation of conventional EUS, especially in patients

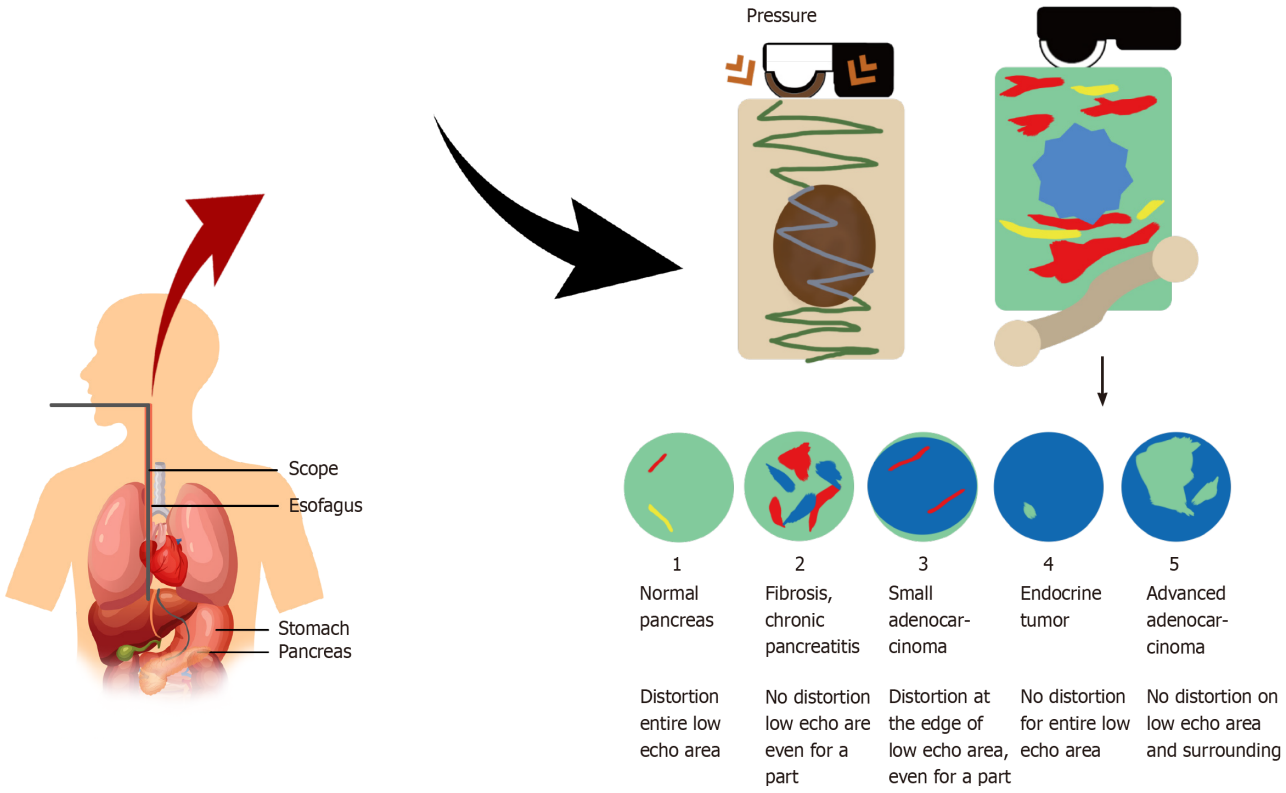

Figure 1 Basic principles of endoscopic ultrasound elastography in pancreatic lesion evaluation. The possibility of combining endoscopy and ultrasonography in evaluating pancreatic lesion through the principle of strain elastography, in which, tissues with higher elasticity will exhibit more deformation after a form of pressure is being applied. The degree of displacement will then be represented as colour pattern analysis to determine the possible diagnosis (Red = Soft tissue; Green = Intermediate tissue; Blue = Hard tissue).

with coexistent chronic pancreatitis or "pseudotumoral" pancreatitis[7]. As one of the most recent approaches in gastrointestinal endoscopy, EUS real-time tissue EG has more diagnostic potentials compared to EUS with only a B-mode imaging ability. In general, EUS EG provides information of tissue elasticity through differences in deformation and displacement among tissue areas, as well as different amount of tissue distortion attained from spatial differentiation. Tissue consistency may correlate with malignancy characteristics, in which malignant tissues have harder consistency than benign tissues[8].

Reported for the first time in 2006 for evaluating pancreatic tissues, EUS EG has been continuously developed for tissue elasticity assessment. Two methods have been differently proposed and compared for each diagnostic performance, *i.e.*, strain and shear-wave EG. Generally, strain elastograms are produced by internal physiological pulsations from respiratory contractions. Estimation of the target tissue's stiffness is conducted with semiquantitative real-time elastography (RTE) using strain histogram (SH), and quantitative strain ration (SR) histogram EG. In particular, SR is a semi-quantitative method to calculate relative tissue stiffness by dividing mean strain of reference area and mean strain in lesion of interest. Meanwhile, the global hardness of a lesion is expressed by the mean histogram value (numerical values from SH)[3,9]. There are three major important principles when RTE is applied for tissue elasticity evaluation, *i.e.*, the stress compression, the region of interest (ROI), and the tissue displacement. Semi-quantitative SH EUS EG uses the manual method through tissue compression effect or pressure application, which will create color-based results. Quantitative strain elastograms or SH needs to calculate the ratio; however, this can be a combined assessment. This software methods usually will be incorporated to the echoendoscope for pancreatic tissue assessment[3,8]. In a healthy pancreatic tissue, the internal structure is isoechoic with soft elastogram. In elderly, the consistency of pancreatic tissue is remarkably harder, but not as hardened as the histogram result of chronic pancreatitis. In acute pancreatitis, softer consistency can be observed in the necrotic zones. Significantly higher stiffness (often unequivocal) can be found in ductal adenocarcinoma. The hue color-based parameter, where it is used for tissue elasticity evaluation, consists of red, green, and blue color. Soft tissue appears as red color, whereas intermediate tissue appears as green color, and blue color will represent hard

tissue. However, perception errors or variability of interpretation between endosonographers may occur in the characterization of hue color-based parameter[8,9].

On the other hand, shear-wave EG is a quantitative tissue elasticity assessment, where it has been mostly used for liver, breast, prostate, rectum, and lymph node. In shear wave EG, focused ultrasound from the probe to target tissue is emitted and evaluation of target tissue's stiffness is performed afterwards by measuring the shear wave's propagation speed. An exploratory study of EUS shear-wave measurement (EUS-SWM) in the assessment and treatment of autoimmune pancreatitis showed approximately 97.6% success rate with no significant difference of success rate in the head, body, and tail of the pancreas (P = 0.4997)[10]. Another preliminary study also demonstrated similarly high success rate (96.8%) without any adverse events. In addition, the elastic value with unique reliability index of the velocity of shear wave measurement also allows more objective and repeated measurement with EUS-SWM [11]. However, compared to strain EG, varying results with EUS-SWM are still found from previous study by Carlsen *et al*[12] This study also showed that target diameter had the most significant effect for all methods of shear-wave EG measurement, while target depth only affected shear-wave velocity measurement in targets with hard consistency.

ENDOSCOPIC ULTRASOUND EG IN PANCREATIC LESION EVALUATION

Throughout the years, evidences related to the use of EUS EG in pancreatic lesion evaluation keep emerging (Table 1). A pioneer study by Giovannini *et al*[13], 2006 showed the impact of endosonoelastography examination for pancreatic masses evaluation in 49 patients, where the sensitivity and specificity in diagnosing malignant lesion were 100% and 67%, respectively. In this study, there were two misdiagnosed cases (neuroendocrine tumor and benign fibromyoblastic tumor of surgically resected pancreas). The sensitivity and specificity of endosonoelastography in assessing malignant lymph node invasion in this study were 100% and 50%, respectively. As mentioned in the previous section, the first experimental study for real-time tissue EG for pancreatic tissue assessment was investigated by Uchida *et al*[6], 2009, in which a linear probe, with B-mode and EG mode, was used to visualize the object. The color-based (blue for hard and red for soft) was used in the ROI. In pancreatic cancer, the lesion was identified with blue color, which was subsequently confirmed through histopathologic examination result. Combination of B-mode and EG mode increased the diagnosis accuracy of pancreatic cancer from 73.3% to 100%, corrected by operator. The sensitivity and specificity between operator and another reviewer showed the same results for EG mode evaluation (64.3% *vs* 60.7% and 88% *vs* 88%). In the case of pancreatic endocrine tumor, the diagnosis accuracy also increased from 66.7% to 100% [6]. In 2009, a prospective study by Iglesias-Garcia *et al*[14], where the EG pattern was compared to histological specimen, showed the blue color pattern supported the malignant pancreatic lesions, whereas the green color pattern excluded malignant lesions. The sensitivity and specificity of EG diagnosis in malignant pancreatic lesions were 100% and 85.5%, respectively. This study concluded that the overall diagnostic accuracy of EUS EG for malignancy was 94%. Further concordance analysis by two endosonographers yielded agreement of elastographic pattern by both of them in 93.1% of the cases. This study also addressed the possibility of EUS EG in tackling the limitation of EUS-guided fine needle aspiration (EUS-FNA). One of the major drawbacks of EUS-FNA was interposition of malignant tissue and vascular structures, which may contribute to false negative results. EUS EG can overcome this limitation by assessing tissue elasticity and discerning hardness between normal and malignant tissues[14].

In contrast to previous evidences, a prospective study by Hirche *et al*[4] showed that EUS-EG had low sensitivity (41%), specificity (53%), and accuracy (45%) in predicting malignant pancreatic lesion. A subgroup analysis in ductal adenocarcinoma also demonstrated poor sensitivity (50%). Moderate intraobserver and interobserver reproducibilities were also demonstrated from the findings. However, in this study, the sample size was considered small. Additionally, some patients were diagnosed with cystic lesion tumor, suggesting that presence of fluid might interfere the elastographic pattern. On the other hand, larger tumor size was causing the inaccurate distance between the EUS probe and the mucosal wall. Incomplete border delineation by EUS- EG was also shown in lesions with a larger diameter, leading to insufficient display of surrounding pancreatic parenchyma[4]. In another small prospective single-center study by Janssen *et al*[15], three groups were classified as normal pancreas,

Table 1 Summary of the studies utilizing endoscopic ultrasound elastography for evaluating pancreatic lesions

Ref.	Population of the study	Key findings
Giovannini *et al* [13], 2006	24 patients with pancreatic masses.	Sensitivity 100% and specificity 67% in diagnosing malignant lesions. Sensitivity 100% and specificity 50% in diagnosing malignant invasion of lymph nodes.
Uchida *et al*[6], 2009	Phase 1: pancreatic cancer (5 subjects), endocrine tumor (2 subjects), chronic pancreatitis (5 subjects), intraductal papillary mucinous neoplasm. Phase 2: 53 consecutive subjects with pancreatic lesions visible on B-mode images.	Diagnostic performance of real-time tissue elastography mode for diagnosing malignancy: Operator *vs* another reviewer Sensitivity: 64.3% *vs* 60.7%. Specificity: 88% *vs* 88%. Positive predictive value: 85.7% *vs* 85%. Negative predictive value: 68.8% *vs* 66.7%.
Iglesias-Garcia *et al*[14], 2009	130 consecutive patients with solid pancreatic masses *vs* 20 subjects with normal pancreases.	Diagnostic performance of EUS elastography in diagnosing malignancy Sensitivity: 100%. Specificity: 85.5%. Positive predictive value: 90.7%. Negative predictive value: 100%. Overall accuracy: 94%.
Hirche *et al*[4], 2008	70 patients with unclassified solid pancreatic lesions *vs* 10 subjects with healthy pancreas.	Diagnostic performance of EUS elastography in predicting the nature of pancreatic lesions Sensitivity: 41%. Specificity: 53%. Accuracy: 45%.
Janssen *et al*[15], 2007	20 patients with chronic pancreatitis *vs* 33 patients with focal pancreatic lesions *vs* 20 subjects with normal pancreas.	Diagnostic performance of EUS elastography in diagnosing chronic pancreatitis Sensitivity: 65.9%. Specificity: 56.9%. Accuracy: 60.2%. Diagnostic performance of EUS elastography in diagnosing focal pancreatic lesions Sensitivity: 93.8%. Specificity: 65.4%. Accuracy: 73.5%. Diagnostic performance of EUS elastography in differentiating pancreatic adenocarcinoma and inflammatory pancreatic masses
Li *et al*[16], 2013	Meta-analysis of 10 studies with 781 patients.	Diagnostic performance of EUS elastography in differentiating pancreatic adenocarcinoma and inflammatory pancreatic masses AUC: 0.8227. In studies with color pattern as the diagnostic standard Sensitivity: 99%. Specificity: 76%. Positive likelihood ratio: 3.36. Negative likelihood ratio: 0.03. Diagnostic odds ratio: 129.96. In studies with hue histogram as the diagnostic standard

		Sensitivity: 92%. Specificity: 68%. Positive likelihood ratio: 2.84. Negative likelihood ratio: 0.12. Diagnostic odds ratio: 24.69.
Xu *et al*[17], 2013	Meta-analysis of 9 studies.	Diagnostic performance of EUS elastography in differentiating benign and malignant pancreatic masses In studies with qualitative color pattern as the diagnostic standard Sensitivity: 99%. Specificity: 74%. AUROC: 0.9624. In studies with quantitative hue histogram value as the diagnostic standard Sensitivity: 85%-93%. Specificity: 64%-76%.
Mei *et al*[18], 2013	Meta-analysis of 13 studies with 1044 patients.	Diagnostic performance of EUS elastography in differentiating benign and malignant solid pancreatic masses Sensitivity: 95%. Specificity: 67%. Diagnostic odds ratio: 42.28.
Altonbary *et al*[19], 2019	97 patients with malignant lesions *vs* 19 patients with benign lesions	Diagnostic performance of combined elasticity score and strain ratio in differentiating benign and malignant pancreatic lesions (cut-off point: 7.75) Sensitivity: 99%. Specificity: 94.6%. Positive predictive value: 98%. Negative predictive value: 98.5%. Accuracy: 97%.
Ignee *et al*[20], 2018	218 patients with solid pancreatic lesions sized ≤ 15 mm and a definite diagnosis.	Diagnostic performance of EUS elastography with high stiffness of the lesion in diagnosing malignancy Sensitivity: 84%. Specificity: 67%. Positive predictive value: 56%. Negative predictive value: 89%. Diagnostic performance of EUS elastography in diagnosing pancreatic ductal adenocarcinoma Sensitivity: 96%. Specificity: 64%. Positive predictive value: 45%. Negative predictive value: 98%.

EUS: Endoscopic ultrasound.

chronic pancreatitis, and focal pancreatic lesions. The elastographic pattern classification (homogenous, different colors, and honeycomb pattern) and elastographic colors classification (blue, green/yellow, and red) were combinedly used. In normal pancreas group, all showed homogenous green color interfered with blue clouds' color. Whereas, in chronic pancreatitis group showed hard (blue) with honeycomb pattern. In pancreatic focal lesions' group, examination showed that almost all patients had blue/green honeycomb pattern. Only one patient which has tumorlike due to

chronic pancreatitis showed blue/green honeycomb pattern. The sensitivity and specificity for group with chronic pancreatitis were 65.9% and 56.9%, respectively, with diagnostic accuracy of 60.2%; while the sensitivity and specificity in group with focal pancreatic lesions were 93.8% and 65.4%, respectively, with slightly higher diagnostic accuracy (73.5%). The findings from this study also addressed the limitation of EUS EG in distinguishing the elastographic patterns of chronic pancreatitis and malignant tumors due to the corresponding amount of fibrous pattern of chronic pancreatitis, which can also be found in desmoplastic pancreatic carcinomas and microcystic adenomas[15]. Another meta-analysis, which evaluated the use of EUS EG in discernment of pancreatic adenocarcinoma and inflammatory masses, indicated slightly better diagnostic performance in studies with color pattern as the diagnostic standard (sensitivity 99%, specificity 76%) compared to studies with hue histogram as the diagnostic standard (sensitivity 92%, specificity 68%)[16]. In differentiating benign and malignant pancreatic masses, better diagnostic performance was also demonstrated by studies using qualitative color pattern as the diagnostic standard (sensitivity 99%, specificity 74%) in comparison to studies using hue histogram as the diagnostic standard (sensitivity 85%-93%, specificity 64%-76%). This meta-analysis also acknowledged the difficulties in distinguishing neuroendocrine tumors and adenocarcinomas due to their similar hardness[17]. Regardless of the low specificity, EUS EG can still be considered as a complementary diagnostic method. A meta-analysis by Mei *et al*[18] showed high pooled sensitivity (95%) with acceptable pooled specificity (67%) and moderate accuracy (summary Receiver Operating Characteristic: 90.46%) of EUS EG in diagnosing solid pancreatic masses. Improvement of diagnostic accuracy may be achieved with application of more meticulous computer-aided diagnosis method for EUS-EG[18]. Recent findings from a single center retrospective study by Altonbary *et al*[19] also demonstrated promising results of EUS EG with combination of elasticity score and strain ratio in discerning solid pancreatic lesions (sensitivity 99%, specificity 94.6%, and accuracy 97%). Moderately well diagnostic performance in ruling out malignancy was also demonstrated by a multicenter study conducted in 218 patients with small (< 15 mm) solid pancreatic lesions (sensitivity 84%). Higher sensitivity (96%) was shown when EUS EG was used in diagnosing Pancreatic Ductal Adenocarcinoma (PDAC)[20].

CLINICAL DILEMMA IN PANCREATIC LESION EVALUATION AND IMPACT OF EUS EG INNOVATION STUDY

Several conditions have been considered as clinical dilemma, such as small pancreatic lesion which also can be found incidentally, pseudo-tumoral in chronic pancreatitis, negative FNA biopsy (FNAB) results, and possibility of needle tract tumor seeding[3-5]. It has been known that pancreatic cancer is mostly dominated by PDAC, a highly aggressive tumor with very poor prognosis and high mortality rate. It has been reported that Negative Predictive Value (NPV) of FNAB result can vary, ranging from 16% to 85%. In the case of negative biopsy, patients with suspicion of PDAC should be referred immediately for surgical approach consideration. Spier *et al*[21] published a small retrospective EUS-FNA study in patients who had suspected pancreatic lesions with negative biopsy results. The study found that 30.9% of patients with negative/non-diagnostic FNA results were later diagnosed with pancreatic cancer (mean time 66 d to 360 d after FNA procedure)[21]. RTE has been proposed as a supplementary method to improve diagnostic performance of EUS-FNA, especially in terms of available rapid on-site tissue evaluation by a cytopathologist[22,23]. A retrospective study in 54 subjects with solid pancreatic lesions highlighted the benefit of combining RTE and EUS-FNA (sensitivity 94.4%, specificity 93.4%, and accuracy 100%) compared to the diagnostic performance of RTE alone (sensitivity 86.9%, specificity 75%, and accuracy 85.1%)[22].

Possibility of tumor seeding has become a challenging issue as it will impact on faster disease progression, patient's clinical-based management, and patient's survival after surgery or non-surgical biliary drainage procedure in patients with bile duct obstruction. There has been a debate on whether this tract seeding issue should be underestimated or overestimated, since most of the studies use retrospective study design. Small sample size and no clear tumor dissemination finding also become issues on the studies of needle tract seeding related to EUS-FNA[5]. The first reported case of EUS-FNA-related tumor dissemination was delivered in 2003, in which peritoneal dissemination occurred in intraductal papillary mucinous tumor (T1N0M0)[5]. Approximately 80% of all needle tract seeding cases following EUS-FNA happened

in pancreatic cancer and pancreatic cystic tumors located in the body or tail of pancreas. In most of the cases, 22-G FNA needle was used, even though the relationship between needle size or number of needle passes and the risk of tumor seeding is still unclear. The range of interval from EUS-FNA procedure to diagnosis of needle tract seeding is 3-48 mo[24].

EG EUS multicenter study by Ignee *et al*[20] in small solid pancreatic lesions showed that sensitivity and specificity were 84% and 67%, respectively, with 56% of positive predictive value and 89% of NPV. In PDAC cases, sensitivity and specificity were 96% and 64%, respectively. Based on this study, it is clear that early detection in less than 15 mm pancreatic lesion might prevent the delay for surgery management even though PDAC tends to be found in larger lesions (> 15 mm)[20]. Another prospective study was conducted by Dawwas *et al*[25] in patients underwent quantitative EUS EG procedure for differentiating pancreatic malignant lesion with pancreatic inflammatory lesion. The examination results were compared to histology or cytology results with follow-up imaging study. The sensitivity and specificity with quantitative EUS EG were 100% and 95.7%, respectively. This study has shown the important value of EUS EG in reducing the need of biopsy as the EUS-FNAB procedure still carries potentially harmful risks, such as pancreatitis and bleeding[25]. In 2018, Dong *et al*[26] reported the role of combination strategy using B-mode ultrasound, contrast-enhanced ultrasound (CEUS), and EUS EG in small case series of isolated pancreatic tuberculosis (PTB) cases. These findings were then compared with the clinical findings of PDAC cases. In PTB cases, common bile duct and pancreatic duct dilatation are considered to be rare findings, however, it is common to find multiple peripancreatic lymph nodes enlargement. The PTB lesion was showing less demarcation, whereas clear demarcation was found in PDAC cases. It might be difficult to differentiate PTB from PDAC cases by using the tissue stiffness result from EUS elastrography alone, however, with CEUS combination, PTB lesion showed hyperenhancement, whereas in PDAC cases showed hypoenhancement. In addition, peripancreatic pseudocysts were more commonly observed in PTB cases. This non-invasive strategy can be an accurate diagnosis tool with or without biopsy as a clinical-based approach in patients with PTB. Consequently, it can also avoid unnecessary surgical management[26].

A former retrospective analysis study by Iordache *et al*[27] in 50 consecutive patients with negative results of EUS-FNA who sequentially underwent EUS EG and CE-EUS, found that EUS EG has similar results with CE-EUS in diagnosing possibility of pancreatic malignancy. However, combination of both methods showed excellent specificity (100%). Another interesting finding from this study is the excellent specificity (100%) exhibited by CEH-EUS in patients with soft/mixed or hard (low strain) appearance from EG. Excellent specificity was shown by CEH-EUS for distinguishing chronic pancreatitis in soft/mixed (high strain) appearance; while in hard appearance, CEH-EUS exhibited outstanding specificity (100%) and sensitivity (88.89%) for distinguishing pancreatic cancer. These results suggested that hard hypovascular masses can indicate the presence of pancreatic adenocarcinoma or other malignant masses, whereas soft hyper-/isovascular masses can indicate the presence of chronic pseudotumoral pancreatitis or other benign masses[27]. Another prospective multi-center study by Costache *et al*[28] about clinical impact of combination between SH EUS EG and CE-EUS in patients with pancreatic masses, showed that combined CE-EUS with SH EUS EG had similar sensitivity. However, higher specificity (81.48%) was found in the combination method for diagnosing pancreatic carcinoma in comparison to SH EUS EG with several cut-offs (80; 60; 40; 33). Meanwhile, the specificity of single method was ranging from 29.63% to 62.96% based on several cut-offs. The overall diagnostic accuracy in combination method reached 93.81% for pancreatic cancer, whereas in the single method only ranged from 79.38 % to 80.41%. Overall, this study indicated that combination of CE-EUS and semi-quantitative EUS EG can be utilized as a supplementary modality for distinguishing benign and malignant pancreatic masses and for continuous follow-up evaluation of patients during neo-adjuvant chemotherapy and/or anti-angiogenic therapy administration[28]. A case series study by Jafri *et al*[29] showed the potential of EUS EG as a complementary method along with conventional EUS for targeting the FNA procedure in patients with suspected pancreatic masses. Also, in this case series, subjects with low risk of malignancy from EUS and EG examinations did not develop any interval cancer during the mean period of 2-year follow-up[29].

CURRENT STATUS AND LIMITATIONS

According to most studies on EUS EG, it has been shown that EUS EG has a big role in managing pancreatic lesions. This method can be a primary choice for diagnosis evaluation in patients who have coagulation disorders or history of anticoagulation drugs consumption, who are not suitable yet for chemotherapy, and who have the possibility for direct surgical approach due to the needle tract seeding risk during FNA procedures. In targeting unclear demarcation and pancreatic lesion image, EUS EG can also be an additional tool. However, it cannot be used for pancreatic cystic mass tumor evaluation. Studies to differentiate between malignant and benign pancreatic mass lesion have not shown any strong evidence yet as some studies were only performed with small sample size, and some only used retrospective study analysis.

The main objectives of performing EG for the pancreas are to ensure that the elastogram is sufficiently meticulous to represent the histological structures and to be reproducible adequately. These objectives, however, are hampered by the small size of the pancreas, the depth of its anatomical location in the center of the body, the technical difficulties in extracting biopsy specimens, and the strong influence of aortic pulsation to pancreas. In addition, EG is an operator-independent modality[30]. Other pitfalls of EUS EG are the difficulty in controlling tissue compression by the EUS transducer, the presence of motion artifacts due to respiratory movement, as well as the careful selection of ROI from its surrounding soft tissues[31].

Overall, the application of EUS EG is one of the most potential roles of artificial intelligence (AI) in pancreaticobiliary disorders. In general, AI refers to the capacity of a computer to imitate the cognitive intelligence or the learning capability of human being in order to perform tasks appropriately. In medicine, AI consists of machine learning and deep learning, which are often utilized reciprocally[32]. A cross-sectional feasibility study in Denmark established the importance of AI in distinguishing pancreatic cancer from chronic pancreatitis through the application of neural network analysis of dynamic sequences of EUS EG. In this study, the sensitivity, specificity, and accuracy were 91.4%, 87.9%, and 89.7%, respectively. In addition, the application of multilayer perceptron neural networks with high training performance was able to reach an accuracy as high as 97%[33]. Another prospective and multicenter study in 258 patients by Săftoiu *et al*[34] also highlighted the efficacy of AI in EUS EG. The utilization of multilayer perceptron as an artificial neural network demonstrated moderately high diagnostic performance (sensitivity 87.59%, specificity 82.94%, AUROC 0.94, training accuracy 91.14%, and testing accuracy 84.27%) in diagnosing focal pancreatic lesions.

CONCLUSION

EUS EG is a promising method to improve the diagnostic accuracy as well as helping to decide which type of management is probably more suitable for patients with pancreatic mass lesion. However, it would still need more studies with further considerations, such as adequate operator training, expertise, availability, and its cost-effectiveness in comparison to other imaging options. Integrating clinical data into artificial intelligence techniques concomitantly with real-time imaging results is potentially favorable for faster and more accurate clinical-decision making in pancreatic lesion evaluation.

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MINIREVIEWS

Artificial intelligence as a means to improve recognition of gastrointestinal angiodysplasia in video capsule endoscopy

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Abstract

Gastrointestinal angiodysplasia (GIAD) is defined as the pathological process where blood vessels, typically venules and capillaries, become engorged, tortuous and thin walled – which then form arteriovenous connections within the mucosal and submucosal layers of the gastrointestinal tract. GIADs are a significant cause of gastrointestinal bleeding and are the main cause for suspected small bowel bleeding. To make the diagnosis, gastroenterologists rely on the use of video capsule endoscopy (VCE) to "target" GIAD. However, the use of VCE can be cumbersome secondary to reader fatigue, suboptimal preparation, and difficulty in distinguishing images. The human eye is imperfect. The same capsule study read by two different readers are noted to have miss rates like other forms of endoscopy. Artificial intelligence (AI) has been a means to bridge the gap between human imperfection and recognition of GIAD. The use of AI in VCE have shown that detection has improved, however the other burdens and limitations still need to be addressed. The use of AI for the diagnosis of GIAD shows promise and the changes needed to enhance the current practice of VCE are near.

Key Words: Artificial intelligence; Video capsule endoscopy; Gastrointestinal angiodysplasia; Detection; Bleeding; Small bowel

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Core Tip: Video capsule endoscopy (VCE) is the primary modality to diagnose gastrointestinal angiodysplasias (GIADs). Typically, gastroenterologists rely on VCE to make a diagnosis of GIAD prior to referral for deep enteroscopy. However, VCE analysis can be cumbersome secondary to reader fatigue, suboptimal preparation, and difficulty in distinguishing images. Use of artificial intelligence in VCE has shown improved GIAD detection, however limitations exist that still need to be addressed. The use of artificial intelligence for GIAD diagnosis shows promise and changes needed to enhance current VCE practices are near.

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INTRODUCTION

Gastrointestinal angiodysplasia (GIAD) is defined as the pathological process where blood vessels, typically venules and capillaries, become engorged, tortuous and thin walled – which then form arteriovenous connections within the mucosal and submucosal layers of the gastrointestinal (GI) tract[1]. GIADs are found throughout the GI tract, but they most often occur in the small intestine (80% jejunum, 57% duodenum), stomach (22.8%) and less frequently the ascending colon (11.4%)[2]. The gold standard in diagnosis of GIAD has been endoscopy, with the addition of video capsule endoscopy (VCE) in 2001. The technology of VCE radically improved the diagnostic yield of GIADs as well as other small bowel diseases. VCE provided a means to target lesions in the small bowel and has played a role in the development of balloon enteroscopy for advanced diagnoses and treatment options. Although, VCE improved the diagnostic yield of GIADs, as well other as small bowel diseases, there are several challenges which a reader continues to face. First, review of these images has been an arduous process, which can last from 30-40 min to over an hour. The abnormalities that are of interest may only present in a couple of frames that last a minute or less. Second, the long reading time may lead to reader fatigue and a reduction in diagnostic accuracy. To address these issues, there have been several advances made to VCE technology such as a Quick-view algorithm, suspected blood indicator and adaptive frame rate technology. None of these technologic advances have improved diagnostic accuracy[3-5]. Despite these limitations, VCE is still the widely used technology to diagnose GIAD and has become a growing focus for the use of artificial intelligence (AI) to improve the identification of GIAD. We discuss the implementation of computer software known as AI, machine programs capable of learning and simulating patterns like the human brain.

TYPES OF AI

Several layers exist within AI and have been utilized throughout the field of gastroenterology, especially endoscopy. One aspect is machine learning (ML), a discipline where large, complex data sets are used to predict outcomes and identify patterns using various algorithms[6]. These algorithms are often trained to differentiate data sets or characteristics such as color, size and shape, which help to distinguish between lesions within the GI tract. Beyond ML, two other types of AI exist, artificial neural networks (ANNs) and convolutional neural networks (CNNs). ANNs utilize the patterns observed within data sets to perform complex task of cross comparison at various points of calculation. Therefore, numerous computed data sets can be collected at any stage and compared to provide one outcome. This simulates the intelligence and neurobiological processes of the human brain, as the computer continues to learn to perform new task through automated analysis. CNNs use real time or still images to distinguish between normal and abnormal, then further investigate abnormal objects to identify a diagnosis with relatively highly accuracy and efficacy (Table 1).

Table 1 Artificial intelligence methods for gastrointestinal angiodysplasia detection[17]

Artificial intelligence	Description	Function	Advantages	Disadvantages
Machine learning	Ability of a computer program to learn	Discern logic-based rules from input and output data	Automation of tasks	Requires high-quality data likely to have some causal link
	Algorithm workflow improves performance		Detect patterns between input and output data	
Artificial neural network	Use of weighted/graded signals to perceive data	Adaptive learning	Mapping performance between input and output data	Requires labeled data
	Use of computational communication		Adaptive learning capability	Requires large volumes of data
Convolutional neural network	Image detection	Computer vision	Highly accurate image recognition and classification	Highly dependent on a training modelor models
	Interpretation through three-dimensional convolutional layers			Limited by image rotation or orientation

CNNs have become one of the most commonly used AI modalities, particularly in VCE, which has significantly aided in the detection of GIADs. The use of AI, particularly CNNs, has created a new era in capsule endoscopy (CE) capable of improving lesion detection rates, reducing capsule reading time, as well as reducing reviewer fatigue. This shift towards computer-aided diagnostic tools in clinical practice may represent a future of common practice. Further investigation with AI in computer-aided diagnosis of GIAD leans heavily towards CE. Three of the most popular areas of CNN implementation include newly developed algorithms, single-shot multibox detection (SSD) and region of interest (ROI) color contrast analysis.

MODALITIES WHERE AI CAN BE USED WHEN DETECTING GIAD

In 2019, Leenhardt *et al*[7] analyzed 2946 still frames with vascular lesions utilizing CNN, where two data sets were used to create a trained algorithm for GIAD detection. The first dataset, also termed the "training and learning phase," consisted of a CNN analysis of 2946 still frame images containing vascular lesions for characteristic analysis of abnormal lesions based on size, shape, color, pattern, and contour. This helped the CNN distinguish GIADs within a still frame. The second data set utilized the learned features from the previous data set, which were applied to new images to detect and located GIAD within a still frame. The primary and secondary endpoints were the sensitivity and specificity of the computer aided diagnosis (CADx) algorithm. These values were 100% and 96% respectively[7].

Similarly, Hwang *et al*[8] developed their own CNN-based AI model bases on a collection of still images later classified as ulcerative or hemorrhagic, which were augmented by rotating each image by 90 degrees 3 times and flipping each rotated image horizontally. As a result, a collection of 30224 abnormal images (11776 hemorrhagic lesions and 18,448 ulcerative lesions) and 30224 normal images were used to train their CNN model by observing similar outcomes in the Leenhardt *et al*[7] study. However, Hwang *et al*[8] went a step further in developing their own CNN based on VGGnet, a CNN that incorporates more convolution filters or layers when screening an image to improve its accuracy of image recognition[9]. Using two training protocols, Hwang *et al*[8] developed a binary model, trained to detect any pathological images as abnormal without distinguishing the types of lesions, and a combined model, trained to detect distinctive hemorrhage or ulcerative lesions.

Another type of CNN is called SSD which is very similar to CNNs described above. However, in this instance, an expert endoscopist will demarcate a rectangular box around a lesion within an image making it much faster to provide a unifying framework for both training and interpretation[10]. Tsuboi *et al*[11] incorporated this technique with 2237 still images of small-bowel GIAD captured by VCE and placed a bounding box where GIAD were found. Through this method, Tsuboi *et al*[11] were able to test their ability to detect GIAD using an area under the receiver operating characteristic (ROC) curve for the probability score, as well as sensitivity, specificity, PPV and NPV of their CNN's detection rate for GIAD and accurately distinguish their

location within an image. Lin *et al*[12] delved deeper into this approach by combining SSD with RetinaNet, a CNN that mimics VGGnet described above, with the enhanced ability to find shortcuts when comparing images in order to limit the number of layers used when training. Otani *et al*[13] was able to analyze and characterize images of erosions and ulcers, GIAD and tumors, then compared the ROC, sensitivity, specificity, and accuracy of their AI detection system for each lesion image.

Another prevalent area of CNN performance is color contrast analysis. Since color is one of the most relevant features in diagnosing GIAD, Noya *et al*[14] used color to detect potential regions of GIAE within an image. This is done in 4 categorized steps: Image preprocessing (contrast enhancement), selection of potential ROI (geometric outline of colored pixels making up the angiodysplastic lesion), feature extraction and selection (labeling a ROI based on color, texture and geometric pattern) and classification of a ROI (recognizing patterns of potential angiodysplasia lesions as pathological vs. non-pathological). Comparably, Iakovidis and Koulaouzidis[15] use color-based pattern recognition to separate pathological vs. normal lesions from 137 still images, which they placed into four categories: vascular, inflammatory, lymphangiectatic, and polypoid. Iakovidis and Koulaouzidis[15] used a 4-step categorization process, like Noya *et al*[14] above, however, they differ with the introduction of salient point saturation (SPS), an automated extraction algorithm which selects salient points in a digital image based on changes in observed color intensity[16].

OUTCOMES OF AI IN DETECTING GIAD

The effects of AI computer-aided diagnosis in GIAD are producing promising results that individual practitioners may hope to incorporate into their practices. The diagnostic yield of GIADs using AI leans heavily on VCE with the use of CNNs. Newly developed algorithms, such as SSD and ROI color contrast analysis have been areas of particular focus in medical literature. Each modality of these CNN implementing tools stands on their own, as very limited research compares these techniques by using the same data set or still images for a head-to-head comparison.

The diagnostic performance of a CADx algorithm for the detection of GIAD using VCE, assess its diagnostic precision as a means for a segmental approach in localizing lesions. Leenhardt *et al*[7] found a sensitivity of 100% [95% confidence interval (CI), 100%-100%]. Secondary endpoints revealed a specificity of 96.0% (95%CI: 93.78%-98.22%), a positive predictive value of 96.15% (95%CI: 93.97%-98.33%), a negative predictive value of 100.0% (95%CI: 100%-100%) and a kappa coefficient of reproducibility at 1.0[7]. Only "clean" images were used in their data set, which meant that images with poor preparation quality or the presence of bubbles would not be included. This is a limitation to the study, which the authors point to. In comparison, the algorithm of Hwang *et al*[8] combined (all images trained separately as hemorrhagic or ulcerative) *vs* binary training (all images trained without segregation) approach in the development of an automated CNN, demonstrated that combined training revealed higher sensitivity (97.61% *vs* 95.07%, $P < 0.001$). Although, accuracy classifying GIADs as small bowel lesions was 100% in both the combined and binary training models.

The use of SSD by Tsuboi *et al*[11] to automatically detect GIAD in VCE images focuses on diagnostic accuracy utilizing t-test analysis. The study reported a ROC curve for CNN detection of GIAD at 0.999. The cut-off value for the probability score was 0.36, exhibiting a sensitivity, specificity, positive predictive value, and negative predictive value of their CNN at 98.8%, 98.4%, 75.4%, and 99.9% respectively at this value[11]. Otani *et al*[13] enhanced CNN by combination of SSD with RetinaNet detection of vascular lesions displayed an AUC 0.950 (95%CI: 0.923-0.978) among the internal cohort (images obtained for training) and 0.884 (95%CI: 0.874-0.893) among the external cohort (randomly obtained imaged for cross-validation). This is an observable difference compared to Tsuboi *et al*[11] study, although still relatively high in automated lesion detection.

Color contrast has been used as well. Iakovidis and Koulaouzidis[15] assessed the validity of color-based pattern recognition in the classification of pathologic lesions with the addition of SPS, including p0 GIAD (low probability of bleeding), p1 GIAD (intermediate probability of bleeding) and p2 GIAD (high probability of bleeding). Classification per type of GIAD revealed an AUC of 69.9 ± 15.8 (P0 GIAD), 97.5 ± 2.4 (P1 GIAD), and 79.6 ± 13.1 (P3 GIAD) respectively[15]. Noya *et al*[14] used the combination of a color-based, texture, statistical and morphological features analysis for GIAD detection. Utilization of this method led to a sensitivity of 89.51% and a

specificity of 96.8%, as well as an AUC 82.33% ± 10.43% detection of GIAD[14].

CONCLUSION

GIADs are a significant cause of GI bleeding and are the main cause for suspected small bowel bleeding. To make the diagnosis, gastroenterologists rely on the use of VCE to "target" GIAD. However, the use of VCE can be cumbersome secondary to reader fatigue, suboptimal preparation, and difficulty in distinguishing images. Humans are imperfect. The human eye is imperfect. The same capsule read by two different readers are noted to have miss rates like other forms of endoscopy. The use of AI in VCE have shown that detection has improved, however the other burdens and limitations still need to be addressed. AI used for the diagnosis of GIAD shows promise and the changes needed to enhance the current practice of VCE are near.

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MINIREVIEWS

Early gastrointestinal cancer: The application of artificial intelligence

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Abstract

Early gastrointestinal (GI) cancer has been the core of clinical endoscopic work. Its early detection and treatment are tightly associated with patients' prognoses. As a novel technology, artificial intelligence has been improved and applied in the field of endoscopy. Studies on detection, diagnosis, risk, and prognosis evaluation of diseases in the GI tract have been in development, including precancerous lesions, adenoma, early GI cancers, and advanced GI cancers. In this review, research on esophagus, stomach, and colon was concluded, and associated with the process from precancerous lesions to early GI cancer, such as from Barrett's esophagus to early esophageal cancer, from dysplasia to early gastric cancer, and from adenoma to early colonic cancer. A status quo of research on early GI cancers and artificial intelligence was provided.

Key Words: Artificial intelligence; Early esophageal cancer; Early gastric cancer; Early colonic cancer

Core Tip: Diagnosis and management of early gastrointestinal (GI) cancer is one of the cores of clinical practice. Endoscopy is the indispensable tool for standard surveillance and management. Artificial intelligence is a novel technology used in some fields of cancer including early GI cancer. Therefore, we provide an overview and introduce how artificial intelligence can be applied to endoscopy on early GI cancer mainly including esophagus, stomach, and colon from the point of view of the clinical diagnosis and management guidelines. Studies with quality control on the diagnosis and management of early GI cancer and their precancerous lesions have also been concluded.

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INTRODUCTION

Artificial intelligence (AI) is essentially a process of learning human thinking and transferring human experience. Recognizing images based on artificial neural networks/convolutional neural networks (CNNs) is one of the novel and main fields of AI. Computer-aided diagnosis (CAD) systems are designed to interpret medical images using advances in AI from method learning to deep learning (DL) and includes mainly three groups (CADe, CADx, and CADm)[1].

AI has been widely involved in cancer[2]. In regard to digestive cancer, it has been utilized to find more intelligent ways to facilitate detection, diagnosis, risk evaluation, and prognosis. For instance, radiomics machine learning signature for diagnosing hepatocellular carcinoma in cirrhotic patients with indeterminate liver nodules was also validated in a multicenter retrospective cohort, which could enhance clinicians' decisions[3].

In the aspect of pancreatic cancer, it continues to be one of the deadliest malignancies with less than 10% overall survival rate. Survival rates will increase if pancreatic cancer can be detected at an early stage[4]. Intraductal papillary mucinous neoplasms are precursor lesions of pancreatic adenocarcinoma. A DL model was shown to be a more accurate and objective method to diagnose malignancies of intraductal papillary mucinous neoplasms in comparison to human diagnosis and conventional endoscopic ultrasonography (EUS) images[5]. Pancreatic cystic lesions are also precursors of pancreatic cancer. Radiomics utilizing quantitative image analysis to extract features in conjunction with machine learning and AI methods helped differentiate benign pancreatic cystic lesions from malignant ones[6]. An artificial neural network was trained to help predict pancreatic ductal adenocarcinoma based on gene expression[7]. An AI-assisted CAD system using DL analysis of EUS images was efficient to help detect pancreatic ductal carcinoma[8]. The artificial neural network model could accurately predict the survival of pancreatic adenocarcinoma patients as a useful objective decision tool in complex treatment decisions[9].

In this review, we concluded the application and research of AI based on endoscopic examination related to early gastrointestinal (GI) cancer mainly including esophagus, stomach, and colon. The progression of carcinogenesis from Barrett's esophagus (BE) to early esophageal cancer (EEC), from dysplasia to early gastric cancer (EGC), and from adenoma to early colonic cancer (ECC) were reviewed in detailed as well as related AI research on the histopathology and invasion depth detection of these GI cancer.

LITERATURE SEARCH

This review was aimed to make a qualitative only review of the application of AI on early GI cancer. We searched the PubMed database for articles that were published in the last 5 years using the term combinations of AI/DL and EEC, esophageal squamous cell carcinoma (ESCC), esophageal adenocarcinoma (EAC), EGC, and ECC for early GI cancer, and term combinations of AI/DL and precancerous lesions [BE/dysplasia/chronic atrophic gastritis (CAG)/gastric intestinal metaplasia/*Helicobacter pylori*/adenoma/polyp/inflammatory bowel diseases] for precancerous lesions of early GI cancer. Endoscopic-related results were qualitatively concluded in Table 1.

SEARCH RESULTS

Initially, a total of 424 articles were identified. After manually screening and reading, 22 studies were tabulated in Table 1, and 2 prospective studies on detecting adenoma were also added in Table 1. Meanwhile, 13 studies on precancerous lesions of early GI cancer were showed in the review. The flowchart was presented in Figure 1.

Table 1 Early gastrointestinal cancer and artificial intelligence

Ref.	Target disease	Prospective/ retrospective	AI	Endoscopy image	Training dataset	Validation dataset	Sensitivity	Specificity	Accuracy[1] /AUC
[1]	Diagnosing ESCC and EAC	Retrospective	CNNs (SSD)	WLI and NBI	8428 images	1118 images	98%	95%	98%[1]
[2]	Diagnosing ESCC	Retrospective	CAD (SegNet)	NBI/videos	6473 images	6671 images	98.04%	95.03%	0.989
[3]	Detecting EEC and BE	Retrospective	CAD (ResNet-UNet)	WLI	494364 images	1704 images	90%	88%	89%[1]
[4]	Detecting E/J cancers	Retrospective	CNNs (SSD)	WLI and NBI	3443 images	232 images	94%	42%	66%[1]
[5]	Detecting ESCC	Retrospective	DCNNs-CAD	NBI	2428 images	187 images	97.80%	85.40%	91.4%[1]
[6]	Diagnosing BE and EAC	Retrospective	CAD (ResNet)	WLI and NBI	148/100	Leave-one patient-out cross validation	97%(WLI)/94%(NBI)	88% (WLI)/80%(NBI)	
[7]	Diagnosing ESCC	Retrospective	CAD (FCN)	ME-NBI		3-fold cross-validation			
[8]	Detecting EAC	Retrospective	CNNs (SSD)	WLI		100 images	96%	92%	
[9]	Detecting EGC	Retrospective	CNNs	WLI	348943 images	9650 images	80.00%	94.80%	
[10]	Diagnosing EGC	Retrospective	CNNs	WLI	21217 images	1091 images	36.8	91.20%	
[11]	Diagnosing EGC	Retrospective	CNNs (Inception-v3)	ME-NBI	1702 images	170 images	91.18%	90.64%	90.91%[1]
[12]	Diagnosing EGC	Retrospective	CNNs (VGG16)	WLI	896 t1a-EGC and 809 t1b-EGC	5-fold cross-validation			Detection (0.981) Depth prediction (0.851)
[13]	Detecting EGC	Retrospective	CNNs (VGG16 and ResNet-50)	WLI/NBI/BLI	3170 images		94.00%	91.00%	92.5%[1]
[14]	Diagnosing EGC	Retrospective	CNNs (ResNet-50)	WLI	790 images	203 images	76.47%	95.56%	89.16%[1]
[15]	Detecting EGC	Retrospective	CNNs (SSD)	WLI	13584 images	2940 images	58.40%	87.30%	0.76
[16]	Classifying EGC	Retrospective	CNNs (Inception-ResNet-v2)	WLI	5017 images	5-fold cross-validation			0.85
[17]	Diagnosing EGC	Retrospective	CNNs (ResNet-50)	ME-NBI	4460 images	1114 images	98%	100%	98.7%[1]
[18]	Detecting and localizing colonic adenoma	Representative	CNNs (VGG16,19, ResNet50)	WLI and NBI	8641 images/9 videos, 11 videos	Cross-validation			
[19]	Detecting ECC	Representative	CNNs	WLI	190 images	3-fold cross-validation	67.50%	89.00%	81.2%[1] /0.871
[20]	Classifying ECC	Representative	CNNs (ResNet-152)	WLI		3-fold cross-validation	95.40%	30.10%	
[21]	Detecting colonic	Prospective	Cade	1058 patients	ADR (29.1% *vs* 20.3%)				

	adenoma				
[22]	Detecting colonic adenoma	Prospective	Cade	962 patients	ADR (34% *vs* 28%)

[1]Accuracy is with "[1]" and AUC is without "[1]", *e.g.*, 100%[1] means accuracy is 100%.
ADR: Adenoma detection rates; AI: Artificial intelligence; AUC: Area under the curve; BE: Barrett's esophagus; BLI: Bright light imaging; CAD: Computer-aided diagnosis; CNN: Convolutional neural network; DCNN: Deep convolutional neural network; EAC: Esophageal adenocarcinoma; ECC: Early colonic cancer; EEC: Early esophageal cancer; EGC: Early gastric cancer; E/J: Esophagogastric junctional; ESCC: Esophageal squamous cell carcinoma; ME-NBI: Magnifying narrow band imaging; NBI: Narrow-band imaging; SSD: Single-Shot Multibox Detector; WLI: White-light imaging.

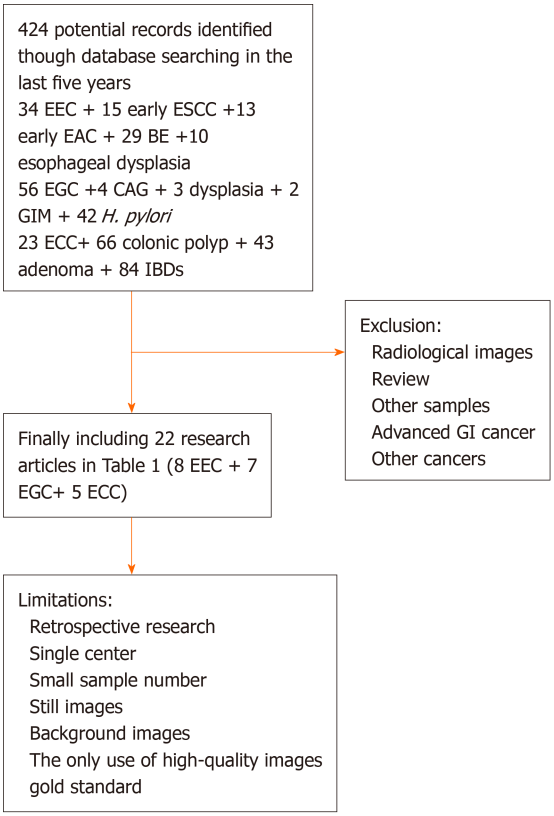

Figure 1 Flow chart of study selection and logic arrangement of review. BE: Barrett's esophagus; CAG: Chronic atrophic gastritis; EAC: Esophageal adenocarcinoma; ECC: Early colonic cancer; EEC: Early esophageal cancer; EGC: Early gastric cancer; ESCC: Esophageal squamous cell carcinoma; GI: Gastrointestinal; GIM: Gastric intestinal metaplasia; *H. pylori*: *Helicobacter pylori*; IBD: Inflammatory bowel diseases.

AI AND EEC FROM PRECANCEROUS LESIONS TO EEC

Esophageal cancer is one of most common cancers related to a considerable decline in health-related quality of life and a reduction in survival rate. ESCC and EAC are two main histological types. Many patients with ESCC have a history of heavy tobacco and alcohol use[10] as well as other risk factors including polycyclic aromatic hydrocarbons, high-temperature foods, diet, oral health, microbiome, and genetic factors [11]. Some risk factors for EAC have been considered mainly as gastroesophageal reflux disease, BE, obesity, and tobacco smoking as well as genetic variants[12]. Chronic gastroesophageal reflux disease can cause metaplasia from the native squamous cell mucosa to a specialized columnar epithelium[13]. BE and dysplasia in squamous epithelium are precancerous lesions to EAC and ESCC, respectively, and they are supposed to be as one of the main aims of early diagnosis. Endoscopic diagnosis of EEC, white-light imaging (WLI), iodine staining, narrow-band imaging (NBI), and biopsy have been widely used clinically[14].

There is also study on AI being involved in preclinical stage. For instance, the diagnostic ability of AI using DL to detect esophageal cancer including superficial and advanced squamous cell carcinoma and adenocarcinoma was characterized as highly sensitive (98%) and efficient based on WLI images. Small cancer lesions less than 10

mm in size could be detected[15].

In terms of EAC, AI using DL to diagnose superficial esophagogastric junctional adenocarcinoma showed favorable sensitivity (94%) and acceptable specificity (42%) of WLI images compared with experts[16]. A CAD using DL (CAD-DL) model was trained by two datasets based on two different kinds of images (WLI and NBI images) used to detect early EAC. The diagnosis of EAC by CAD-DL reached sensitivities/specificities of 97%/88% for WLI images and sensitivities/specificities of 94%/80% for NBI images, respectively (Augsburg dataset) and 92%/100% (another dataset) for WLI images[17]. Additionally, one research compared several AI methods including regional-based CNN (R-CNN), Fast R-CNN, Faster R-CNN, and Single-Shot Multibox Detector. Single-Shot Multibox Detector outperformed other methods achieving a sensitivity of 96% in automatically identify EAC[18].

In terms of ESCC, the endocytoscopic system (ECS) helps in virtual realization of histology. The CNN method was applied to detect ESCC with an overall sensitivity of 92.6% based on ECS images aimed at replacing biopsy-based histology[19]. NBI is currently regarded as the standard modality for diagnosing ESCC. A CNN model was applied to detect ESCC based on NBI images and showed significantly higher sensitivity (91%), specificity (51%), and accuracy (63%) than those of endoscopic experts[20]. Besides NBI and ECS, AI was also applied in magnified endoscopy (ME). The accuracy, sensitivity, and specificity of AI based on ME images were 89%, 71%, and 95% for the AI system, respectively[21]. Accuracy, sensitivity, and specificity with WLI images were 87%, 50%, and 99%, respectively. Furthermore, as endoscopic resection (ER) is often used to treat ESCC when invasion depths are diagnosed as intraepithelial–submucosal layer (tumor invasion is within 0.5 mm of the muscularis mucosae). The invasion depth of superficial ESCC was also calculated by a CNN method based on WLI and NBI images, which demonstrated higher accuracy. The diagnosis accuracy of the CNN method was higher in the intraepithelial-lamina propria and muscularis mucosa groups (91.2% and 91.4%, respectively) than that in the submucosal layer group (67.8%)[22].

Recently, there have been some application and research of AI on precursor lesions of EEC including BE and dysplasia in squamous epithelium. For instance, AI could enhance the image of volumetric laser endomicroscopy to facilitate the surveillance BE [23]. The CNN method was developed to recognized early esophageal neoplasia in BE. It could correctly detect early neoplasia with the sensitivity of 96.4%, the specificity of 94.2%, and the accuracy of 95.4%. In addition, the object detection algorithm was able to draw a localization box around areas of dysplasia with a mean average accuracy of 75.33% and sensitivity of 95.60%[24]. Another similar research demonstrated that a CAD system used five independent endoscopy datasets to detect early neoplasia in patients with BE. In dataset 4, the CAD classified images as containing neoplasms or non-dysplastic BE with 89% accuracy, 90% sensitivity, and 88% specificity. The CAD also identified the optimal site for biopsy of detected neoplasia in 97% of cases in dataset 4[25].

Moreover, AI was also applied in esophageal histopathology; attention-based deep neural networks were used to detect cancerous and precancerous esophagus tissue on histopathological slides. Classification accuracies of the proposed model were 85% for the BE-no-dysplasia class, 89% for the BE-with-dysplasia class, and 88% for the adenocarcinoma class[26].

AI AND EGC FROM CAG AND DYSPLASIA TO EGC

EGC is defined as a cancer confined to the mucosa or submucosa, regardless of lymph node metastasis (LNM). Standard WLI and image enhancement endoscopy, such as NBI and ME, have been widely used in screening and surveillance of EGC as well as EUS, which can enable the precise assessment of the risk of LNM of EGC[27]. Risk factors include *Helicobacter pylori* infection, age, high salt intake, diets low in fruit and vegetables, and genetic factors[28]. ER is a minimally invasive treatment for EGC with negligible risk of LNM[29]. Patients with CAG, intestinal metaplasia, or dysplasia are at risk for gastric adenocarcinoma and are recommended to accept the regular endoscopic surveillance. Virtual chromoendoscopy can guide biopsies for staging atrophic and metaplastic changes and can target neoplastic lesions[30]. The 5-year survival rate of EGC patients is significantly higher than that of advanced GC patients [31,32]. Early detection and treatment are always one of the top priorities.

In regard to the application of AI in EGC, there are some considerations both related on the promise such as the benefits for endoscopists and patients and limitations[33].

To detect and diagnose EGC *via* ME with NBI (ME-NBI) requires considerable experience; AI-assisted CNN CAD system based on ME-NBI images was constructed to diagnose EGC, and the overall accuracy, sensitivity, and specificity of the CNN were 98.7%, 98.0%, and 100%, respectively, in a short period of time[34]. Different deep CNN methods have been designed (such as VGG, Single-Shot Multibox Detector, and ResNet) based on different image types (such as WLI, NBI, and chromoendoscopy) and mucosal backgrounds (normal mucosa, superficial gastritis, and erosive mucosa) (shown in Table 1). There was also research on differentiating EGC from gastritis[35] and peptic ulcer[36] achieving reliable accuracy.

Moreover, training with video is considered to improve accuracy in a real clinical setting. A CNN model based on videos demonstrated a high detection rate (94.1%) with a high processing speed[37]. Furthermore, CNN-CAD was applied to diagnose the invasion depth of GC based on WLI images and distinguish EGC from advanced GC, with the sensitivity of 76.47%, specificity of 95.56%, and accuracy of 89.16%[38]. Another model was also involved in invasion depth. For instance, a CNN method (lesion-based VGG-16 model) was used to classify EGC with of sensitivity (91.0%), specificity (97.6%), and accuracy (98.1%), respectively. The prediction of invasion depth achieved sensitivity (79.2%), specificity (77.8%), and accuracy (85.1%), respectively, higher than results of non-lesion-based models, indicating a lesion-based CNN was an appropriate training method for AI in EGC[39].

In terms of histopathology, a CNN model trained with pixel-level annotated hematoxylin and eosin stained whole slide images achieved a sensitivity near 100% and an average specificity of 80.6% in diagnosing GC, aimed at alleviating the workload and increasing diagnostic accuracy[40]. Similarly, AI automatically classified GC in hematoxylin and eosin stained histopathological whole slide images from different groups and demonstrated favorable results[41,42]. Besides endoscopic images, machine learning based on radiographic-radiomic images could help predict adverse histopathological status of GC[43]. Dual-energy computed tomography based DL radiomics could improve LNM risk prediction for GC[44]

In the aspect of gastric precancerous conditions, the application of AI has also been focused. For example, atrophic gastritis, as a kind of precancerous condition was diagnosed by the pretrained CNN based on WLI images achieved an accuracy of 93% in an independent dataset, outperforming expert endoscopists[45]. The CNN method was trained by WLI images of gastric antrum in diagnosing CAG, and the diagnostic accuracy, sensitivity, and specificity were 94.2%, 94.5%, and 94.0%, respectively, which were higher than those of experts. The further detection rates of mild, moderate, and severe atrophic gastritis were 93%, 95%, and 99%, respectively[46]. *Helicobacter pylori* infection, as a dominant cause of CAG and GC, has also been detected *via* AI method based on endoscopic images, such as CNN (GoogLeNet) and CNN (ResNet-50 model), and achieved the higher accuracy and reliability in a considerably shorter time[47-49].

AI AND ECC FROM POLYPS AND ADENOMA TO ECC

ECC has been defined as a carcinoma with invasion limited to the submucosa regardless of lymph node status and according to the Royal College of Pathologists as TNM stage $T_1N_XM_0$[50]. If the dysplasia is restricted to the layer of epithelium, it is defined as low-grade or high-grade intraepithelial neoplasia. Mild or moderate dysplasia is the pathological character of low-grade intraepithelial neoplasia, and severe dysplasia is the pathological character of high-grade intraepithelial neoplasia or preinvasive carcinoma[51]. Colonic precancerous lesions include traditional serrated adenoma and sessile serrated adenoma/polyps[52,53]. The submucosal invasion in clinical practice is considered as the superficial depth of tumor invasion and further as a surrogate for nominal LNM risk. Meanwhile, it can be a general criterion to identify whether patients are eligible for local ER or surgery[54]. Curative ER is indicated for lesions confined to the mucosal layer or invading less than 1 mm into the submucosal layer[50]. Endoscopic screening is proven to decrease the risk of disease-specific morbidity and mortality[55]. Current guidelines recommend screening beginning at age 50 and continuing until age 75 with fecal immunochemical test every year, flexible sigmoidoscopy every 5 years, and/or colonoscopy every 10 years[56]. Early diagnosis and treatment are pivotal. When colon carcinoma is detected in a localized stage, the 5-year relative survival is 91.1%. However, the 5-year relative survival of colon carcinoma patients with regional metastasis or distant metastasis were 71.7% and 13.3%, respectively[57].

AI has been widely involved in the research of ECC on the aspect of detection, diagnosis, classification, invasion depth, and histopathology as well as inflammatory bowel diseases associated with inflammation-dysplasia-colon cancer pattern. Regarding the detection and diagnosis, a research trained Faster R-CNN with VGG16 based on WLI images and videos covering ECC (Tis or T_1) and precursor lesions including hyperplastic polyps, sessile serrated adenoma/polyps, traditional serrated adenoma, low-grade intraepithelial neoplasia, high-grade intraepithelial neoplasia, and submucosal invasive cancer was conducted. It showed the sensitivity and specificity were 97.3% and 99.0%, respectively[58]. Another research used two CNN methods trained by WLI images. ResNet-152 showed a higher mean area under the curve for detecting tubular adenoma + lesions (0.818), and the mean area under the curve for detecting high-grade intraepithelial neoplasia + lesions reached 0.876 by ResNet-v2[59]. Regarding the invasion depth, for deeply invasive cT_1 (SM) (hereafter, cT_{1b}) or deeper colorectal cancer (CRC), there is a 10%–15% or higher risk of lymph node metastases. Further surgical resection including lymph node dissection is required[60]. For an accurate depth of invasion diagnosis, the CNN method was used to assist in cT_{1b} diagnosis and demonstrated that cT_{1b} sensitivity, specificity, and accuracy were 67.5%, 89.0%, and 81.2%, respectively[61].

In the research of AI application in precancerous lesions such as polyps, there has been some research of AI, especially retrospective research related to polyp detection and diagnosis with high accuracy[62,63]. For example, a local-feature-prioritized automatic CADe system could detect laterally spreading tumors and sessile serrated adenoma/polyps with high sensitivity from 85.71% to 100%[64]. Besides retrospective research, AI has been designed into some associated prospective research. For instance, a multicenter randomized trial used CAD to detect colorectal neoplasia. It showed a significant increase in adenoma detection rates and adenomas detected per colonoscopy without increasing withdrawal time (54.8% *vs* 40.4%). Additionally, the detection rate of adenomas 5 mm or smaller was significantly higher in the CAD group (33.7%) than in the control group[65]. Another randomized study used CAD to detect adenomas and achieved increased adenoma detection rates (29.1% *vs* 20.3%) and the mean number of adenomas per patient (0.53 *vs* 0.31). Similarly, a higher number of diminutive adenomas were found (185 *vs* 102)[66]. In addition, inflammatory bowel diseases including Crohn's disease and ulcerative colitis are also associated precancerous lesions, and some AI methods aiding in scoring have been trained, such as DL model in grading endoscopic disease severity of patients with ulcerative colitis[67] and in predicting remission in patients with moderate to severe Crohn's disease[68].

In the aspect of histopathology, AI has been used in ECC and precancerous lesions. A systematic review has concluded that AI use in CRC pathology image analysis included gland segmentation, tumor classification, tumor microenvironment characterization, and prognosis prediction[69]. A DL approach was developed to recognize four different stages of cancerous tissue development, including normal mucosa, early preneoplastic lesion, adenoma, and cancer and obtained an overall accuracy more than 95%[70]. Prediction of LNM for early CRC is critical for determining treatment strategies after ER. An LNM prediction algorithm for submucosal invasive (T_1) CRC based on machine learning showed better LNM predictive ability than the conventional method on some datasets[71-82].

PROSPECTS AND CHALLENGES OF AI APPLICATION ON EARLY GI CANCER

Endoscopy is usually the first choice in the diagnosis and management of early GI cancer. According to the Clinical Practice Guideline, ER is now a standard treatment for early GI cancers without regional LNM. Early GI cancers can completely be removed by *en bloc* fashion (resection of a tumor in one piece without visible residual tumor) *via* endoscopic mucosal resection and/or endoscopic submucosal dissection. High-definition white light endoscopy, chromoendoscopy, and image-enhanced endoscopy such as ME-NBI can be used to assess the edge and depth of early GI cancers for delineation of resection boundaries and prediction of the possibility of LNM before the decision of ER. Histopathological evaluation can confirm the depth of cancer invasion and lymphovascular invasion[83]. From this review, we can see AI as a novel technology has been penetrated in early GI cancer detection, diagnosis, boundaries, invasion depth, lymphovascular invasion, and prognosis prediction based on endoscopic images and videos and pathological tissue slides obtained after ER.

Both high-quality endoscopy and high-quality AI model construction research are crucial to ensure better health outcomes and benefits of patients. Some AI methods have been designed to identify and assure the quality of endoscopy to improve the detection rate of early GI cancer. In upper GI tract, missed EGC rates are an important measure of quality. A deep CNN model was built to monitor blind spots, time the procedure, and automatically generate photo-documentation during esophagogastroduodenoscopy[84]. Meanwhile, in colonoscopy, poorer adenoma detection rates are associated with poorer outcomes and higher rates of post-colonoscopy colonic cancer[85]. A deep CNN model was developed for timing withdrawal phase, supervising withdrawal stability, evaluating bowel preparation, and detecting colorectal polyps[86].

In the aspect of quality control of AI studies related to endoscopy, some limitations should be concerned. Different CNN models have demonstrated high accuracies or area under the curve and 7 out of 22 more than 90%/0.9 with high sensitivities and specificities in Table 1. These limitations were concentrated on the retrospective research, the single center, the small sample number, still images, background images, the only use of high-quality images, and not all images with lesions identified by gold standard such as pathology. They may discount the reliability of the results. As most endoscopic-related algorithms are trained in a supervised manner, labeling data is important. Meanwhile, videos and large, heterogenous, and prospectively collected data are less prone to biases[87].

CONCLUSION

AI has been widely used in medicine, although most studies have remained at the preclinical stage. In this review, we provided an overview of the associated application of AI in early GI cancer including EEC, EGC, and ECC as well as their precancerous lesions. Detection, diagnosis, classification, invasion depth, and histopathology have been involved. Indeed, AI will bring benefits to patients and doctors. It will provide useful support during endoscopies to achieve more precise diagnosis of early GI cancer after more intelligent detection and biopsy with high efficiency and reduce workload to fill the lack of clinical resources in the future.

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