

Artificial Intelligence in *Gastrointestinal Endoscopy*

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Artificial Intelligence in Gastrointestinal Endoscopy

Contents

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Contents

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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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Artificial intelligence: Applications in critical care gastroenterology

Deven Juneja

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Abstract

Gastrointestinal (GI) complications frequently necessitate intensive care unit (ICU) admission. Additionally, critically ill patients also develop GI complications requiring further diagnostic and therapeutic interventions. However, these patients form a vulnerable group, who are at risk for developing side effects and complications. Every effort must be made to reduce invasiveness and ensure safety of interventions in ICU patients. Artificial intelligence (AI) is a rapidly evolving technology with several potential applications in healthcare settings. ICUs produce a large amount of data, which may be employed for creation of AI algorithms, and provide a lucrative opportunity for application of AI. However, the current role of AI in these patients remains limited due to lack of large-scale trials comparing the efficacy of AI with the accepted standards of care.

Key Words: Artificial intelligence; Critical care; Gastroenterology; Hepatology; Intensive care unit; Machine learning

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Core Tip: The scope and applications of artificial intelligence (AI) are rapidly increasing. It is being increasingly applied in various fields, even in healthcare settings. The data generated by critically ill patients admitted in intensive care units (ICUs) is huge, which may be helpful in developing AI algorithms aimed to aid in their management. Patients with primary gastrointestinal diseases may frequently require ICU admission for management of advanced disease or related complications. Use of AI may aid the critical care physicians in managing such patients by helping in early diagnosis, prediction of complications, assessing response to therapy and overall prognostication.

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INTRODUCTION

Artificial intelligence (AI), in simple terms, may be defined as the simulation of human intelligence in machines which are programmed to react like humans, mimicking their actions by means of multi-disciplinary approach[1]. Unlike human mind, which can assimilate only a finite amount of data, machines can accumulate and process unlimited amount of data which can be used in different applications. AI is increasingly influencing every aspect of our life, including healthcare[2].

AI is a complex and rapidly evolving technology. More subsets of AI are being introduced regularly, and each of them have their own unique properties, advantages and limitations. Certain subsets of AI are more commonly employed in healthcare settings than others. The broad subsets of AI include machine learning (ML), deep learning, and cognitive computing. ML involves learning from the prior data to predict the future data. Artificial neural network (ANN) is a subset of ML inspired by the neuronal connections of the human brain. Its further subsets include deep neural network and convolutional neural network (CNN). Other AI algorithms commonly employed in healthcare settings include decision trees, random forest, support vector machines (SVMs), and Naïve Bayes.

Modern intensive care units (ICUs) produce a vast amount of data which is conducive for formation of AI algorithms [2]. A significant proportion of ICU patients are admitted with gastrointestinal (GI) disease or develop GI complications during their ICU course, necessitating further diagnostic and therapeutic interventions. As these patients form a vulnerable group, prone to develop side effects and complications, all measures must be undertaken to reduce invasiveness and ensure safety of ICU procedures. AI can potentially aid the critical care physicians by helping in early diagnosis, predicting complications and response to therapy and providing clinical prognostication in several GI disorders in critically ill patients (Table 1).

PANCREATIC DISORDERS

Almost 25% patients with acute pancreatitis (AP) develop complications or organ failure necessitating ICU admission[3]. Severe acute pancreatitis (SAP) is associated with high morbidity and mortality, requiring intensive monitoring and organ support. Early recognition of risk factors associated with progression to severe disease and development of complications, may help in initiating therapeutic measures and improve outcomes.

Diagnosis

Diagnosis of AP is based on the clinical presentation, laboratory parameters (serum amylase and lipase levels) and imaging (ultrasonography/computed tomography scans). As per the revised Atlanta classification, two out of three diagnostic criteria should be positive to make the diagnosis[4]. However, diagnosis may sometimes be missed due to non-specific clinical presentation, difficulty in imaging and low sensitivity of the revised Atlanta criteria, which may delay the treatment[5].

Integration of AI technology may aid in early diagnosis of acute pancreatitis[6]. ANNs can accurately diagnose AP using clinical and radiological data[7]. In 10%–20% of AP cases, acute necrotizing pancreatitis (ANP) develops, thus further increasing the risk of morbidity and mortality[8,9]. AI based models may also be useful in diagnosing acute necrotizing pancreatitis, which may affect treatment and prognosis[10].

Severity prediction and assessment

Several clinical scores, based on clinical, laboratory, and radiological risk factors, have been devised to assess severity and predict outcomes in patients with SAP. However, no single score has been proven to be superior to others and the search for an ideal scoring system continues[11]. Even though these tools are commonly used in clinical practice, they have low accuracy (60%-80%)[12]. Further, these models are complex, difficult to compute and have low specificity and positive predictive value. Moreover, some of these scoring systems, like Glasgow and Ranson scores, take 48 h to complete and are not devised for serial measurements[13].

AI tools like ANN have been utilised to develop algorithms based on routine blood and serum biochemical parameters to reliably predict severity of AP[14]. When compared to different clinical scores, ANN based models have performed better than Ranson's, APACHE II, and modified Glasgow score in predicting severity in patients with AP[15-17]. Additionally, ANN based tools require lesser parameters and may be computed within 6 h of presentation, as opposed to some scores which may require up to 48 h.

Prediction of complications and organ failure

Majority of deaths due to AP, especially those occurring in the first week, are secondary to progressive organ failure[18, 19]. Moreover, progressive organ failure is the primary determinant of SAP, irrespective of any local pancreatic complication. Hence, it is imperative to determine patients at risk of developing organ failure and ensure an early

Table 1 Potential clinical applications of artificial intelligence in critical care gastroenterology

Organ involved	Clinical condition	Clinical applications
Pancreas	Acute pancreatitis	Prediction of severity; Prediction of local and systemic complications; Prediction of organ failure; Prediction of mortality
Liver	Chronic liver disease	Diagnosis; Staging of fibrosis; Prediction of complications; Predicting disease progression; Prognosis; Predicting need for liver transplantation
	Liver lesions/tumours	Diagnosis and classification; Differentiating between benign and malignant lesions
	Hepatocellular carcinoma	Diagnosis; Staging; Response to therapy
Intestine	Gastroesophageal reflux disease	Diagnosis
	<i>Helicobacter pylori</i> infection	Diagnosis
	Intestinal lesions	Diagnosis; Differentiating between benign and malignant lesions
	Intestinal bleeding	Predicting risk of bleeding and re-bleeding; Diagnosis; Identifying source of bleeding
Gall bladder and bile duct	Gall stones	Diagnosis; Removal of stones; Predicting need and difficulty of ERCP
	Bile duct obstruction	Diagnosis
Gastro-surgery	Appendicitis	Diagnosis
	Liver transplantation	Predict post-operative course; Predict graft failure; Predict recurrence of HCC; Predict in-hospital mortality
	Abdominal aortic aneurysm	Diagnosis; Prediction of post-operative complications; Prediction of post-operative mortality

ERCP: Endoscopic retrograde cholangiopancreatography; HCC: Hepatocellular carcinoma.

diagnosis of any organ dysfunction. ANN based model utilising commonly employed patient and laboratory parameters have been shown to accurately predict development of organ failure in AP patients[20].

AI based tools like regression tree algorithms and ANN have been used to predict complications such as acute lung injury, ARDS, portal vein thrombosis and porto-spleno-mesenteric vein thrombosis in patients with AP and AI has been proven to be more accurate than logistic regression based models in predicting these complications[21-25].

Prognostication

In spite of recent advances, mortality associated with SAP remains significant[26]. The overall mortality of ANP is approximately 15%–20%, of which there is a further twofold increase in a third of ANP cases where the necrotic tissue becomes infected[27,28]. Better understanding of risk factors associated with poorer clinical outcomes may help the physicians in instituting therapeutic measures and prognostication, as early intervention, within first 48 h, may help in improving outcomes[29].

Even though several clinical scores are commonly employed to aid in prognostication, these scores have several limitations. AI algorithms based on ANN have been shown to be better than these clinical scores in predicting clinical outcomes including length of hospital stay in patients with acute pancreatitis. Keogan *et al*[30] used ANN based on radiological and laboratory data from pancreatitis patients which performed better than both the Balthazar and Ranson scoring systems.

Data collected from acute pancreatitis patients from the Medical Information Mart for Intensive Care-III (MIMIC-III) database has shown that AI based algorithm can be effectively used to predict in-hospital mortality with an area under the curve (AUC) of 0.769. Further, AI based algorithms performed better than the commonly used scoring systems including SOFA score (AUC 0.401) and Ranson score (AUC 0.652) and logistic regression analysis (AUC 0.607) in predicting in-hospital mortality[14,31,32].

LIVER DISORDERS

Acute liver failure is a common indication for ICU admission. Patients with chronic liver disease (CLD) may also require ICU support in case of acute decompensation, development of acute on chronic liver disease or due to natural progression of CLD. Even ICU patients may develop liver dysfunction necessitating early diagnosis and intervention for improving prognosis. AI may have a potential role in early diagnosis of acute decompensation, identification of complications and prognostication in patients with liver disease.

Diagnosis of CLD

In critically ill patients, bedside ultrasonography is primarily used for diagnosis of CLD. However, it is operator dependant, qualitative in nature and have limited accuracy. Further, it may be difficult to distinguish fatty changes from early cirrhosis because of overlapping features[33]. Machine learning algorithms based on ultrasound have been applied for analysis of steatosis and the staging of liver fibrosis. Using ultrasound images, CNN based AI model has been shown to effectively assess the amount of liver steatosis with an area under the receiver operating curve (AUROC) of 0.98[34]. Deep learning-based algorithms have shown to improve accuracy for diagnosis of CLD with an AUROC of 1.0 as compared to conventional AI algorithms developed using SVM[35]. Furthermore, ML algorithms based on simple patient (age) and laboratory parameters (aspartate aminotransferase, albumin, and platelet count) have also been shown to accurately predict advanced fibrosis[36].

Liver fibrosis strongly correlates with development of hepatocellular cancer (HCC) and poor outcomes in patients with CLD. Liver biopsy remains the gold standard for detection and quantification of fibrosis. As it is an invasive procedure, it is associated with several inherent complications, especially in more vulnerable critically ill patients. Hence, non-invasive tests like bedside transient elastography measuring liver stiffness are being evaluated for such clinical conditions helping in bedside diagnosis and staging of liver fibrosis. Even though it is a comparatively newer test, it may find better applicability in ICU patients because of its high accuracy, easy repeatability, and non-invasive nature[37]. It has been shown that, AI based on transient elastography scans may further improve its accuracy and reduce subjectivity and inter-observer variations[38,39].

As AI based tools including ANN have been shown to reliably predict significant fibrosis in patients with chronic hepatitis, AI may be helpful in accurately staging liver fibrosis and may help in reducing the need for invasive procedures like liver biopsy[40,41].

Prediction of complications

CLD patients are at risk of developing local and systemic complications which may sometimes be life-threatening. Among the local complications, variceal bleed remains a common cause for increased morbidity and mortality in CLD patients. Hence, prediction and prevention of variceal bleed may improve clinical outcomes. Certain clinical scores (Child-Pugh score) and clinical parameters (hepatic-venous pressure gradient) have been successfully used as prognostic factors to stratifying the risk of variceal rebleeding[42]. However, they have limited accuracy. Diagnosis of varices requires endoscopy, which may not be feasible in many critically ill patients due to its invasive nature. ANN and ML based tools have been used to accurately predict presence of esophageal varices, obviating the need for invasive endoscopy[43,44]. AI based algorithms also have the potential to accurately predict the risk of rebleeding in patients with liver cirrhosis which may aid the clinicians in managing such patients[45].

Prognosis

Short term prognosis of CLD depends upon development of complications and other organ dysfunction. ICU patients with CLD have high mortality rates especially if they develop other organ dysfunction requiring renal replacement therapy or invasive mechanical ventilation support[46]. On the other hand, long term prognosis depends on disease progression. Studies have shown that AI may be instrumental in identifying the cirrhotic patients at risk for disease progression and development of liver related complications including HCC, death, hepatic decompensation and even need for liver transplantation[47,48]. In CLD patients, DL-based model has been shown to be a good predictor of transplant-free survival at 1 and 3 years after diagnosis[48]. ANN algorithms based on clinical and laboratory parameters have been shown to accurately predict 1 year mortality in patients with CLD. This may aid in patient selection for liver transplantation[49].

Development of HCC may also impact clinical outcomes in such patients. ML has been employed for predicting development of HCC, diagnosis of HCC and even prediction of response to therapy[50-52].

AI may also be helpful in diagnosing focal liver lesions. AI based tools have shown to be useful in diagnosing and classifying liver nodules (cysts, hemangiomas, HCC) using ultrasound images[53,54]. DL and CNN based algorithms using MRI images, have also been shown to be effective in differentiating benign and malignant liver tumors, and classifying HCC and other tumors[55,56].

Response to therapy

In patients with liver disease it may be useful to identify patients who may respond to therapeutic interventions. This may aid in patient prognostication and triaging of limited ICU resources. ANN based models have been used to accurately predict the response to therapy with pegylated interferon alpha and ribavirin in patients with chronic hepatitis C infection, with sensitivity and specificity approaching 90%[57]. AI may also aid in predicting outcomes and risk for complications in post-liver transplantation patients[58].

INTESTINAL DISORDERS

Endoscopy is frequently employed to evaluate the gastro-intestinal tract. As it is an invasive procedure, it may be difficult to perform and associated with significant complication rates especially in critically ill ICU patients[59].

Diagnosis

Diagnosis of common GI disorders can be aided with AI based technology. ANN based model has been shown to reliably diagnose gastroesophageal reflux disease non-invasively by employing only clinical parameters[60]. CNN model based on endoscopic images has been shown to accurately diagnose *Helicobacter pylori* infection. Further, it was shown that the time required by AI to analyze the endoscopy images and make a diagnosis was significantly less as compared to experienced endoscopists (3 min and 14 s vs 230.1 min)[61]. Even a recently published meta-analysis reported that CNN may be as accurate as experienced physicians in making the diagnosis of *Helicobacter pylori* infection[62].

AI based algorithms have been developed to diagnose and differentiate between malignant and non-malignant esophageal diseases like Barrett's esophagus and squamous cell carcinoma[63]. Moreover, AI may even be helpful in identifying early neoplastic changes to ensure timely diagnosis which may enable early intervention and aid in improving outcomes[64].

Gastrointestinal bleed

GI bleed remains a common indication for ICU admission. Additionally, increased stress, use of steroids and presence of sepsis can predispose general ICU patients to develop GI bleed during their ICU course. Some bleeds, especially those involving the small bowel, may be difficult to identify and manage. Even though the causes for upper and lower GI bleed may be relatively easier to identify using endoscopic techniques, repeated endoscopies may be required in a significant proportion of patients at risk for recurrent bleed. This may be especially difficult in critically ill ICU patients, who may benefit most from such procedures. ML based algorithms using endoscopic images have been developed which may be useful in identifying the patients at risk of rebleed and increased mortality with up to 90% accuracy[65-68]. ML models based only on clinical parameters like age, presence of gastric ulcers or gastrointestinal disease, presence of underlying malignancy or infections and serum hemoglobin levels have also been developed which have shown to predict risk of rebleed up to 1 year with an accuracy of 84.3% which may obviate the need for repeated bronchoscopies[69].

AI, using various algorithms, have been shown to be helpful in more accurately identifying the source of bleed in patients with small bowel bleed using images from capsule endoscopy, which may avoid further invasive tests[70-73].

Hence, AI have the potential to reduce the need for endoscopies, allow for quicker procedures (by shortening the time required for observation and analysis), and also decrease the necessity for performing endoscopic biopsies, which may be particularly beneficial for critically ill patients.

BILIARY DISORDERS

Endoscopic retrograde cholangiopancreatography (ERCP) is commonly employed to diagnose disorders of the gall bladder, bile duct and the pancreas. However, it may be difficult to perform and may be associated with significant complications. Hence, careful patient selection is of paramount importance. An ANN model has been shown to have better discriminant ability and accuracy than a multivariate logistic regression model in selecting patients for therapeutic ERCP[74]. Using data collected from endoscopic images, AI has also been used to predict difficult ERCP which may help in reducing the failure rates and performing safer procedures[75,76]. AI model based only on clinical markers has been shown to be an important adjunct to more invasive procedures in evaluation of bile duct obstruction[77].

AI may also support the physicians performing the ERCP by helping to differentiate between benign and malignant lesions and aid in their classification[78,79]. AI based algorithms may also be useful in therapeutic ERCPs by increasing the probability of successful removal of biliary stones[75]. Further, data suggests that AI based interventions have the potential to reduce post-ERCP complications including acute pancreatitis[80].

Endoscopic ultrasound (EUS) has been introduced recently to aid in the diagnosis of pancreatobiliary diseases. However, the diagnostic accuracy of EUS also remains limited with most studies reporting the range to be 80%-95%[81]. AI may be instrumental in increasing the efficacy and accuracy of EUS in the diagnosis and prognostication of GI diseases [82].

GASTROINTESTINAL SURGERY

Patients frequently require ICU care in the peri-operative period of major GI surgeries for clinical stabilisation and optimisation of therapy. These patients require close monitoring for development of any post-operative complications which may affect their hospital course and increase morbidity or mortality. AI based tools may be instrumental in recognising patients at risk of developing post-operative complications who may benefit from intensive care and early intervention.

Acute appendicitis remains a common and dreaded abdominal emergency. However, its diagnosis is often missed, which may increase morbidity and mortality. ANN has shown promising results in diagnosis of acute appendicitis and has performed better than clinical scores like Alvarado clinical scoring system. This may aid in screening of patients presenting with acute abdomen and making an early diagnosis[83].

In patients undergoing liver transplantation, AI has been used to predict post-operative course, graft failure, recurrence of HCC and even survival after surgery[84-87]. ANN has also been used to predict in-hospital mortality in patients after primary liver cancer surgery[88].

Certain acute abdominal emergencies like abdominal aortic aneurysm (AAA) rupture may be associated with high mortality rates. Prompt recognition and early intervention may improve outcomes in such cases. CNN based model has been shown to have high accuracy of 99.1% with an AUROC of 0.99 for detecting AAA. Also, CNN based models may be effective in accurately detecting presence of any leak post AAA repair and predict in-hospital mortality in the post-operative period[89-91]. Further, AI using easily definable pre-operative parameters, has been shown to provide a simple and highly discriminant adjunct in accurately recognising patients at higher risk of death after AAA repair surgery[91].

Similarly, AI based algorithms have been used to predict clinical outcomes including post-operative complications and mortality in other major or emergency abdominal surgeries including bariatric and metabolic surgeries, duodenal switch surgeries, and even after inguinal hernia repair[92-95].

NON-CLINICAL APPLICATIONS

Apart from these clinical applications, AI may be helpful in several non-clinical applications in GI critical care. AI can help in assimilating and analysing huge databases, help in reducing human errors in data entry, and assist in conducting large scale multi-center trials[96]. These intelligent database systems can also improve adherence to current clinical guidelines and protocols and aid in performing clinical audits and improve performance. Further, AI may also be instrumental in providing a more individualised patient care, and hence pave the way for precision medicine in the field of gastroenterology[97].

LIMITATIONS TO AI APPLICATIONS

The literature regarding use of AI in healthcare settings is increasing. However, most of the present studies have small sample sizes and are retrospective in nature. The literature on ICU patients is even more limited, restricting the use of AI in these patients. Moreover, comparison between different studies is difficult, as they have used different types of AI tools, with new tools being added frequently. Use of patient data for developing AI algorithms may lead to privacy and medico-legal issues which need to be adequately addressed by designing and implementing appropriate regulations and guidelines. Further, issues related to liability, reliability and safety of AI applications need to be addressed before widespread implementation and acceptance of AI in the current healthcare system becomes possible.

FUTURE DIRECTIONS

AI may form an important component of healthcare management and a lucrative adjunct to intensive care physicians in the future. However, large scale trials need to be conducted, especially in ICU patients, to evaluate and validate the efficacy and safety of AI. Further, standardisation of AI tools and algorithms must be done to ensure their comparability. For AI to be integrated in the routine clinical practice, healthcare workers need to be trained regarding safe and effective use of AI to ensure its proper utilisation and interpretation. Appropriate rules and regulations must be implemented to prevent any violation of patient privacy and maintain confidentiality of patient data.

CONCLUSION

With a huge increase in digitalisation of data and increased availability of big data, AI holds immense promise to change the landscape of healthcare in the not-so-distant future. It has the potential to improve diagnostics, predict progression and complications, and predict outcomes of critically ill gastroenterology patients thereby, reducing medical errors, increasing efficiency and improving clinical outcomes. AI can potentially reduce the number of invasive procedures and hence, reduce complication rates and provide a safer environment. However, there still remains issues regarding its safety, liability, legality, and patient privacy, which need to be addressed before it is incorporated in mainstream clinical care. Even though it may not be able to replace the physician's clinical acumen, it can be a good supplement and may aid in improving patient care and safety.

FOOTNOTES

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Prospective Study

Artificial intelligence for characterization of diminutive colorectal polyps: A feasibility study comparing two computer-aided diagnosis systems

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Abstract

BACKGROUND

Artificial intelligence (AI) has potential in the optical diagnosis of colorectal polyps.

AIM

To evaluate the feasibility of the real-time use of the computer-aided diagnosis system (CADx) AI for ColoRectal Polyps (AI4CRP) for the optical diagnosis of diminutive colorectal polyps and to compare the performance with CAD EYE™

(Fujifilm, Tokyo, Japan). CADx influence on the optical diagnosis of an expert endoscopist was also investigated.

METHODS

AI4CRP was developed in-house and CAD EYE was proprietary software provided by Fujifilm. Both CADx-systems exploit convolutional neural networks. Colorectal polyps were characterized as benign or premalignant and histopathology was used as gold standard. AI4CRP provided an objective assessment of its characterization by presenting a calibrated confidence characterization value (range 0.0-1.0). A predefined cut-off value of 0.6 was set with values < 0.6 indicating benign and values ≥ 0.6 indicating premalignant colorectal polyps. Low confidence characterizations were defined as values 40% around the cut-off value of 0.6 (< 0.36 and > 0.76). Self-critical AI4CRP's diagnostic performances excluded low confidence characterizations.

RESULTS

AI4CRP use was feasible and performed on 30 patients with 51 colorectal polyps. Self-critical AI4CRP, excluding 14 low confidence characterizations [27.5% (14/51)], had a diagnostic accuracy of 89.2%, sensitivity of 89.7%, and specificity of 87.5%, which was higher compared to AI4CRP. CAD EYE had a 83.7% diagnostic accuracy, 74.2% sensitivity, and 100.0% specificity. Diagnostic performances of the *endoscopist alone* (before AI) increased non-significantly after reviewing the CADx characterizations of both AI4CRP and CAD EYE (*AI-assisted endoscopist*). Diagnostic performances of the AI-assisted endoscopist were higher compared to both CADx-systems, except for specificity for which CAD EYE performed best.

CONCLUSION

Real-time use of AI4CRP was feasible. Objective confidence values provided by a CADx is novel and self-critical AI4CRP showed higher diagnostic performances compared to AI4CRP.

Key Words: Artificial intelligence; Colorectal polyp characterization; Computer aided diagnosis; Diminutive colorectal polyps; Optical diagnosis; Self-critical artificial intelligence

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Core Tip: In this study, two computer-aided diagnosis systems (CADx) [Artificial intelligence for ColoRectal polyps (AI4CRP) and CAD EYE] were compared head-to-head and showed that real-time use was feasible in clinical practice, but does not yet meet quality standards for optical diagnosis. AI4CRP provided characterizations accompanied by confidence values, enabling self-critical AI4CRP in which low confidence characterizations were excluded. Self-critical AI4CRP resulted in considerably higher diagnostic performances compared to AI4CRP. The AI-assisted endoscopists, optically diagnosing colorectal polyps after reviewing both CADx characterizations, had non-significantly higher diagnostic performances compared to the endoscopist alone (before CADx).

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INTRODUCTION

Endoscopists' task in performing colonoscopies increasingly involves optical diagnosis, the endoscopic characterization of colorectal polyps. Recently, diagnostic performance of optical diagnosis increased due to optimization of technologies such as high definition imaging, magnification, and image enhancement techniques like blue light imaging (BLI)[1,2]. Despite these optimizations, endoscopists do not consistently meet quality standards set by the American society for gastrointestinal endoscopy (ASGE) and the European society of gastrointestinal endoscopy (ESGE) for implementation of the resect-and-discard and diagnose-and-leave strategies based on optical diagnosis[3,4]. The first strategy entails diminutive (≤ 5 mm) colorectal polyps to be resected and discarded without histopathological assessment under the condition of a $\geq 90\%$ agreement in the post-polypectomy surveillance interval between the optical and histopathological diagnosis. The second strategy states that diminutive hyperplastic polyps in the rectosigmoid can be left in situ if a negative predictive value (NPV) of $\geq 90\%$ is reached for the optical diagnosis of adenomatous polyps. Large, multicenter studies demonstrated disappointing results on optical diagnosis, even for additionally trained (bowel cancer screening) endoscopists, hampering implementation in clinical practice[5,6]. Diagnostic performances are operator dependent, showing high interobserver variability, and rely on training and expertise[3,7,8].

Optical diagnosis with artificial intelligence (AI) has the potential to overcome this high interobserver variability by minimizing the operator dependence and providing objective optical diagnoses[9]. Accurate characterization of colorectal polyps with computer-aided diagnosis systems (CADx) may facilitate the implementation of the resect-and-discard and diagnose-and-leave strategies by meeting the set quality standards. Implementation of these strategies may lead to a reduction in unnecessary polypectomies, thereby decreasing the risk of post-polypectomy complications, reducing histopathology costs, and improving the cost-effectiveness of colonoscopy[10,11].

The primary aim of this study was to evaluate the feasibility of the real-time use of the CADx AI for ColoRectal polyps (AI4CRP) for the optical diagnosis of diminutive (≤ 5 mm) colorectal polyps. Secondary aims were a head-to-head comparison of AI4CRP with CAD EYE™ (Fujifilm, Tokyo, Japan), evaluating the diagnostic performances of self-critical AI4CRP (providing only high confidence diagnoses), the diagnostic performances of an expert endoscopist (endoscopist alone), and the influence of CADx on the optical diagnosis of an expert endoscopist (AI-assisted endoscopist).

MATERIALS AND METHODS

This prospective study was conducted at the Catharina Hospital Eindhoven, the Netherlands. The study was performed in accordance with the declaration of Helsinki and the General Data Protection Regulation. The Medical Research Ethics Committees United (W20.239, July 2021) approved the study (ClinicalTrials.gov NCT05349110).

AI4CRP

AI4CRP, developed in-house by our research group (Video Coding & Architectures, Eindhoven University of Technology, the Netherlands), is an image-based CADx exploiting convolutional neural networks. AI4CRP was previously validated and a technical explanation has been published[12,13]. AI4CRP was trained multicenter and tested using prospectively collected datasets from multiple endoscopy vendors (Fujifilm and Pentax) (Supplementary Table 1). Characterizations were made in three image modalities: high-definition white light (HDWL), BLI, and linked color imaging (LCI). AI4CRP characterized colorectal polyps as benign (hyperplastic polyp) or premalignant [adenoma and sessile serrated lesion (SSL)]. The characterization was provided by a green assist bar for benign and a red assist bar for premalignant polyps. A heatmap pointed out the area of interest (Figure 1). Distinctive from other CADx-systems, AI4CRP provided calibrated confidence characterization values (range 0.0-1.0) representing the objective confidence level of AI4CRP in its characterization. A predefined cut-off value of 0.6 was set with values < 0.6 indicating benign and values ≥ 0.6 indicating premalignant colorectal polyps. A value close(r) to 0.0 implies high confidence for a benign colorectal polyp and a value close(r) to 1.0 high confidence for a premalignant colorectal polyp. Providing these confidence values enabled a self-critical AI4CRP in which low confidence characterizations were excluded. Low confidence characterizations were defined as values 40% around the cut-off value of 0.6 (< 0.36 and > 0.76). To explore the added value of our self-critical CADx and allowing for an exploration of self-critical AI4CRP, the system was compared head-to-head with CAD EYE.

CAD EYE

CAD EYE is a commercial, video-based CAD-system developed to detect and characterize colorectal polyps. CAD EYE exploits convolutional neural networks[11]. For this study, only the characterization mode (BLI) was used. CAD EYE characterized colorectal polyps as hyperplastic (hyperplastic polyp and SSL) or neoplastic (adenoma) (note the difference in SSL characterization compared to AI4CRP). A status bar indicated the status of the characterization (complete or incomplete), a visual assist circle colored green for hyperplastic and yellow for neoplastic, a position map indicated the position of the colorectal polyp, and a characterization was displayed (Figure 1)[14].

Patients

Patients, aged ≥ 18 years, referred for screening colonoscopies, symptoms, or surveillance were eligible for participation. Consecutive patients were included if at least one diminutive colorectal polyp was encountered. Exclusion criteria were polyposis syndromes, inflammatory bowel diseases, inadequate bowel preparations (Boston bowel preparation scale < 6), and emergency colonoscopies. Patients were informed during a screening visit at the outpatient clinic before the colonoscopy. All patients provided written informed consent.

Endoscopic procedure

Colonoscopies were performed by one expert endoscopist (R.M.S.). The endoscopist was additionally trained in optical diagnosis (succeeding several training sessions in optical diagnosis organized by the ESGE), performed optical diagnoses on a regular basis according to the ESGE curriculum for optical diagnosis[1], and is a teacher in optical diagnosis training sessions. The endoscopist was familiarized with both CADx-systems. He was involved in the development of AI4CRP and used CAD EYE in clinical practice for 6 months before the start of this study. A maximum of three diminutive colorectal polyps per patient were included due to time restrictions. If more than three diminutive colorectal polyps were encountered, the first three were included to minimize selection bias. The endoscopist optically diagnosed colorectal polyps real-time (*endoscopists alone*) as benign (hyperplastic polyp) or premalignant (adenoma and SSLs) using BLI and according to Japan NBI Expert Team and BLI adenoma serrated international classification (BASIC)[15,16]. The endoscopist provided a confidence level [low or high ($\geq 90\%$)] for each optical diagnosis. Subsequently, all colorectal polyps optically diagnosed by the endoscopist were characterized by both CADx-systems in sequence. AI4CRP characterized images captured from the real-time video output in each image modality separately and calculated an overall

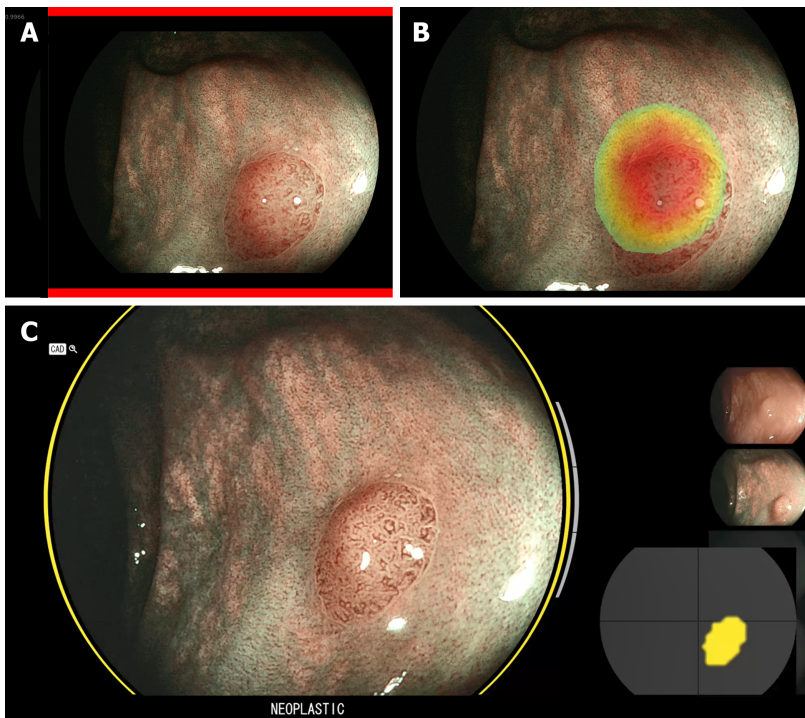


Figure 1 Endoscopic images of a tubular adenoma in blue light imaging. A: Artificial intelligence for ColoRectal Polyps (AI4CRP's) neoplastic prediction [indicated by the red assist bar and characterization value of > 0.6 (0.9966)]; B: The corresponding heatmap (pointing out the area of interest of the AI4CRP prediction); C: CAD EYE's predicted characterization [indicated by a complete (grey) status bar, a yellow visual assist circle, yellow position map, and 'neoplastic' description].

characterization using all three image modalities (multimodal imaging). Images were manually captured by a research physician. Motion-blurred images and images out-of-focus were excluded. Afterwards, CAD EYE was activated by the endoscopist to provide a characterization. Both CADx characterizations were recorded and saved. Lastly, the endoscopist optically diagnosed the colorectal polyps after reviewing both CADx characterizations (*AI-assisted endoscopist*) and again provided a confidence level.

Despite proper endoscope positioning, CAD EYE provided inconclusive characterizations, defined as unstable characterizations over time (switching diagnoses between hyperplastic and neoplastic) despite a complete status bar. The video-recorded CAD EYE characterizations were assessed by two independent expert endoscopists blinded to histopathology. Upon agreement of inconclusiveness, these characterizations were excluded from the analyses.

Outcomes

The primary outcome was the feasibility of the real-time use of AI4CRP. Feasibility was defined as seamless video output reception from the endoscopy processor without noticeable clinically relevant latency (the time from capturing the endoscopic image to outputting the analyzed results)[17] and seamless operation of the software in obtaining characterizations. Latency was not measured by AI4CRP itself or by the investigators since it is known from previous studies that small differences in latency were not noticeable for endoscopists, and therefore only clinically noticeable latency was deemed relevant[12]. Secondary outcomes were real-time diagnostic performances of (self-critical) AI4CRP and a head-to-head comparison of (self-critical) AI4CRP with CAD EYE and an expert endoscopist (endoscopist alone and AI-assisted endoscopist). Histopathology was used as gold standard and assessed according to the revised Vienna classification. Involved pathologists were specialized in gastrointestinal histopathology. Differences in characterization of SSLs by AI4CRP, CAD EYE, and the endoscopist were accounted for by histopathology in computing measures of diagnostic performance. Outcomes were reported according to the STARD (standard for reporting diagnostic accuracy studies) checklist.

Statistical analyses

Due to the feasibility design of the study, no formal sample size calculation was performed. The sample size ($n = 30$ patients) was based on a previous CADx feasibility study[18]. Baseline characteristics are presented as proportions (%) for categorical variables or as mean [standard deviation (SD)] for numerical variables. Feasibility was described qualitatively. Diagnostic performances were investigated in terms of diagnostic accuracy, sensitivity, specificity, and negative and positive predictive values (NPV, PPV), expressed with 95% confidence intervals. As sensitivity analysis, cluster bootstrapping was performed to account for multiple colorectal polyps per patient. Self-critical AI4CRP was analyzed post-hoc. Differences between (self-critical) AI4CRP, CAD EYE, and the endoscopist were analyzed using the McNemar test for paired proportions. Two-sided P values ≤ 0.05 were considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics (IBM Corp., United States) and R (R Foundation, Austria). The statistical methods of

this study were reviewed by B. Winkens from the Department of Methodology and Statistics of Maastricht University.

RESULTS

Study population

Patients who underwent a colonoscopy at Catharina Hospital Eindhoven between August and November 2021 were screened for eligibility. In total, 30 patients with 51 colorectal polyps were included (Figure 2). Patient characteristics are provided in Table 1. Mean polyp size was 2.8 mm (SD 1.0). Histopathology showed 32 tubular adenomas (62.7%), 1 tubulovillous adenoma (2.0%), 6 SSLs (11.8%), and 12 hyperplastic polyps (23.5%) (Table 2).

Feasibility

Real-time use of AI4CRP was deemed feasible in clinical practice. By means of plug-and-play AI4CRP was easily connected to the endoscopy processor. No noticeable clinically relevant latency was observed in receiving the video output from the processor and the software worked flawless without interruptions.

AI4CRP

AI4CRP was able to characterize all 51 colorectal polyps. Eight images were excluded because the images were out of focus and four because of motion blur. For these colorectal polyps, a second image was taken by the endoscopist. AI4CRP showed a sensitivity of 82.1% (95%CI 0.66-0.92) and a diagnostic accuracy of 80.4% (95%CI 0.66-0.90) in BLI, which was significantly higher compared to HDWL (sensitivity 59.0%, $P = 0.022$ and diagnostic accuracy 66.7%, $P = 0.007$) (Table 3, Supplementary Figure 1). NPV was also highest in BLI (56.3%, 95%CI 0.31-0.79), but not significantly different from other image modalities. Self-critical AI4CRP excluded 14 low confidence characterizations [27.5% (14/51), tubular adenomas $n = 7$, SSLs $n = 3$, hyperplastic polyps $n = 4$]. Self-critical AI4CRP showed higher diagnostic performances on all metrics compared to AI4CRP (sensitivity 89.7% and diagnostic accuracy 89.2%) (Table 4).

CAD EYE

CAD EYE was able to provide a characterization for all but two colorectal polyps ($n = 49$, 96.1%), which were diagnosed inconclusively. CAD EYE had a sensitivity of 74.2% (95%CI 0.55-0.87), a specificity of 100.0% (95%CI 0.78-1.00), a NPV of 69.2% (95%CI 0.48-0.85), and a diagnostic accuracy of 83.7% (95%CI 0.70-0.92) (Table 4).

Expert endoscopist

The endoscopist (endoscopist alone) optically diagnosed 47 (92.2%, 47/51) colorectal polyps with high confidence. Before AI (endoscopist alone), sensitivity was 97.4% (95%CI 0.85-1.00), specificity 77.8% (95%CI 0.40-0.96), NPV 87.5% (95%CI 0.47-0.99), and diagnostic accuracy 93.6% (95%CI 0.81-0.98) (Table 4). Although this study was not powered to detect a difference between the endoscopist alone and the AI-assisted endoscopist, after reviewing characterizations of both CADx-systems specificity, PPV, NPV, and diagnostic accuracy increased non-significantly for the AI-assisted endoscopist (Table 4, Supplementary Figure 2). The number of optical diagnoses made with high confidence also increased [endoscopist alone 92.2% (47/51) vs AI-assisted endoscopists 96.1% (49/51), $P = 0.500$] (Supplementary Table 2).

Diagnostic performances of the AI-assisted endoscopist were higher compared to both CADx-systems, except for specificity for which CAD EYE performed best. Comparing diagnostic performances of AI4CRP with the endoscopist alone showed a significantly higher sensitivity ($P = 0.031$) and a non-significantly higher specificity and diagnostic accuracy for the endoscopist ($P = 1.000$ and $P = 0.180$, respectively) (Supplementary Figure 2). The AI-assisted endoscopist also had a significantly higher sensitivity ($P = 0.031$) and a non-significantly higher specificity and diagnostic accuracy ($P = 0.500$ and $P = 0.289$, respectively) than AI4CRP. Self-critical AI4CRP did not show any significant difference with the endoscopist alone and the AI-assisted endoscopist. Compared with CAD EYE, the endoscopist alone had a significantly higher diagnostic accuracy ($P = 0.004$) and sensitivity ($P = 0.016$), while specificity was non-significantly lower ($P = 0.500$) (Supplementary Figure 2). The same accounted for the comparison between CAD EYE and the AI-assisted endoscopist. Performing cluster bootstrapping to correct for multiple colorectal polyps per patient did not change the conclusions (Supplementary Table 3). Analysis according to colorectal polyp location are presented in Supplementary Table 4.

DISCUSSION

AI4CRP use for the optical diagnosis of diminutive colorectal polyps was feasible and showed promising results. The novelty of our AI4CRP lies in providing objective confidence values. Self-critical AI4CRP achieved considerably higher diagnostic performances compared to AI4CRP. Reviewing characterizations by AI4CRP and CAD EYE did non-significantly increase the performance of the AI-assisted endoscopist.

Real-time use of AI4CRP was feasible and did not obstruct clinical workflow. No clinically relevant time delays in obtaining CADx characterizations were observed. This study compared two CADx-systems head-to-head, namely AI4CRP and CAD EYE. By comparing a commercially available CADx with an in-house developed CADx, comparison between the systems and a self-critical system was possible. Diagnostic performances of both CADx-systems were non-significantly inferior compared to the performance of the expert endoscopist, with the exception of specificity, were CAD

Table 1 Baseline characteristics of patients, n (%)

	Patients, n = 30
Gender, female	13 (43.3)
Age in years, mean (SD) [range]	65.8 (8.4) [50-78]
Indication colonoscopy	
Bowel cancer screening program	15 (50.0)
Surveillance	10 (33.3)
Symptoms	5 (16.7)
Family history positive for CRC	5 (16.7)
BBPS, mean (SD)	6.6 (1.4)
Number of colorectal polyps per patient¹	
1 colorectal polyp	15 (50.0)
2 colorectal polyps	9 (30.0)
3 colorectal polyps	6 (20.0)

¹A maximum of three colorectal polyps were included per patient.

BBPS: Boston bowel preparation scale; CRC: colorectal cancer.

Table 2 Baseline characteristics for colorectal polyps, n (%)

	Colorectal polyps, n = 51
Location	
Cecum	7 (13.7)
Ascending colon	8 (15.7)
Transverse colon	15 (29.4)
Descending colon	5 (9.8)
Sigmoid	10 (19.6)
Rectum	6 (11.8)
Size, mean (SD) [range]	2.8 (1.0) [2-5]
Morphology	
Sessile (Paris Is)	45 (88.2)
Flat-elevated (Paris IIa)	6 (11.8)
Histopathology	
Tubular adenoma, LGD	32 (62.7)
Tubulovillous adenoma, LGD	1 (2.0)
Sessile serrated lesion, no dysplasia	6 (11.8)
Hyperplastic polyp, no dysplasia	12 (23.5)
Resection technique - cold snare	51 (100.0)

LGD: Low grade dysplasia.

EYE demonstrated the best performance. This difference in specificity between (self-critical) AI4CRP and CAD EYE, can be explained by the differences in characterizing SSLs. Performances of both CADx-systems should be improved for utility in clinical practice.

Objective assessment of the confidence level as performed by self-critical AI4CRP is a novelty. Diagnostic performances were considerably higher for self-critical AI4CRP compared to AI4CRP. CAD EYE does not provide a confidence value while inconclusive diagnoses occurred (3.9%). However, these inconclusive diagnoses were marked by expert consensus

Table 3 Diagnostic performances of artificial intelligence for ColoRectal polyps in different image enhancement modes

	AI4CRP (n = 51)			
	BLI, % (95%CI)	HDWL, % (95%CI)	LCI, % (95%CI)	Multimodal imaging, % (95%CI)
Sensitivity	82.1 (0.66-0.92)	59.0 (0.42-0.74)	76.9 (0.60-0.88)	71.8 (0.55-0.84)
Specificity	75.0 (0.43-0.93)	91.7 (0.60-1.00)	83.3 (0.51-0.97)	91.7 (0.60-1.00)
PPV	91.4 (0.76-0.98)	95.8 (0.77-1.00)	93.8 (0.78-0.99)	96.6 (0.80-1.00)
NPV	56.3 (0.31-0.79)	40.7 (0.23-0.61)	52.6 (0.29-0.75)	50.0 (0.29-0.71)
Diagnostic accuracy	80.4 (0.66-0.90)	66.7 (0.52-0.79)	78.4 (0.64-0.88)	76.5 (0.62-0.87)

AI4CRP: Artificial intelligence for ColoRectal polyps; BLI: Blue light imaging; CI: Confidence interval; HDWL: High definition white light; LCI: Linked color imaging; NPV: Negative predictive value; PPV: Positive predictive value.

Table 4 Diagnostic performance of artificial intelligence for ColoRectal polyps, self-critical artificial intelligence for ColoRectal polyps, CAD EYE, and the endoscopist

	AI4CRP ¹ , % (95%CI), n = 51	Self-critical AI4CRP ¹ , % (95%CI), n = 37	CAD EYE, % (95%CI), n = 49	Endoscopist alone ² , % (95%CI), n = 47	AI-assisted endoscopist ^{2,3} , % (95%CI), n = 49
Sensitivity	82.1 (0.66-0.92)	89.7 (0.72-0.97)	74.2 (0.55-0.87)	97.4 (0.85-1.00)	97.4 (0.85-1.00)
Specificity	75.0 (0.43-0.93)	87.5 (0.47-0.99)	100.0 (0.78-1.00)	77.8 (0.40-0.96)	90.9 (0.57-1.00)
PPV	91.4 (0.76-0.98)	96.3 (0.79-1.00)	100.0 (0.82-1.00)	94.9 (0.81-0.99)	97.4 (0.85-1.00)
NPV	56.3 (0.31-0.79)	70.0 (0.35-0.92)	69.2 (0.48-0.85)	87.5 (0.47-0.99)	90.9 (0.57-1.00)
Diagnostic accuracy	80.4 (0.66-0.90)	89.2 (0.74-0.96)	83.7 (0.70-0.92)	93.6 (0.81-0.98)	95.9 (0.85-0.99)

¹AI4CRP and self-critical AI4CRP both in BLI mode.

²Optical diagnosis by the endoscopist only taking into account diagnoses made with high confidence.

³Optical diagnosis by the endoscopist after reviewing predictions of both AI4CRP and CAD EYE.

AI4CRP: Artificial intelligence for ColoRectal polyps; AI: Artificial intelligence; BLI: Blue light imaging; CI: Confidence interval; NPV: Negative predictive value; PPV: Positive predictive value.

and are not objective as for self-critical AI4CRP. Rondonotti *et al*[19] reported higher numbers of CAD EYE characterizations being unstable over time (7.9%) or not possible (1.3%). Self-critical AI4CRP made low confidence characterizations in 27.5%. Providing an objective confidence level can be seen as a form of explainable AI which may increase endoscopists' trust in CADx and therefore has potential applicability in real-time endoscopy practice. At the same time, one can argue that CADx should be of added value particularly in colorectal polyps deemed difficult by endoscopists. Interestingly, the low confidence diagnoses made by the endoscopist were high confidence diagnoses by AI4CRP in 75.0% of cases. Furthermore, self-critical AI4CRP was performed post-hoc. In real-time colonoscopy, endoscopists could do another attempt in gaining a high confidence characterization by repositioning the colonoscope and thereby optimize the endoscopic imaging possibly lowering the number of low confidence characterizations. Future studies should investigate if defining low confidence characterizations as diagnosis with a confidence value of 40% around the cut-off value is sufficient.

CADx utility in clinical practice will not be in a stand-alone fashion, but in aiding endoscopists. A strength of this study is the AI-assisted performances of the endoscopist, in contrast to previous studies in which endoscopist alone or AI-assisted non-expert endoscopist *vs* CADx were investigated[11,20]. The non-significant increase between the diagnostic performances of the endoscopist alone and the AI-assisted endoscopist is comparable with results of Hassan *et al*[21]. Furthermore, Jin *et al*[22] only showed an increase for non-experts and not for experts. Here, the number of optical diagnoses made with high confidence did increase for AI-assisted optical diagnosis.

Most CADx-systems have been trained to operate in a single image enhancement modality, i.e. narrow band imaging (NBI) or BLI. Zachariah *et al*[23] and Biffi *et al*[24] trained their systems using both HDWL and NBI or BLI, respectively. They compared the diagnostic performances of their CADx in HDWL with the performances in the image enhancement modality and found no significant differences. This favors the use of HDWL since the interpretation of image enhancement modalities requires training[25], limits generalizability, and hampers the utility of AI-assisted CADx by undertrained endoscopists. A strength of our study is that AI4CRP was trained with multiple image enhancement modalities, namely HDWL, BLI, LCI, and i-scan 1, 2, and 3. In contrast to Zachariah *et al*[23] and Biffi *et al*[24], AI4CRP's diagnostic performances were significantly higher in BLI compared to HDWL. Future research should, therefore, investigate the effect of different image enhancement modalities (especially BLI) on the output of CADx compared to

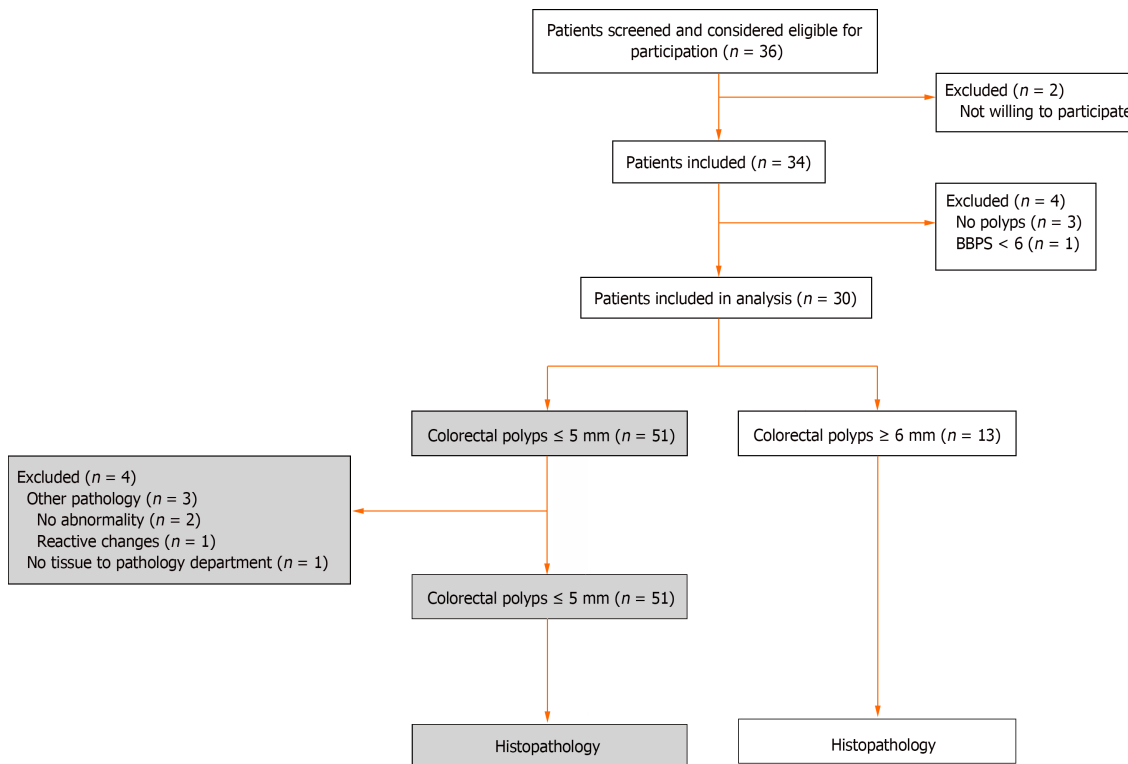


Figure 2 Study flow chart of patient enrolment and colorectal polyp inclusion. BBPS: Boston bowel preparation scale.

HDWL.

Self-critical AI4CRP and CAD EYE reached a NPV of $\geq 90\%$ for rectosigmoid polyps according to the quality standard for the diagnose-and-leave strategy by the ASGE[3]. Both CADx-systems also met the quality standard of the ESGE for the diagnose-and-leave strategy and self-critical AI4CRP also the ESGE quality standard for the resect-and-discard strategy[4]. Previously, CAD EYE and GI-Genius (Medtronic, United States) also met the PIVI quality standards[26,27]. Although the risk of cancer in diminutive colorectal polyps is very low, misdiagnosis does pose risks when leaving adenomatous polyps in situ[28,29]. In an international survey, two-thirds of endoscopists considered implementation of resect-and-discard not feasible because of the fear of making incorrect optical diagnoses[30]. Studies should investigate if this fear of incorrect optical diagnosis may be leveraged with CADx.

No consensus exists on the characterization of SSLs between different CADx-systems. Where CAD EYE, a CADx by Sánchez-Montes *et al*[31], and Zachariah *et al*[24] characterizes SSLs as hyperplastic, other systems excluded SSLs[9,11,32-34]. Rondonotti *et al*[19] marginalized the clinical relevance of SSLs because of their low prevalence among diminutive rectosigmoid polyps. Albeit this low prevalence, given that SSLs bear a malignant potential[35,36], differentiating them from hyperplastic polyps is advocated and promotes clinical utility of CADx. AI4CRP, characterizing SSLs as premalignant, pursued to do just that because of the high need of improving SSL diagnosis[31]. Expanding CADx characterizations to multiple-class characterizations, allowing for the separate diagnosis of SSLs, more in line with clinical practice, would facilitate CADx implementation into clinical practice even further.

The main strength of this study is the head-to-head comparison of two CADx-systems characterizing the same colorectal polyps in sequence. Certain limitations of our study should also be acknowledged. Due to the feasibility design, no formal sample size calculation was performed and the number of included colorectal polyps was limited. Both CADx-systems were compared with only one expert endoscopist and testing was performed single center, limiting generalizability. AI4CRP is an image-based CADx, whereas CAD EYE is video-based. Both systems characterized the same colorectal polyps in a sequential approach rather than a parallel approach. The sequential approach led to both CADx-systems analyzing slightly different colorectal polyp frames potentially introducing bias. Bias could also have occurred since AI4CRP was trained with data from the same hospital in which it was tested in this study, possibly favoring AI4CRP performances, while this is not true for CAD EYE. An important limitation was the semi-automated use of AI4CRP. Images had to be manually captured by a research physician, limiting functional use of AI4CRP in clinical practice. A fully automated approach is currently under development. Furthermore, images out of focus or motion blurred imaged were excluded and a new image had to be taken. Although inconvenient, this only hampered the work flow minimally, but could have introduced bias. An image quality indicator alongside the CADx characterization, could be helpful in quantifying and reducing this bias.

CONCLUSION

In conclusion, real-time use of AI4CRP was feasible and achieved promising results. Self-critical AI4CRP, excluding low confidence characterizations, showed increased diagnostic performances compared to AI4CRP. The objective assessment of the confidence level is a novelty with great potential applicability in real-time endoscopy practice. Diagnostic performances of the AI-assisted endoscopist, after reviewing both CADx characterizations, were higher compared to both CADx-systems. Diagnostic performances of the AI-assisted endoscopist were non-significantly superior to the endoscopists alone. In the future, larger sized studies should expand on our findings.

ARTICLE HIGHLIGHTS

Research background

The importance of optical diagnosis, the endoscopic characterization of colorectal polyps, increases. However, correct endoscopic characterization and differentiation between benign and premalignant polyps remains difficult even for experienced endoscopists.

Research motivation

The ability of modern-day computer-aided diagnosis systems (CADx) to automatically recognize informative patterns in datasets can potentially improve accurate characterization of colorectal polyps and facilitate the implementation of treatment strategies based on optical diagnosis by meeting set quality standards.

Research objectives

Aim of this study was to evaluate the feasibility of the real-time use of the in-house developed CADx-system artificial intelligence for ColoRectal polyps (AI4CRP) for the optical diagnosis of diminutive (≤ 5 mm) colorectal polyps. Secondary aims were a head-to-head comparison of AI4CRP with CAD EYE™ (Fujifilm, Tokyo, Japan), evaluating the diagnostic performances of self-critical AI4CRP (providing only high confidence diagnoses), the diagnostic performances of an expert endoscopist (endoscopist alone), and the influence of CADx on the optical diagnosis of an expert endoscopist [artificial intelligence (AI)-assisted endoscopist].

Research methods

The two CADx-systems (AI4CRP and CAD EYE) were compared head-to-head. Colorectal polyps were characterized as benign or premalignant and histopathology was used as gold standard. AI4CRP provided characterizations accompanied by confidence values, enabling self-critical AI4CRP in which low confidence characterizations were excluded. The AI-assisted endoscopists, optically diagnosed colorectal polyps after reviewing both CADx characterizations.

Research results

Real-time use of AI4CRP was deemed feasible in clinical practice. AI4CRP showed a sensitivity of 82.1%, a specificity of 75.0%, a negative predictive value of 56.3%, and a diagnostic accuracy of 80.4%. Self-critical AI4CRP excluded 14 low confidence characterizations, resulted in considerably higher diagnostic performances compared to AI4CRP. CAD EYE had a sensitivity of 74.2%, a specificity of 100.0%, a negative predictive value of 69.2%, and a diagnostic accuracy of 83.7%. Diagnostic performances of the endoscopist alone (before AI) increased non-significantly after reviewing the CADx characterizations of both AI4CRP and CAD EYE (AI-assisted endoscopist). Diagnostic performances of the AI-assisted endoscopist were higher compared to both CADx-systems, except for specificity for which CAD EYE performed best.

Research conclusions

Real-time use of AI4CRP was feasible. Objective confidence values provided by a CADx is novel and self-critical AI4CRP showed higher diagnostic performances compared to AI4CRP. Reviewing characterizations by AI4CRP and CAD EYE did not increase the performance of the AI-assisted endoscopist.

Research perspectives

Future studies should expand on our findings and further investigate the added value of self-critical CADx-systems.

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FOOTNOTES

Author contributions: van der Zander QEW, Schreuder RM, Masclee AAM, and Schoon EJ substantially contributed to the study design; van der Zander QEW developed the study protocol under supervision of Masclee AAM and Schoon EJ, Kusters CHJ, Dehghani N, Scheeve T, de With PHN, and van der Sommen F developed the in-house CADx-system AI4CRP; van der Zander QEW, Schreuder RM, Thijssen A, and van der Ende - van Loon MCM did the data acquisition and processed the data; van der Zander QEW did the data analyses; Winkens B oversaw the data analyses and provided critical review of the data analyses; van der Zander QEW did the data interpretation and drafted the manuscript; Schreuder RM, Thijssen A, Kusters CHJ, Dehghani N, Scheeve T, Winkens B, van der Ende - van Loon MCM, de With PHN, van der Sommen F, Masclee AAM, and Schoon EJ provided a constructive review of the manuscript for important intellectual content. All authors approved the final version of the manuscript before submission. All authors had full access to all the data in the study and accept responsibility for all aspects of the work regarding accuracy, integrity, and publication.

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Data sharing statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request. This data includes deidentified participant data. Additional documents that will be made available are the study protocol, the statistical analysis plan, and the informed consent forms. Data will be available following publication with no end date. Requests should be methodologically sound proposals with the purpose to achieve aims in the approved proposal. Data requestors will need to sign a data access agreement after approval of a proposal.

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Contents

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REVIEW

Bangolo A, Wadhwani N, Nagesh VK, Dey S, Tran HHV, Aguilar IK, Auda A, Sidiqui A, Menon A, Daoud D, Liu J, Pulipaka SP, George B, Furman F, Khan N, Plumptre A, Sekhon I, Lo A, Weissman S. Impact of artificial intelligence in the management of esophageal, gastric and colorectal malignancies. *Artif Intell Gastrointest Endosc* 2024; 5(2): 90704 [DOI: [10.37126/aige.v5.i2.90704](https://doi.org/10.37126/aige.v5.i2.90704)]

Ghosh NK, Kumar A. Ultra-minimally invasive endoscopic techniques and colorectal diseases: Current status and its future. *Artif Intell Gastrointest Endosc* 2024; 5(2): 91424 [DOI: [10.37126/aige.v5.i2.91424](https://doi.org/10.37126/aige.v5.i2.91424)]

MINIREVIEWS

Lingam G, Shakir T, Kader R, Chand M. Role of artificial intelligence in colorectal cancer. *Artif Intell Gastrointest Endosc* 2024; 5(2): 90723 [DOI: [10.37126/aige.v5.i2.90723](https://doi.org/10.37126/aige.v5.i2.90723)]

SYSTEMATIC REVIEWS

Dương TQ, Soldera J. Virtual reality tools for training in gastrointestinal endoscopy: A systematic review. *Artif Intell Gastrointest Endosc* 2024; 5(2): 92090 [DOI: [10.37126/aige.v5.i2.92090](https://doi.org/10.37126/aige.v5.i2.92090)]

Contents

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ABOUT COVER

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AIMS AND SCOPE

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

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

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Impact of artificial intelligence in the management of esophageal, gastric and colorectal malignancies

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Abstract

The incidence of gastrointestinal malignancies has increased over the past decade at an alarming rate. Colorectal and gastric cancers are the third and fifth most commonly diagnosed cancers worldwide but are cited as the second and third leading causes of mortality. Early institution of appropriate therapy from timely diagnosis can optimize patient outcomes. Artificial intelligence (AI)-assisted diagnostic, prognostic, and therapeutic tools can assist in expeditious diagnosis, treatment planning/response prediction, and post-surgical prognostication. AI can intercept neoplastic lesions in their primordial stages, accurately flag suspicious and/or inconspicuous lesions with greater accuracy on radiologic, histopathological, and/or endoscopic analyses, and eliminate over-dependence on clinicians. AI-based models have shown to be on par, and sometimes even outperformed experienced gastroenterologists and radiologists. Convolutional neural networks (state-of-the-art deep learning models) are powerful computational models, invaluable to the field of precision oncology. These models not only reliably classify images, but also accurately predict response to chemotherapy, tumor recurrence, metastasis, and survival rates post-treatment. In this systematic review, we analyze the available evidence about the diagnostic, prognostic, and therapeutic utility of artificial intelligence in gastrointestinal oncology.

Key Words: Artificial intelligence; Gastrointestinal malignancies; Machine learning; *Helicobacter pylori*; State-of-the-art deep learning models

Core Tip: Application of artificial intelligence in the realm of gastrointestinal malignancies has burgeoned over the past decade as its incorporation has streamlined the work-up of gastrointestinal malignancies to address the alarming mortality statistics, largely resulting from delayed interception. The latter juxtaposed with the abundant array of contemporary diagnostic, predictive, and prognostic tools, is a testament to their underperforming status and calls for the development of digital tools that can optimize the oncologic work-up and pave the way for personalized therapies.

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INTRODUCTION

Artificial intelligence (AI) is a broad term encompassing the utilization of computer systems to perform tasks that traditionally require human intelligence. This encompasses various fields, including machine learning (ML), which itself includes specialized areas such as deep learning (DL). ML involves training machines to recognize patterns within input data to make predictions in clinical settings. This process relies on extensive datasets to identify correlations between different variables and develop predictive models that can be applied to new data. The accuracy of ML algorithms is directly influenced by the volume of data fed into the model. DL, on the other hand, is rooted in complex neural networks with multiple layers that learn from extensive datasets. These models continuously improve through repeated iterations [1]. The rapid advancement of AI algorithms in healthcare is attributed to the abundance of electronic health records, genomic information, biomedical research, and the integration of telemedicine. This progression has significantly transformed the healthcare sector into a rich source of data [2]. Gastrointestinal (GI) cancer is one of the most prevalent malignancies in the world with over 2.8 million deaths annually [3]. Recent advancements in the diagnosis and treatment of GI tumors have led to improved clinical outcomes. Nevertheless, the amount of data on these malignancies is beyond the interpretation of human intelligence. Gastroenterologists rely heavily on radiological and endoscopic imaging. AI has shown promise in expeditious cancer diagnosis, reduction of misdiagnosis, and interobserver variability in visual classification, and radiologic/histopathologic interpretation [4]. In this review, we explore the utility of AI models in the diagnosis, treatment, and prognostication of GI malignancies (Table 1).

AI-ASSISTED DIAGNOSIS AND STAGING OF ESOPHAGEAL CANCER

Esophageal cancer (EC) is the seventh most commonly diagnosed cancer and sixth leading cause of cancer mortality worldwide [3]. Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) are the two primary histological subtypes of EC, with the latter being more prevalent in the US. Upper endoscopy or, in the cases of metastases, image-guided biopsy of a metastatic site may be used to obtain a diagnostic biopsy. Endoscopically, superficial plaques, nodules, or ulcerations represent early EC. Endoscopic biopsy using tissue sampling is the gold standard for EC diagnosis. A single biopsy has a 93% diagnostic accuracy, and multiple biopsies improve the yield to over 98%. Nonetheless, about 6.5% of cases of EC are missed during diagnostic endoscopy [5].

A mere 20% average five-year overall survival (OS) rate is indicative of the need for improvement in currently available EC diagnostics. AI-driven imaging analysis plays a pivotal role in early detection and diagnosis of EC. DL algorithms can analyze endoscopic images and radiological scans to identify suspicious lesions or abnormalities. AI models have been shown to interpret these images with phenomenal precision, distinguishing between normal cells, malformations, and malignant growth [6]. These techniques enable accurate detection that is difficult to obtain through human interpretation. AI accelerates diagnosis by simplifying the analysis of medical images, guaranteeing that even slight or minor anomalies are not overlooked. This speeds up the start of suitable treatment, which may improve outcomes for patients. ESCC diagnosis is primarily contingent on the endoscopist's level of expertise, thereby limiting its detection at early stages. Various AI techniques that analyze endoscopic, radiologic, clinicopathologic, and genetic factors have been developed to improve the unfavorable prognosis associated with this condition. The development of AI-based EC diagnostics is geared toward the identification of high-grade dysplasia, or early-stage ESCC and EAC (T1 cancers) originating from Barrett's esophagus (BE) [7]. A recent meta-analysis looking at the efficacy of AI in detecting ESCC showed that AI increases the detection of early-stage EC and precisely evaluates tumor depth invasion compared to endoscopists alone [8]. AI has shown efficacy in the detection of esophageal metaplasia and neoplasia in BE. It is not unusual for endoscopists to miss neoplastic lesions in the esophagus. Computer-aided detection (CADE) systems have an accuracy rate of 89% in identifying early neoplasia in people diagnosed with BE and have outperformed endoscopists in some studies [9]. Additionally, a meta-analysis by Islam *et al* [10] analyzing over 700000 images from 28 studies

Table 1 Application of artificial intelligence in gastrointestinal malignancies

Esophageal cancer	Lesion characterization (Barrett's esophagus <i>vs</i> dysplasia <i>vs</i> ESCC[7-9])
	Predicting histological response to therapy[30-32]
	Prognostic assessment[33-37]
Gastric cancer	Endoscopic detection of early GC[44-46]
	Differentiation between stage IV GC and PGL[48,49]
	Accurate TNM staging[54-57]
Colon cancer	Higher adenoma detection, reduced neoplasia "miss rate"[72-74]
	Superior LNM estimation[81-85]
	Intraoperative guidance during colorectal resection[92-95]

ESCC: Esophageal squamous cell cancer, GC: Gastric cancer, PGL: Primary gastric lymphoma, LNM: Lymph node metastases.

demonstrated that DL-based diagnosis of EC had a pooled accuracy, sensitivity, and specificity of 92.90%, 93.80%, and 91.73% respectively.

Gastrointestinal artificial intelligence diagnostic system uses DL to diagnose upper GI malignancies through analysis of imaging data from clinical endoscopies with high diagnostic accuracy and sensitivity, similar to that of expert endoscopists, and superior to that of non-expert endoscopists[11]. CADe using deep neural networks (DNNs) for screening of early ESCCs has also demonstrated high accuracy and sensitivity and can assist endoscopists in detecting lesions previously ignored under white-light imaging[12].

AI-based convolutional neural networks (CNNs) are models made of convolutional filters whose primary function is to learn and extract necessary features for efficient medical image understanding. There is evidence that CNNs can detect early neoplasia with a sensitivity of 96.4%, a specificity of 94.2%, and an accuracy of 95.4%. The object detection algorithm with AI draws a localization box around the areas of dysplasia with high precision and at a speed that allows for real-time implementation[13,14]. Another form of CNN called the single shot multi-box, which detects objects in images using a single DNN, was used in a pilot study and it showed a sensitivity, specificity, and diagnostic accuracy of 96.2%, 70.4%, and 90.9% respectively in EC detection[15]. CNN models have been used to analyze computed tomography (CT) images for EC detection with a diagnostic accuracy of 84.2%, sensitivity of 71.7%, and specificity of 90.0%[16].

A study employing a fully convolutional network, a technique that can obtain segmentation using only CNN to enable end-to-end learning, also showed promising results. The mean diagnostic accuracy of the model was 89.2% and 93% at the lesion and pixel levels, respectively. The interobserver agreement between the model and the gold standard was 0.72. The accuracy of the model for inflammatory lesions (92.5%) was superior to that of the mid-level (88.1%) and junior (86.3%) groups ($P < 0.001$). For malignant lesions, the accuracy of the model (B1, 87.6%; B2, 93.9%) was significantly higher than that of the mid-level (B1, 79.1%; B2, 90.0%) and junior (B1, 69.2%; B2, 79.3%) groups ($P < 0.001$)[17].

A new form of diagnosis called the volumetric laser endomicroscopy (VLE) which is a new promising imaging tool for finding dysplasia in BE at an early stage, by acquiring cross-sectional images of the microscopic structure of BE up to 3-mm deep. Unfortunately for clinicians, interpretation is complex due to both the size and subtlety of the gray-scale data. Studies for development of CADe algorithms, using deep learning strategies by encoding data from VLE, are underway [18].

The utilization of magnifying electronic chromoendoscopy with narrow band imaging or blue light imaging (ME-NBI/BLI) enhances the detection of subtle changes in intramucosal capillary loops, crucial for early ESCC diagnosis. However, its effectiveness heavily relies on the operator's expertise and necessitates an objective and precise evaluation method. A study employing AI-assisted ME-NBI in ESCC diagnosis demonstrated an average diagnostic accuracy of 93.0% at the image level. The model's diagnostic accuracy for inflammatory lesions (92.5%) surpassed that of intermediate-level (88.1%) and primary-level (86.3%) endoscopists. Moreover, the model's diagnostic accuracy for malignant lesions (B1, 87.6%; B2, 93.9%) significantly exceeded that of the intermediate (B1, 79.1%; B2, 90.0%) and junior (B1, 69.2%; B2, 79.3%) endoscopist groups[19]. Recent evidence has reiterated that AI models confer higher diagnostic accuracy compared with stand-alone endoscopist detection of early-stage EC. Studies have demonstrated comparable and often superior efficacy of AI *vs* clinician-based diagnosis[20]. A recent study employing a robustly trained and validated AI model in the identification of early ESCC found that the newly developed computational algorithm had significant per-patient accuracy, with sensitivity, and specificity of 99.5% and 100% respectively, for white light imaging and 97.0%, 97.2%, and 96.4%, for optical enhancement/iodine staining using non-magnifying pictures. The model had 88.1% per-patient accuracy for diagnosing magnified pictures, outperforming beginner endoscopists[21]. A recent meta-analysis by Zhang *et al*[22] looking at the accuracy of AI reiterated that detection solely reliant on endoscopists yielded inferior sensitivity (85%) compared with AI-assisted (94%) diagnosis.

Circulating tumor cells (CTC) have predictive potential to estimate prognosis, distant metastases, and response to treatment. CNNs are highly accurate and efficacious tools for CTC detection, successfully identifying different KYSE cell lines with minimal variance in epithelial cell adhesion molecule expression. Akashi *et al*[23] demonstrated that AI outperformed conventional diagnostics by correctly recognizing cancer from non-cancer cells (accuracy 100% *vs* 91.8%) with

phenomenal processing times (0.74 sec for AI *vs* 630.4 sec for researchers; $P = 0.012$).

Accurate staging of EC is critical for identifying the best treatment option. Based on medical and radiological information, AI offers ML simulations that assist in tumor staging. These simulations take into account many variables, including but not limited to the location and size of the tumor and involvement of lymph nodes. Zhang *et al*[24] employed an AI-based CADe to detect pre-operative lymph node metastases (LNM) in patients with ESCC. AI-CADe model demonstrated an accuracy of 74.4% in predicting LNM, and markedly augmented the clinicians' diagnostic performance based on positron emission tomography-computed tomography (PET-CT) imaging analyses (accuracy 83.3% *vs* 71.2%; specificity 89.1% *vs* 69.7%) amongst patients in the validation cohort. Radiomics and DL models have been shown to yield reliable risk estimates for LNM in ESCC patients. Tan *et al*[25] developed a radiomics signature consisting of five features that were significantly associated with presence of LNM in resectable ESCC cases, with an area under the curve (AUC) of 0.758 and 0.773 in the training and validation sets respectively. Interestingly, the discriminatory power of the radiomics nomogram exceeded that of size criteria in both cohorts. Wu *et al*[26] devised a multiple-level CT radiomics model with a demonstrable efficacy in predicting preoperative LNM in ESCC patients. The model integrated numerous radiomics signatures into clinical risk factors and exhibited a robust discrimination performance with a C-statistic of 0.840 in an independent external validation cohort.

EC is a challenging entity to manage with significant global impact. Treatment outcomes greatly depend on early and accurate diagnosis. Incorporation of AI-based diagnostic algorithms is paramount to circumvent the existential shortcomings in this space. AI-powered staging tools aid in the optimization of the treatment of patients, resulting in customized and efficacious therapies[27].

AI-ASSISTED TREATMENT AND PROGNOSTICATION OF ESOPHAGEAL CANCER

EC exhibits significant heterogeneity, and treatment responses may vary among patients. AI-powered precision medicine has the potential to tailor therapies based on individual patient characteristics, optimizing treatment efficacy and minimizing adverse effects. This section explores the evolving role of AI in the treatment of EC, highlighting its applications in treatment planning, precision medicine, treatment response prediction, and post-surgical prognosis prediction.

By integrating genomic data, medical histories, and treatment outcomes, AI algorithms can identify predictive biomarkers and potential drug targets. Li *et al*[28] have discussed the role of AI in single-cell sequencing and spatial transcriptomics, which are crucial for understanding cell compositions and novel cell types in EC. AI algorithms can analyze patient-specific imaging data, allowing for improved target delineation and more precise radiation planning[29]. Such advancements improve patients' quality of life and treatment compliance.

Adequate treatment response impacts further therapeutic decisions. Several investigators have trained AI models to predict histologic response to therapy. Li *et al*[30] conducted a multicenter study to assess the therapeutic efficacy of chemoradiotherapy in patients with locally advanced ESCC using a 3D-radiomics model based on pretreatment CT images. Response to treatment was predicted with a positive predictive value of 100% and AUC of 0.8 in radiation therapy plan, radiation field and prescription dose utilized. Ypsilantis *et al*[31] trained a CNN using pre-treatment PET-CT images, to predict response to neoadjuvant chemotherapy, and were able to attain accuracy of 73.4%, with sensitivity and specificity of 80.7% and 81.6% respectively. Warnecke-Eberz *et al*[32] developed an artificial neural network (ANN) system to analyze 17 genes with TaqMan low-density arrays in treatment of naive patients. Histologic response to neoadjuvant chemoradiotherapy was predicted with an accuracy of 78.1%, sensitivity and specificity of 75.0% and 81.0% respectively. This highlights that AI can play a crucial role in determining response to treatment modalities, which may greatly influence the care of EC patients.

Prognosis for patients with EC varies considerably, and several patients benefit from surgical resection if amenable. AI models can be used prognostically to guide post-operative treatment decisions. Xu *et al*[33] constructed 5 ML models for survival risk stratification in 810 patients who underwent surgery for ESCC. Of the five models, the XGBoost model demonstrated optimal performance with an AUC of 0.85. This model accurately predicted 5-year OS estimates in both training and validation cohorts across all three (low, moderate and high-risk) categories. PET scans are routinely employed in functional assessment of ESCC patients. Studies have trained 3D-CNN models using PET scan imagery to identify tumors with aggressive histopathological features and survival estimates in this group. Presence of variables like lymphovascular invasion (LVI) or perineural invasion (PNI) portend unfavorable prognosis[34,35]. Yeh *et al*[36] trained a 3D-CNN model using PET imaging to predict LVI/PNI, and obtained promising results. Yang *et al*[37] developed a deep-CNN model with 798 PET scans of ESCC to predict outcomes in this cohort, and notably obtained 1 and 5-year survival estimates with remarkable accuracy.

FUTURE PERSPECTIVES FOR AI IN ESOPHAGEAL CANCER

AI has demonstrated immense potential in transforming the landscape of EC treatment. AI can assist with treatment planning in radiation therapy by optimizing radiation dose distribution and minimizing damage to surrounding healthy tissues. AI-assisted therapeutic regimen guarantees that radiation dosage is correctly given to the tumor while shielding adjacent normal tissues as this framework considers the shape and location of the tumor and its relation to vital components[29]. AI models have the potential to predict histologic response to chemoradiotherapy and can also yield reliable survival estimates for patients undergoing surgical resection. This information could enable accurate prognostication and serve as a guiding tool for clinicians and patients during the decision-making process[33-35].

CHALLENGES FOR AI IN ESOPHAGEAL CANCER

The successful integration of AI into clinical practice necessitates rigorous validation, collaboration between AI developers and medical experts, and adherence to ethical standards. AI can be pivotal in ushering in an era of personalized and targeted therapies for EC patients based on specific tumor heterogeneity. The gap between AI model development and clinical implementation needs to be closed. Educating clinicians and fostering research in this arena can augment the incorporation of AI models into clinical practice, which could prove instrumental in optimizing survival outcomes.

AI-ASSISTED DIAGNOSIS AND STAGING OF GASTRIC CANCER

Gastric cancer (GC) is the fifth most common cancer and the third most common cause of cancer death globally. It is diagnosed histologically after endoscopic biopsy and staged using CT, endoscopic ultrasound, PET, and laparoscopy[38, 39]. Most cases are diagnosed at an advanced stage when the prognosis is poor and treatment options are limited. Unfortunately, the existing circulating diagnostic and prognostic biomarkers have low sensitivity and specificity and hence the diagnosis is based only on endoscopy. Some recently discovered circulating molecules (miRNAs, lncRNAs, circRNA) hold promise for development of new strategies for early diagnosis of GC, and discrimination between early GC and healthy subjects, with a sensitivity of more than 77.5%[40].

GC develops through a series of precancerous stages, including *helicobacter pylori* (*H. pylori*)-induced atrophic gastritis (AG), gastric intestinal metaplasia (GIM), dysplasia, and finally GC. Identifying these stages is essential for early detection and treatment of GC. AI-assisted diagnosis of AG and GIM has achieved an accuracy of approximately 90%, which is more accurate than predicting *H. pylori* infection[41-43]. Sensitivities ranging from 92.2% to 94.5% have been observed in AI-assisted early GC detection. Furthermore, AI-assisted detection systems have proven effective in reducing blind spots during endoscopy and enhancing early GC detection rates among less experienced endoscopists[44].

Recognizing that the ability of endoscopists to identify gastric lesions can vary, an AI system was developed and trained on 29809 images from 8947 patients, resulting in an accuracy rate of 85.7% in diagnosing six common gastric lesions. When integrated into clinical practice, the AI system notably enhanced the overall accuracy of both senior and junior endoscopists to 89.3% and 86.2%, respectively[45]. Goto *et al*[46] showed that AI-enabled assessment of invasion depth for early GC was superior compared to stand-alone endoscopist assessment (F1 measure - 0.78 *vs* 0.66). However, contemporary literature indicating comparable diagnostic efficacy of computer-aided models and experts for EGC exists, thereby warranting more well-powered prospective studies[47].

Primary gastric lymphoma (PGL) is a commonly diagnosed gastric malignancy that is difficult to differentiate from Borrmann type IV GC using conventional CT. The management for these two conditions varies significantly, with surgery being the primary treatment for GC, whereas PGL is best managed with chemotherapy and radiotherapy. A radiomics model demonstrated effective differentiation between Borrmann type IV gastric cancer and PGL with an AUC of 0.90[48], whereas a transfer learning model utilizing CT and whole slide images achieved high accuracy in distinguishing PGL from Borrmann type IV GC, with AUCs ranging from 0.92 to 0.99[49].

The prognosis of gastric adenocarcinoma (GA) is closely linked to its stage determined at diagnosis. GA is typically categorized into two groups: early GA (EGA) and advanced GA (AGA). EGA, involving the mucosa and submucosa (T1), boasts an impressive 5-year survival rate exceeding 90%. In contrast, AGA, with deeper infiltration (T2-T4), exhibits a 5-year survival rate ranging from 7% to 27%[50]. Clinical staging of GC is essential for determining the most appropriate treatment strategy. Endoscopic ultrasound (EUS) is used to assess tumor depth (T category) and nodal involvement (N category). However, its diagnostic accuracy can range from 57% to 88% for T staging and 30% to 90% for N staging. CT scanning is routinely employed for preoperative staging but has an overall accuracy ranging from 43% to 82% in measuring the depth of tumor invasion. (18)F-Fluorodeoxyglucose (FDG)-PET/CT imaging offers advantages over FDG-PET or CT alone, with a significantly higher accuracy rate in preoperative staging (68%) compared to FDG-PET (47%) or CT (53%) alone. In regions without screening programs for early detection, about 50% of patients present with advanced disease at diagnosis, which is associated with a poorer prognosis. Furthermore, the presence of metastases, poor performance status, and an alkaline phosphatase level ≥ 100 U/L are predictive of a less favorable outcome. The number of positive lymph nodes also significantly influences survival in patients with localized resectable disease[51].

Conventional CT-based GC staging is often erroneous, with accuracies ranging from 51.6% to 91.5%. For T-staging, distinguishing between different T stages, especially T1 and T2, a DL model namely Residual Neural Network, *i.e.* ResNet101, has demonstrably improved the accuracy to 91.4%-94.6%. However, AI models have not yet been implemented in clinical practice compared to EUS, which remains the preferred method. DL radiomics models have shown promise in serosal invasion assessment for T4a staging, achieving AUCs ranging from 0.76 to 0.90, but further clinical validation is needed. In addition, these models have enhanced detection rates for peritoneal metastasis and occult peritoneal masses (OPM) on CT scans, with AUC values ranging from 0.72 to 0.90, thereby outperforming conventional clinical models[52]. However, these models require manual segmentation of tumors[53].

Accurate assessment of tumor invasion depth is a critical factor in the diagnosis and treatment of GC. Traditional visual examination of endoscopic images is replete with challenges due to subtle morphological differences and subjective judgments, often requiring invasive histopathological examinations for definitive diagnosis. Kubota *et al*[54] applied the back-propagation algorithm to train a multilayer perception model, achieving acceptable diagnostic accuracies for different T stages of GC; 77.2% for T1, 49.1% for T2, 51% for T3, and 55.3% for T4. This AI-based approach demonstrated similar performance to expert endoscopists, particularly in T1a and T1b staging. Another study using

ResNet to classify lesions as P0 (T1a or T1b) and P1 (deeper than T1b), achieved an AUC score of 0.94, surpassing the sensitivity and specificity of endoscopists[55]. Yoon *et al*[56] applied the Visual Geometry Group (VGG) model, a type of deep CNN model, to classify T1a and T1b-EGC, that yielded an AUC of 0.85, with incorrect predictions associated with undifferentiated-type histology and T1b staging. Furthermore, Nagao *et al*[57] extended AI-based depth prediction to various endoscopic image modalities, including narrow band imaging (NBI) and Indigo-carmin dye contrast imaging, achieving high AUC scores of 94.5%, 94.3%, and 95.5% for white light imaging, NBI, and Indigo-carmin dye images, respectively.

AI-ASSISTED TREATMENT AND PROGNOSTICATION OF GASTRIC CANCER

Chemotherapy along with endoscopic or surgical resection is indicated for locally advanced GC. However, both neoadjuvant and adjuvant chemotherapy confer varying results in terms of their efficacy and survival benefit in these patients. Ensuring proper selection of chemotherapy agents and patient populations is important to improve outcomes and reduce adverse events from chemotherapy. AI-based models can be used to accurately predict treatment response in GC.

A DL radiomics model, adapted from multiphasic contrast-enhanced CT imaging, was developed by Li *et al*[58] to predict the profile of patients with signet ring cell carcinoma (SRCC) likely to benefit from postoperative chemotherapy. The model was applied to pathologically confirmed, advanced SRCC patients and it could accurately differentiate between patients with a high likelihood of chemotherapy resistance and shorter OS (without *vs* with chemotherapy median OS 31.0 *vs* 54.4 months, $P = 0.036$) *vs* those with low risk of resistance and substantial chemotherapy benefit (without *vs* with chemotherapy median OS 26.0 *vs* not reached, $P = 0.013$).

AI can also be used to find new biomarkers that would correlate with increased response to certain chemotherapeutics. Sundar *et al*[59] built a random forest machine learning model to analyze surgical samples and results from the Stomach cancer Adjuvant Multi-Institutional group Trial, a 2×2 factorial randomized phase III trial testing the efficacy of paclitaxel (Pac) as an additional chemotherapy agent to tegafur-gimeracil-oteracil (S-1) and tegafur-uracil (UFT). Out of 476 initial genes in their panel, the AI model was trained with the top 19 genes and applied to the Pac S-1 and PAC UFT cohorts. Those with low gene expression were shown to have increased survival benefit with paclitaxel compared to those with high gene expression in both cohorts.

Several ML models have shown promise in predicting GC prognosis including survival and risk of recurrence, by combining multiple factors. The Logistic Regression, Support Vector Machine, and Extreme Gradient Boosted Decision Tree models showed remarkable accuracy (89%) and AUC (0.87), outperforming a currently used risk assessment tool named ogRAT, *i.e.*, oesophagogastric cancer risk-assessment tool, and also had a higher sensitivity for cancer diagnosis compared with ogRAT[60].

Several studies have utilized ANNs in their risk prediction models. Que *et al*[61] predicted the 3-year OS using a preoperative ANN that showed an accuracy, sensitivity, and specificity of 75.2%, 86.5%, and 43.8% respectively. Another study showed that ANN-based survival prediction (AUC 0.81) was comparable with actual 5-year survival estimates, and survival outcomes were accurately classified with ANN when compared with the AJCC staging system[62]. Based on these findings, prognostication can be performed with an acceptable degree of certainty. Notably, these studies evaluated clinicopathological parameters like tumor diameter and TNM factors. Alternative stratification to the TNM classification to predict outcomes was not explored in these models.

Zhang *et al*[63] utilized CT imaging to train a DL model for GC prognostication with acceptable accuracy with C-indexes of 0.82 and 0.78 in the training and test datasets respectively. Jiang *et al*[64] developed a multitask DL model to predict peritoneal recurrence (PR) after curative intent surgery in GC patients, and showed that adjuvant chemotherapy improved disease-free survival (DFS) only for patients with a predicted high risk of PR and low survival, as opposed to patients with a low predicted PR risk and high survival. Similarly, Sun *et al*[65] trained a radiomics model using CT images to predict the likelihood of PR and benefit from chemotherapy in patients undergoing radical gastrectomy. The radiomics signature accurately predicted PR with AUCs of 0.73 and 0.72 in the training and validation cohort respectively. It significantly improved the diagnostic accuracy of PR by 10%-19% for clinicians ($P < 0.001$). Also, it was an independent predictor of PR and survival. Patients who had high scores for PR benefitted from adjuvant chemotherapy, unlike patients with low scores who didn't have any impact on their survival from chemotherapy. Prospective studies are required to validate such models to delineate the subset of high-risk patients that could potentially benefit from adjuvant therapies.

Cheong *et al*[66] developed an AI algorithm called NTriPath to identify prognostic molecular pathways in gastric cancer. The algorithm integrated pan-cancer somatic mutation data, gene-to-gene interaction networks, and pathway databases to identify prognostic cancer-associated molecular pathways. They then tested the clinical relevance of these subtypes and created a risk-scoring model to predict both OS and response to therapies including chemotherapy and immune checkpoint blockade. Kuwayama *et al*[67] evaluated GC prognosis using blood collection data, excluding clinicopathological features such as tumor depth and LNM, which are typically employed in the conventional TNM classification. These strategies were able to predict the 5-year OS and recurrence-free survival with acceptable accuracy. These advancements highlight the potential of AI in improving the prognosis and prediction of GC.

FUTURE PERSPECTIVES FOR AI IN GASTRIC CANCER

AI-assisted GC screening is a rapidly developing field with the potential to significantly reduce GC incidence and improve patient outcomes. AI-assisted endoscopic detection of GC has achieved comparable or higher performance than endoscopists, with an accuracy greater than 80%[41,42]. DL radiomics models can accurately distinguish between T stages, and also reliably predict PM and OPM[52]. AI-driven approaches offer promising solutions for accurate tumor invasion depth estimation in endoscopy, which is crucial for determining appropriate treatment strategies, such as endoscopic resection, and improving diagnostic accuracy[54-57]. AI models can also be used to predict treatment response and risk of recurrence in GC patients. This information could be used to develop customized treatment plans based on specific patient and tumor profiles[61-66].

CHALLENGES FOR AI IN GASTRIC CANCER

Challenges such as data scarcity, poor interpretability, and generalization persist. AI models are often convoluted and lack transparency. Also, DL radiomics models used for GC staging require manual segmentation of tumors, which is time-consuming and has not been validated in many external validation cohorts. This remains a persistent challenge across TNM staging studies, limiting their practical application in clinical practice[53]. Unified processing procedures, data regulation, and advanced algorithms are needed to build more accurate and robust AI models.

AI-ASSISTED DIAGNOSIS AND STAGING OF COLORECTAL CANCER

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of death worldwide. AI models have demonstrated potential in predicting the risk of CRC development in individuals. ML algorithms can analyze vast datasets, encompassing genetic, lifestyle, and medical history information, to identify patterns and risk factors associated with the disease. Such risk prediction models can aid clinicians in identifying high-risk patients who may benefit from increased surveillance or preventive measures[68].

Colonoscopy has always been regarded as the gold standard procedure for diagnosing CRC. Because of significant inter-operator variability and frequent inadequate preparation, the detection rate of polyps and adenomas during early CRC screening can fluctuate substantially. To address this issue, researchers have employed CAde systems utilizing DL algorithms to enhance the efficiency and precision of CRC clinical detection while minimizing the likelihood of missed lesions[69]. Certain adenomas and polyps identified through real-time CAde may be small and pose low risk, yet they are often overlooked and missed during conventional colonoscopy examinations. Missed colorectal neoplasia is associated with post-colonoscopy CRC development. AI-assisted colonoscopy can effectively improve the adenoma detection rate (ADR) and help reduce the incidence and mortality of CRC patients[70]. Additionally, AI-based colon capsule endoscopy increases the sensitivity of polyp detection through enhanced polyp visibility and better delineation of morphology and significantly reduces the screening time[71].

In a multicenter randomized control trial, overall ADR per colonoscopy was significantly higher in the AI-assisted colonoscopy group compared to the conventional colonoscopy group, for both advanced and non-advanced adenomas, for adenomas < 5 mm and ≥ 10 mm, for non-pedunculated adenoma, and in both proximal and distal colon. Consequently, there were more adenoma resections which may translate to improved long-term cancer prevention[72]. Similar conclusions were obtained in a prospective study, with the results showing that AI-assisted experienced endoscopists identify more adenomatous lesions that are otherwise difficult to identify[73].

CAde systems do not address exposure errors, but new computer-aided quality-assessment systems are being investigated. An AI-based system for measuring fold evaluation quality (FEQ) demonstrated a significant correlation with expert scores, historical ADR, and withdrawal time. For colonoscopies performed by colonoscopists with previously low ADRs (< 25%), AI assistance significantly improved the FEQ[74], and reduced the incidence of missed adenomas during colonoscopy as nearly 80% of these lesions that get overlooked by endoscopists, are detected by AI. AI serves as a complementary "eye" for the endoscopist, unaffected by distractions and fatigue. However, approximately 20% of missed adenomas are not even visible on the screen, often located behind folds, in challenging flexure positions, or concealed under fecal content in cases of poor bowel preparation[75].

Nodal metastases are invariably a key determinant of DFS and OS in patients with CRC[76]. It has a substantive impact on the staging process, consequentially dictating the implementation of appropriate adjuvant and neoadjuvant therapies. Staging is based upon contrasted CT imaging in CRC cases, with additional MR imaging in patients with rectal cancer. Staging accuracy is contingent on a multitude of factors, namely reporting radiologist's expertise, equipment performance, employed imaging protocols, and patient-related factors. Current evidence suggests that CT and MR imaging have a diagnostic accuracy (for nodal metastases detection) measuring 70 and 69% respectively with the application of standard criteria[77,78]. Pre-operative MRI-based staging has mainstreamed neoadjuvant chemoradiation into locally advanced rectal cancer (LARC) management, and afforded superior blueprints for resectability, and enhanced locoregional control. Neoadjuvant therapy, however, is not commonplace in colon cancer management due to subpar nodal staging accuracy in this cohort[79]. Notably, the results of the FOXTROT trial demonstrating robust safety and efficacy estimates for neoadjuvant therapy could potentially alter the current paradigm[80]. Augmentation of nodal staging modalities is paramount to bring about this change, and AI is a powerful tool that can overcome the shortcomings of contemporary diagnostics.

Ito *et al*[81] demonstrated that CNN-based diagnosis of cT1bCRC yielded a sensitivity, specificity, accuracy, and AUC of 67.5%, 89.0%, 81.2%, and 0.871 respectively. Another study showed that AI-based determination of the need for surgery after endoscopic resection of T1CRC is more accurate compared with the current guidelines, thereby preventing unwarranted surgeries in this select group of patients. The model employed in this study, which took into account 45 clinicopathologic factors, yielded a sensitivity, specificity, and accuracy of 100%, 66%, and 69%, respectively[82].

MRI is the gold standard tool for detecting CRC LNM before surgery. Of note, studies utilizing faster region-based CNNs have outperformed senior radiologists in metastatic LN detection with MR imaging[83,84]. Lu *et al*[83] showed that their CNN-based model (AUC 0.91) clinched diagnosis in 20 s compared with radiologists who took 600 s. Another study looking at the utility of a LASSO-based ML algorithm incorporating histopathologic variables and tumor-infiltrating leukocytes outperformed conventional criteria in predicting LNM in T1CRC cases[85]. An AI-based model developed with 152 CT-based tumor variates and 6 clinical variates, to detect CRC hepatic metastases, enhanced the accuracy of both validation (85.5%) and training sets (90.63%) with an AUC of 0.87 and 0.96 respectively[86]. Additionally, highly accurate and expeditious DL models have been developed recently for CRC localization and segmentation on MR imaging, which need to be iterated and validated further with randomized controlled studies[87,88].

AI-based radiomics nomograms and DL algorithms have remarkably impacted the accuracy of radiologic diagnosis and staging. Radiomics models analyze a vast number of investigator-determined characteristics from a large database using advanced computational tools. AI models have attained partial success in the detection of nodal metastases thus far, but several studies have concluded that DL algorithms can successfully search through and filter out anomalies that are elusive to conventional staging diagnostics[89,90]. Further research to yield advanced iterations of these AI models can prove instrumental in obtaining robust diagnostic and staging estimates.

AI-ASSISTED TREATMENT AND PROGNOSTICATION OF COLORECTAL CANCER

AI can integrate and analyze vast amounts of data generated during colon cancer diagnosis and treatment, and provide real-time decision support to clinicians. Newer technologies in colorectal surgery are using mathematical algorithms, 3D imaging, and AI to improve patient outcomes. 3D image processing and reconstruction are being used in colorectal surgical oncology, specifically focusing on complete mesocolic excision and D3-lymphadenectomy in colon cancer cases. The system effectively delineates the margins around the tumor, including the vascularization, and provides critical information for surgical planning[91]. Several AI models have been evaluated in the context of laparoscopic colorectal resections. Kitaguchi *et al*[92] constructed a multicentric dataset of 300 Laparoscopic colorectal surgery videos and were able to recognize phase, action, and tool with high accuracy. Overall accuracies for action task classification and surgical phases were 83.2% and 81% respectively, with a reasonable tool segmentation performance, as depicted by an intersection of union (IoU) value of 51.2%. Accuracy for the phase and action recognition was 81% and 87% for transection and anastomosis phases, respectively. Semantic segmentation of surgical instruments resulted in mean IoUs ranging from 33.6% to 68.9%. Kitaguchi *et al*[93] developed another AI model using 50 transanal total mesorectal excision videos that yielded an overall accuracy of 93.2% for phase recognition and 76.7% for combined phase and step recognition. Supervised ML models are being used during robotic rectal resection procedures. In a recent study, ML-based intraoperative guidance during total mesorectal excision (TME) yielded higher mean F1 scores for Gerota's fascia (0.78) and mesocolon (0.71), but lower scores for the dissection plane (0.32) and exact dissection line (0.05)[94]. Igaki *et al*[95] developed a DL model using 600 intraoperative TME images that could accurately delineate the oncologic dissection plane with a dice coefficient of 0.84.

Robotic surgery, novel computer-assisted drug delivery techniques, and ML models can potentially revolutionize CRC treatment and personalize cancer care. AI models have been developed to predict the half-maximal inhibitory concentration of anti-cancer drugs against the human colon carcinoma HCT116 cell line with an overall prediction accuracy of over 63%[96]. DNNs have also been used to develop anticancer drugs that inhibit PI3K alpha and tankyrase, with promising results[97]. Nanoparticles are being explored as pharmaceutical carriers for tumor targeting[98]. Computer-aided magnetotactic displacement techniques have been proposed to navigate and deliver drug-loaded magnetotactic bacteria MC-1 toward the hypoxic areas of tumors[99]. MRI-based AI models have also been developed to predict the pathological complete responder and non-responder patients with LARC after neoadjuvant chemoradiotherapy with an AUC of 0.86 and 0.83, respectively[100].

ML can extract disease severity prediction models from electronic medical records, and address aspects of timeliness, imprecision, and integrity. ML can be used to develop multi-method integrated models trained with large data input to prognosticate CRC patients by analyzing data pertaining to genetic and environmental variations amongst CRC patients and cancer-free controls[101]. Reliable multistage survival prediction models have also been developed for prognostication of patients with advanced CRC[102]. Semi-supervised learning methods use labeled or unlabeled data and graph regularization to predict patient survival and cancer recurrence. Recent literature has shown that the use of semi-supervised learning models can improve generalizability for CRC risk prediction models. A recent study employed a semi-supervised learning logistic regression model to establish a clinical prediction model of CRC survival risk that reportedly had good correction ability, popularization, interpretability, and clinical practicability after its performance was strictly compared with that of other existing supervised learning models[103]. Bychkov *et al*[104] trained a deep network using convolutional and recurrent architectures to predict outcomes based on tissue morphology. The model could accurately prognosticate these patients using small tissue areas as input and interestingly outperformed human experts on both tissue spot and whole slide levels across high and low-risk patient strata.

Chemotherapy plays a crucial role in influencing the prognosis of patients with both surgically removable and non-removable colorectal liver metastases (CRLM). AI models can predict chemotherapy response and early local tumor progression after ablative therapies in CRLM patients. Maaref *et al*[105] developed a DL- CNN that achieved an accuracy of 0.91 (95%CI: 0.88-0.93) for distinguishing treated and untreated lesions, and 0.78 (95%CI: 0.74-0.83) for predicting response to a chemotherapeutic regimen (AUC 0.82), and 92% sensitivity and 86% specificity for predicting therapeutic response in patients with HER2 amplification (AUC 0.78). Wei *et al*[106] used CECT imaging to train a DL radiomics model that accurately predicted CRLM response to different chemotherapeutic regimens with an AUC of 0.82 in the validation cohort. The predictive power increased to 0.93 when the DL model was used in conjunction with serum CEA level. Taghavi *et al*[107] developed predictive models using radiomics, and clinicopathological characteristics, that were highly predictive of CRLM development within the next 2 years with an AUC of 86% in the validation cohorts. These models have the potential to enhance oncological outcomes in CRLM patients, but further research is needed to elucidate and integrate these models into clinical practice[108].

FUTURE PERSPECTIVES FOR AI IN COLORECTAL CANCER

AI-driven decision support systems can present relevant patient information, suggest appropriate treatment plans, and offer insights into potential clinical trial options. CRC risk prediction models can be useful in the identification of high-risk individuals who can benefit from closer cancer surveillance[68]. Routine use of CADe systems can significantly increase the colonoscopic yield of neoplastic lesions[69]. Augmentation of pre-operative MR imaging with ML algorithms to detect LNM can help identify candidates for neoadjuvant therapy in LARC cohort[83,84]. AI models can also help with surgical planning and guide surgeons intra-operatively by delineating the best oncologic resection plane(s)[92-94]. AI-based risk prediction models can yield accurate estimates for survival, cancer recurrence, and the likelihood of response to therapy[102,105-107].

CHALLENGES FOR AI IN COLORECTAL CANCER

Detection of nodal metastases using AI-based models has achieved only partial success so far. Also, the literature available on AI-based CRC management is sparse. The robustness of these AI algorithms depends on the amount and quality of data inputted. Unfortunately, several existing AI models are based on retrospective analyses, and have strict inclusion and exclusion criteria, thereby limiting widespread clinical application. Further well-powered prospective studies are needed to yield advanced iterations of these AI models, and test their performance in the real world.

CONCLUSION

Development of diagnostic and prognostic tools where AI interfaces with humans to enable accurate pathologic, endoscopic, and radiologic tumor detection and assessment. An integrative approach harnessing the computational efficacy of these novel algorithms for image-based diagnosis and prognostication, combined with existing clinical expertise could synergistically prove instrumental in reducing the miss rates of neoplastic lesions. AI can be pivotal in ushering in an era of personalized and targeted therapies based on specific tumor heterogeneity. However, we need well-powered, randomized trials to determine the diagnostic and prognostic potential of these algorithms. Challenges like interpretability, data scarcity, and generalization remain. AI models are often complex and lack transparency, making it difficult to understand how these decisions are made. These shortcomings can be addressed by training and validating AI models using large amounts of high-quality data. The gap between AI model development and clinical implementation needs to be closed. Successful integration of AI into clinical practice necessitates rigorous validation, collaboration between AI developers and medical experts, and adherence to ethical standards.

FOOTNOTES

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Ultra-minimally invasive endoscopic techniques and colorectal diseases: Current status and its future

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Abstract

Colorectal diseases are increasing due to altered lifestyle, genetic, and environmental factors. Colonoscopy plays an important role in diagnosis. Advances in colonoscope (ultrathin scope, magnetic scope, capsule) and technological gadgets (Balloon assisted scope, third eye retroscope, NaviAid G-EYE, dye-based chromoendoscopy, virtual chromoendoscopy, narrow band imaging, i-SCAN, etc.) have made colonoscopy more comfortable and efficient. Now *in-vivo* microscopy can be performed using confocal laser endomicroscopy, optical coherence tomography, spectroscopy, etc. Besides developments in diagnostic colonoscopy, therapeutic colonoscopy has improved to manage lower gastrointestinal tract bleeding, obstruction, perforations, resection polyps, and early colorectal cancers. The introduction of combined endo-laparoscopic surgery and robotic endoscopic surgery has made these interventions feasible. The role of artificial intelligence in the diagnosis and management of colorectal diseases is also increasing day by day. Hence, this article is to review cutting-edge developments in endoscopic principles for the management of colorectal diseases.

Key Words: Colorectal disorders; Ultra-minimally invasive scopes; Advanced gadgets; Endoscopic intervention; Combined endo-laparoscopic surgery

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Core Tip: Diagnostic and therapeutic endoscopy is evolving in the management of colorectal diseases. The rigid scopes have given way to flexible and capsule scopes. Conventional white light endoscopes have been replaced by high-definition and modified image enhancements. Now, both diagnosis and *in-vivo* histology assessment could be feasible. Therapeutic endoscopy has evolved to manage selective colorectal disorders for which surgery was considered the standard of care in the past. The role of robotics and artificial intelligence is indispensable.

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INTRODUCTION

Diseases of the colorectum encompass various benign and malignant conditions with varied morbidity and mortality. Proximity to the anal opening makes the colon and rectum accessible to diagnostic and therapeutic colonoscopy. The first colonoscopy was developed from one made by Philipp Bozzini (1805), the father of endoscopy[1]. The initial colonoscopes were limited by less flexibility and poor illumination. Modern scopes facilitate cecal intubation, prevent loop formation, and patient satisfaction with fewer adverse events[2]. Thin-caliber colonoscopes, magnetic flexible colonoscopes, and capsule colonoscopes are getting popular due to lesser patient discomfort and better efficiency. The technical developments in colonoscopes include light sources, flexible and torque-stable shafts, fiber optics, four-way angulation control, charge-coupled devices for image sensing, and the ability to produce a high-quality digital image. Nevertheless, it is multifunctional as it can be used for suction, insufflation with air or water, and biopsy with a shaft. Presently, high-definition-white light endoscopy is the standard vision system[3] and the developments in this field are expanding (Table 1). Other advancements include endocuff vision, amplify EYE, and G-EYE devices to enhance the mucosa and improve the gaze of vision. The introduction of artificial intelligence (AI) algorithms has made endoscopists' jobs easier and more efficient for the detection of missing lesions which are prone to human errors.

Along with the diagnostic evolution of colonoscopes, the realm of therapeutic intervention is expanding. The first colonoscopic intervention was a polypectomy using loop snare-cautery[4]. Nowadays, therapeutic colonoscopy can be used for the management of lower gastrointestinal (GI) bleeders, colorectal strictures, malignant large bowel obstructions, colorectal perforations, foreign body removal, *etc.* The endoscopic resection of early colorectal cancer (CRC) becoming the standard of care as it is associated with fewer morbidity[5,6]. Hirschsprung's disease where surgery was once considered the only treatment, nowadays per-rectal endoscopic myotomy has shown good results in a few case reports. Similarly for malignant colonic polyps, segmental colectomy was considered the standard of care, where endoscopic polypectomy is considered a reasonable treatment modality and recommended by NCCN guidelines[4]. Similarly, for post-colonoscopy perforation, surgical management was considered as the standard of treatment, with the advent of endoscopic skills, and gadgets like clips, it is possible to avoid surgery in these patients. In this article, we shall discuss the role of minimally invasive endoscopic techniques in the diagnosis and management of colorectal disorders and their prospects.

DEVELOPMENT OF ULTRA-MINIMALLY INVASIVE ENDOSCOPE

It's a narrow caliber scope to reduce discomfort, require less sedation, and improve therapeutic efficacy. A randomized controlled trial (RCT) of 220 females in whom pain following colonoscopy was reported to be higher, has shown that ultra-thin colonoscopy was reportedly less painful than conventional colonoscopy[7]. It can be easily negotiated beyond the stenotic segment to assess the proximal bowel. In a prospective study on 100 stenotic CRC patients, Ito *et al*[8] found 65.5% synchronous lesions in the proximal colon. Magnetic flexible colonoscopy has a similar function as a conventional colonoscopy; however, it is more patient-friendly due to less looping of the scope[9]. The mechanism includes a "front-pull" rather than a "push technique". The forward mechanism prevents buckling of the instrument and resultant pain, and perforation. Capsule colonoscopy is a non-invasive method of screening; however, it requires aggressive bowel preparation as a small amount of debris can affect the capsule mobility. European Society of Gastrointestinal Endoscopy guideline recommends the use of second-generation capsules for screening of average risk of CRC where previous colonoscopy failed due to difficult scope progression[10].

DEVELOPMENT OF NEWER ENDOSCOPIC TOOLS AND GADGETS

Enhanced field of vision of colonoscope

The Third Eye Retroscope (TER; Avantis Medical Systems, Sunnyvale, CA, United States) is an optical technology to detect polyps located at the proximal folds and the flexures. In a pilot study of 29 human subjects, out of 38 polyps, 34 polyps could be detected with a forward scope whereas 4 additional polyps were detected using TER (11.8% increase in

Table 1 Technological advancement in endoscopic diagnosis and treatment of colorectal diseases

No.	Techniques	Technology	Clinical use diagnostic/therapeutic	Ref.
1	Chromoendoscopy	Real-time tissue enhancement using biocompatible dyes	Polyp and adenoma detection, differentiation of benign from malignant lesions, dysplasia associated with IBD	[111-114]
2	Narrow band imaging	Physical spectral filters generate narrow bands of 415 and 540 nm in center wavelength	Adenoma detection, dysplasia associated with IBD	[115, 116]
3	Blue light imaging	Narrowed spectrum LED light of 410 nm and 450 nm enabling haemoglobin excitation and a positive mucosal contrast	Differentiation of non-neoplastic from neoplastic lesions, <i>in vivo</i> histology	[117-119]
4	Autofluorescence endoscopy	Fluorescence of fluorophores differentiate tissues	Adenoma detection, differentiation of non-neoplastic lesions from neoplastic lesions	[120-123]
5	Flexible spectral imaging color enhancement	This differentiation is based on the surface capillary pattern	Differentiation of non-neoplastic from neoplastic lesions, <i>in vivo</i> histology	[124-126]
6	Linked color imaging	Pre-processing narrow band LED radiation and post-processing color technology to separate imported colors into red, green, and blue what enhances color differences	Polyp detection	[127-129]
7	i-SCAN	Enhancement of the image contrast through a real-time post-processing algorithm, basing the different reflective properties of normal and abnormal mucosa	Adenoma detection, <i>in vivo</i> histology, disease activity in IBD, detection of neoplasia in IBD	[130-133]
8	i-SCAN OE	Incorporation of a digital pre-processor optical enhancement to improve visualization of mucosal vascular pattern	Detection of pre-malignant lesions	[134]

IBD: Inflammatory bowel disease; LED: Light emitting diode.

the yield)[11]. The newer version, Third Eye Panoramic (Avantis Medical Systems) uses a video cap containing two side viewing lenses fitted into the standard colonoscope limits the drawbacks of primitive TER *i.e.*, technical learning curve, duration of the procedure, and cost[12].

The Fuse Full Spectrum Endoscopy® colonoscopy (EndoChoice Inc., Alpharetta, GA, United States) has a high resolution and 330° field of view. In a multicentre RCT, Fuse colonoscopy reported a significantly lower adenoma miss rate (7.5% *vs* 40.8%, $P < 0.0001$)[13]. Hence, the use of Fuse colonoscopy for colorectal screening and surveillance can be more useful. The extra wide-angle view colonoscope could detect significantly more polyps compared to the standard one (68% *vs* 51%, $P < 0.0001$)[14], and the detection of polyps behind the folds was also significant (62% *vs* 47%, $P = 0.0009$)[14].

Technical advances to improve colonoscopic access

The NaviAid G-EYE System (SMART Medical Systems Ltd, Ra'anana, Israel) comprises the G-EYE balloon colonoscope and the NaviAid SPARK2C inflation system which facilitates the straightening of haustral folds and flexures. In a RCT, compared to standard colonoscopy, NaviAid G-EYE balloon colonoscopy could detect an additional 17 (81%) adenomas among 106 patients[15]. Cap-assisted colonoscopy is used to improve the visualization of colonic epithelium. A meta-analysis including 12 studies (6185 patients) reported the detection of significantly more number of polyps [odds ratio (OR) = 1.13; $P = 0.030$], lower polyp miss rate (12.2% *vs* 28.6%), and higher cecal intubation rate (OR = 1.36, $P = 0.020$) with cap-assisted colonoscopy compared to conventional colonoscopy[16]. EndoCuff and EndoRings are similar to the cap-assisted colonoscopy, the device mounted over the scope helps to flatten the colonic folds during the withdrawal, hence, improving visualization. An RCT of 500 individuals reported a higher adenoma detection rate (ADR) with Endocuff-assisted colonoscopy compared to standard scope (35.4% *vs* 20.7%, $P < 0.0001$)[17]. A meta-analysis (6038 patients) comparing the Endocuff *vs* conventional colonoscopy demonstrated an increase in ADR [risk ratio (RR) = 1.18], especially in those endoscopists with an ADR < 35%, thus, improving the efficiency of novice endoscopists[18]. The EndoRings works with similar principles and an RCT (CLEVER Study) has shown a lower adenoma miss rate (10.4% *vs* 48.3%, $P < 0.001$) and a lower polyp miss rate (9.1% *vs* 52.8%, $P < 0.001$)[19].

Image enhancing techniques

Conventional white light endoscopy has several limitations which were minimized by various techniques. Chromoendoscopy uses various stains during endoscopy to enhance differences in the mucosa, and dysplastic or neoplastic lesions that are not apparent in white light. A prospective trial of targeted use of dye in patients with inflammatory bowel disease (IBD), demonstrated a significantly higher detection of dysplastic lesions than in standard colonoscopy[20]. Currently, SCENIC guidelines for the management of dysplasia in patients with IBD strongly recommend the use of chromoendoscopy[21].

The limitations of dye-based chromoendoscopy (operator dependency, time-consuming, lack of standardization of dilution methods, need for additional instruments, risk of met-hemoglobinuria, cost-effectiveness, risk of carcinogenesis, *etc.*) can be abrogated with the use of digital chromo-endoscopy including narrow-band imaging (NBI), Fuji intelligent

chromo-endoscopy, i-SCAN, blue laser imaging, linked color imaging, *etc.*[22-25]. American Society for Gastrointestinal Endoscopy strongly recommends the use of advanced imaging techniques by expert endoscopists[26].

In-vivo histology

Various technical advancements can be used to assess the type of epithelium during colonoscopy. Confocal laser endomicroscopy can help to differentiate benign from malignant lesions, advanced adenomas, and adenomatous polyps with high sensitivity and specificity without histology[27]. Endocytoscopy involves staining the colorectal mucosa and visualization at a higher magnification and its accuracy in differentiating benign from malignant lesions was 94.1% compared to 96% on histopathology for differentiating neoplastic lesions from non-neoplastic lesions[28]. Optical coherence tomography is based on the use of infrared light to measure the optical reflectivity of tissue and hence; the differentiation of benign from malignant lesions in real-time based on microstructural images with high resolution[29]. Spectroscopy is based on the principles of light scattering and the vibrational and rotational aspects of molecules provide clues about the type of tissue (benign *vs* malignant, adenomatous *vs* non-adenomatous)[30]. A study has reported an accuracy of 83% to 88% in spectroscopy in differentiating benign from malignant lesions[31].

Robotics in colonoscopy

Since the inception of robotics, its use in the medical field has been growing. The unique locomotion and adaptability of the colorectum make it feasible to use these new-generation colonoscopes[32]. The robotic colonoscope is more comfortable and less painful to the patient[33]. Currently, only the Endotics system (Era Endoscopy, Cascina, Pisa, Italy) is available for use and it is based on an electro-pneumatic self-advancing locomotion mechanism. This colonoscope is controlled by a hand-held device and consists of a disposable scope (called E-Worm) and it advances using two claspers located at both ends of the scope. Repetitive movements of lengthening and shortening allow the locomotion of the probe as that of a worm which is generated by a hydro-pneumatic system inside the probe. The advantages of the current Endotics system include reduced pressure on the colonic wall during advancement, reduced pain, discomfort, learning curve, complications, and comparable adenoma detection to conventional colonoscopes[34-36]. However, it requires a higher degree of colon cleansing due to the small suction channel[36]. Small series have reported fewer cecal intubation rates[34,35]. Other robotic systems that are not available for clinical practice are NeoGuide Endoscopy System, Invendoscope SC40, Aer-O-Scope System, ColonoSight System, Robotic-assisted Colonoscopy Capsule, *etc.* To curb the drawbacks of the Robotic Colonoscope, Li *et al*[37] developed a visual servo-based semi-autonomous manipulation of an electromagnetic actuated soft-tethered colonoscope which will improve the autonomy of conventional robotic colonoscope, to decrease the user workload, and promote its use in clinical practice.

AI in colonoscopy

Mr. John McCarthy coined the term “Artificial intelligence (AI)”, and since then it has evolved and infiltrated into day-to-day life and facilitated diagnostic and therapeutic interventions of medicine[38]. It helps to increase the ADR (CADe; computer-aided detection), and characterization of the lesion (CADx; computer-aided diagnosis). In a study by Abdelrahim *et al*[39] AI technique can detect more polyps compared to endoscopists (for < 5 mm polyps, AI can detect 81.2% polyps *vs* endoscopist 66%, $P < 0.001$, for > 5 mm polyps, AI can detect 87.5% polyps *vs* 42.3% with endoscopists, $P < 0.001$). The CADx can provide histopathological diagnosis using NBI, linked-color imaging, blue-color imaging, magnifying endoscopy, confocal laser endoscopy, autofluorescence imaging, *etc.* A recent systematic review and meta-analysis of RCTs (33 trials involving 27404 patients) of AI-aided colonoscopy *vs* conventional colonoscopy showed a significantly higher polyp detection rate [RR = 1.238; 95% confidence interval (CI): 1.158-1.323], ADR (RR = 1.242; 95%CI: 1.159-1.332), polyps and adenoma per colonoscopy[40]. The role of AI in the management of IBD is immense. In cases of ulcerative colitis, it helps to assess endoscopic remission. In a systematic review and meta-analysis of 18 studies (13687 patients), the pooled sensitivity and specificity of diagnosis of endoscopic remission were 87% and 92%, respectively and the area under the curve (AUC) was 0.96 (95%CI: 0.94-0.97)[41]. In Crohn’s disease, an AI algorithm based on computed tomography enterography can be used to assess the bowel and mesentery, which can predict the time interval to surgery with an AUC of 0.896[42]. Table 2 shows various commercially available CAD systems. Though AI-based colonoscopy algorithms have shown the potential to expedite diagnosis and further therapeutic intervention, however, there are a few limitations including ethical challenges, privacy, transparency and trust, cybersecurity, responsibility, bias, and data quality assurance[43,44]. These technical and technological advancements have made colonoscopy more comfortable and efficient (Figure 1).

ADVANCES IN MINIMALLY INVASIVE ENDOSCOPIC THERAPEUTICS

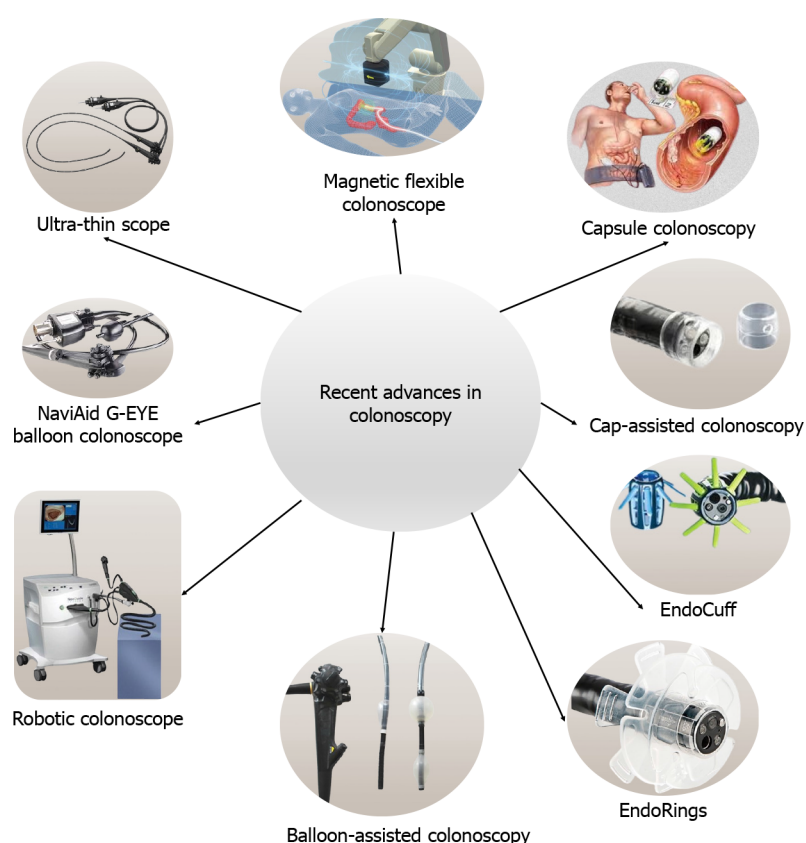
Colonoscopy has evolved from a diagnostic modality to interventions, for which surgery was once considered the standard of care. The first colonoscopic intervention was a polypectomy performed in the year 1969 using a loop snare-cautery device[45]. Colonoscopy has its place in interventions including localization of lower GI bleeding and management, dilatation of colorectal stenosis, management of colorectal perforation, foreign body removal, and many more[5,6].

Lower GI bleeding

The indications for surgery in lower GI bleeding are decreasing as 80% of lower GI bleeding resolves spontaneously and the majority of the rest can be managed endoscopically or through intervention radiology[46]. Most of the patients with

Table 2 Commercial artificial intelligence algorithms and its clinical use in colorectal diseases[135]

No.	Product name	Company	Integration	CAD mode	Regulatory (country, year)	Clinical use
1	EndoBRAIN	Cybernet System Co. (Tokyo, Japan)	CF-290ECI, Olympus Co.	CADx	Japan, 2018	Colorectal polyps endocytoscopy-computer-aided diagnosis
2	EndoBRAIN-EYE	Cybernet System Co.	Olympus colonoscopes	CADe	Japan, 2020	Colorectal polyps endocytoscopy-computer-aided diagnosis
3	EndoBRAIN-PLUS	Cybernet System Co.	CF-290ECI, Olympus Co.	CADx	Japan, 2020	Image enhanced colonoscopy
4	EndoBRAIN-UC	Cybernet System Co.	CF-290ECI, Olympus Co.	CADx	Japan, 2020	Image enhanced colonoscopy
5	GI Genius	Medtronic Co. (Dublin, Ireland)	Multi vendors possible	CADe	United States, Europe, 2019	Colorectal polyps
6	DISCOVERY	Pentax Medical Co. (Tokyo, Japan)	Pentax colonoscope	CADe	Europe, 2020	Colorectal polyps
7	ENDO-AID	Olympus Co. (Tokyo, Japan)	Olympus colonoscopes	CADe	Europe, 2020	Colorectal polyps, real-time aid, texture and color enhancement imaging
8	CAD-EYE	Fujifilm (Tokyo, Japan)	Fukifilm colonoscope	CADe CADx	Europe, Japan, 2020	Colorectal polyps, real-time aid
9	EndoScreener	Shanghai Wision AI Co. (Shanghai, China)	Multi vendors	CADe	Europe, United States, 2021	Colorectal polyps
10	WISE VISION	NEC Co. (Tokyo, Japan)	Multi vendors	CADe	Japan, Europe, 2020	Colorectal polyps


Figure 1 Recent advances in colonoscopy.

lower GI bleed are at high risk for surgical intervention and the mortality rate for emergency surgery is nearly 10%[47]. Endoscopic treatment is commonly used are diverticular bleeding and angiodysplasias. The treatment options include clipping, band ligation, endoscopic detachable snare ligation, thermal cauterization, and epinephrine injection[48-50]. Epinephrine injection has a 20% rebleeding rate[51]. A clip can be applied to the neck of the diverticulum to stop bleeding [51]. Many studies have shown the superiority of band ligation for controlling diverticular bleeding and can be performed safely by trainees[52]. Similarly, in a meta-analysis of 384 colonic diverticular patients, band ligation was more efficacious than clips[50]. Colonic angiodysplasia accounts for 3%-15% of lower GI bleeding and it increases with age, argon plasma coagulation is the preferred treatment and reported efficacy in various studies[53].

Lower GI obstruction

Therapeutic colonoscopy can be used to manage lower GI obstruction. In cases of malignant colorectal obstruction metallic stent has shown its use[54]. In a meta-analysis of 12 studies, metallic stenting has shown a higher primary anastomosis rate, lower complications, and no difference in mortality when compared to emergency surgery[55]. Decompressive colonoscopy can be used for the management of pseudo-obstruction (Ogilvie syndrome)[56,57]. Colorectal stenosis is amenable to pneumatic dilatation. In a study of 40 patients with postoperative colorectal anastomotic site stricture, the restructure rate following pneumatic dilatation was 12.5% after a median follow-up of 5 years[58]. For ileocolic stricture in Crohn's disease surgical resection is associated with more complications (32.2% *vs* 4.7%; $P < 0.0001$), however, there is less requirement for secondary surgery and longer surgery-free survival (11.1 ± 0.6 *vs* 5.4 ± 0.6 years; $P < 0.001$)[59]. Recently, endoscopic incision has shown potential use for anastomotic stricture dilatation [60].

Endoscopic access to sub-epithelial space is limited, however, recent developments in third-space endoscopy have expanded the use of endoscopic techniques in the diagnosis and management of mesenchymal tissues of the GI tract. Inoue *et al*[61] reported the first case of per-oral endoscopic myotomy for the treatment of achalasia cardia. Kulkarni *et al* [62] reported a case of per-rectal endoscopic myotomy in a 19-year-old girl for Hirschprung's disease with clinical and manometry improvement at 9 months follow-up.

Colorectal malignancy

For endoscopically detected non-pedunculated colorectal polyps > 10 mm the conventional endoscopic mucosal resection (CEMR) is considered as an effective method with a technical success rate between 90% and 100%[63]. In conventional EMR, a cushion is created between the lesion and the muscle layer with a submucosal injection which decreases the risk of thermal injury and perforation, however, it increases the technical difficulties[63-66]. The risk of recurrence following CEMR is between 15%-50%[67]. To curtail the limitations of CEMR, Binmoeller *et al*[68] proposed an alternative way or EMR, underwater EMR (UEMR). Water emersion has certain advantages including reduction of haustral folds making easy snare capture[69]. Lenz *et al*[70] compared CEMR with UEMR in an RCT and UEMR reduced the recurrence rate from 15% with CEMR to 2%.

Endoscopic submucosal dissection (ESD) is considered a better alternative to EMR with higher curative resection and lower recurrence rates[71-74]. However, it is performed using one endoscope which limits traction during the procedure leading to technical challenges. The recent development of traction wire (ProdiGI Traction Wire®; Medtronic, Minneapolis, MN) can provide continuous traction throughout the procedure making it easier[75]. Another development is the use of double-scope ESD, where 2 separate endoscopes were used for separate traction and cutting, being used for upper GI and colorectal lesions[76,77]. Several modifications of traction during ESD include clip with line method, spring-and-loop with clip, clip and snare method, and magnetic method. Endoscopic full-thickness resection (EFTR) is indicated in adenomas, intramucosal carcinomas, and limited submucosal invasion (< 1000 µm below the muscularis mucosa) without any evidence of lymphovascular invasion. Other indications include technical difficulty in ESD and carcinoid tumors. Authors have reported that in the presence of fibrosis in the case of right-sided colonic lesions, recurrent lesions, or giant pedunculated polyps, EFTR remains a good treatment option[78-80]. The resection can be purely endoscopic or laparoscopic-assisted and closure of the defect can be performed using a clip, endo-loop, or a full-thickness resection device. However, these are technically challenging and yet to be used in humans.

Flexible endoluminal robotics helps to overcome the limitations of endoscopic resection by providing multidirectional traction using two robotic arms[81]. To meet the requirements various modified flexible endoluminal robots have been designed *i.e.*, EndoMaster EASESystem (EndoMaster Pte Ltd, Singapore), Flex Robotic System (Medrobotics, Raynham, MA, United States), EndoLuminal Surgical System (ELS, ColubrisMX, Houston, TX, United States), flexible auxiliary single-arm transluminal endoscopic robot (FASTER system), *etc.* Preclinical studies on animal models have shown the utility of the EndoMaster EASE system in performing colonic ESD[82]. The Flex Robotic System was initially designed for trans-oral minimal access surgeries and it can be used for colorectal lesions extending up to 25 cm from the anal verge [83]. Fok *et al*[84] have reported a case series of rectal polyps at a mean distance of 8.3 cm from the anal verge, resected using Flex Robotic System. The ELS flexible robotic system uses wristed instruments and an endoscope and this platform is similar to the current robotic surgical system[85]. Compared to the EndoMaster EASE system, it can accommodate a 6-mm endoscope with 3 degrees of freedom, 2 instrument channels, 2 insufflation channels, and 1 working channel[85]. It can be used to perform endorectal surgery up to 55 cm from the anal verge. Pre-clinical studies on *ex vivo* resection in the porcine colon using an ELS flexible system have been performed[85]. The FASTER system uses a module attached to the distal tip of the endoscope which is a robotic arm with a grasper with 4 degrees of freedom[86]. It is mostly used for gastric lesions in pre-clinical studies and is yet to be applied to the colorectum[86].

Role in the management of post-surgical complications

Surgical re-exploration was considered the standard procedure for post-surgical complications even for small anastomotic leaks. However, with the use of various modalities *i.e.*, clips, stents, and EndoSPONGEs, these morbid re-explorations could be avoided and a delay in adjuvant treatment could be minimized[87]. Anastomotic leak following restorative colorectal resection is the most feared complication as it can lead to morbidity and mortality with a reported incidence of 1%-19% among various studies[88-90]. Construction of a diverting stoma decreases morbidity following the leak, however, it doesn't prevent a leak[91,92]. Radiological drainage is sometimes challenging due to the anatomical location of purulent fluid in the deep pelvis. The use of an Endo-SPONGE can be useful in these conditions which consists of a polyurethane sponge placed trans-anally into the leak cavity using a flexible sigmoidoscope. It drains the collection and helps to promote granulation tissue formation. The sponge can be cut into various sizes to allow it to fit into the cavity and it is changed every 48-72 h till the cavity heals[93]. However, the efficacy is better for acute leaks (75%) compared to chronic leaks (38%)[94]. Another method for closure of anastomotic dehiscence is the OverStitch™ suturing system described by Kantsevov and Thuluvath[95] for the closure of post-polyethylene glycol tube removal long-standing gastrocutaneous fistula. Though it seems appealing, it is technically challenging in locations like the right colon due to poor angulation, margin maneuverability, and incompatibility with colonoscopy[96]. Endoscopic closure of small GI perforations has been known since 1997, however, the newly developed Over the scope clip® system (OVESCO Endoscopy AG, Tuebingen, Germany) which consists of larger endo-clips can be used for colorectal anastomotic leaks. Radziunas *et al*[97] reported faster healing of post-LAR fistula using OESCO clips. Other methods of management of anastomotic leaks are the use of covered stents and fibrin glue. Though studies have reported positive outcomes with endoscopic techniques, however, it is important to realize that patient selection is paramount in treatment decision-making.

Colorectal anastomotic site stricture dilatation can be performed using a Hegar dilator or a balloon dilator. The use of endoscopic electro-incision can be performed by experienced endoscopists experienced in per-oral endoscopic myotomies. The endoscopic incision has shown 100% effectiveness at a follow-up of 33.75 months by Acar *et al*[98]. The reported incidence of perforation is also less in electroincision compared to bougie dilatation (0.1%-0.4% *vs* 4%)[99].

ROLE AS SURGICAL OPTIONS (ENDO-LAPAROSCOPIC SURGERY)

Trans-anal surgery

Trans-anal resection of rectal lesions has the risk of chronic pain after coccygectomy, rectal-cutaneous fistulae, wound infection, anal stenosis, and fecal incontinence[100,101]. Presently, there are trans-anal endoscopic microsurgery, trans-anal endoscopic operation, and transanal minimally invasive surgery and the basic difference among them is the platform and instruments used to perform local excision. These techniques are used for the excision of benign rectal polyps, and malignant lesions as a part of multimodality treatment of early rectal cancers, and in patients who are deemed unfit for radical surgery. A multicenter trial (The CARTS study) has assessed the role of long-course chemoradiotherapy followed by trans-anal endoscopic surgery after 6-8 wk for T1-3, N0 rectal cancers and reported a pathological complete response of 55%; however, local recurrence developed in 8.5%[102]. Similarly, The ACOSOG Z6041 study reported a 3-year survival rate of 88.2% for T2N0 rectal cancers for neoadjuvant treatment followed by transanal surgery[103]. Recently published GRECCAR 2 trial comparing total mesorectal excision and local excision in patients with < 4 cm T2-T3 rectal cancers with good response to treatment following neoadjuvant treatment showed no difference in local recurrence after long-term follow-up (local excision: 84% *vs* total mesorectal excision: 82%, *P* = 0.85)[104]. The upcoming STAR-TREC trial can answer the feasibility of wait and watch *vs* local excision *vs* total mesorectal excision for early rectal cancer (cT1-3b N0 tumors, ≤ 40 mm in diameter) following chemoradiotherapy[105]. The ASCRS recommends local excision for T1No rectal cancers and selective neoadjuvant treatment followed by local excision for T2 rectal cancers[106].

Combined endoscopic-laparoscopic surgery

Polypectomy of adenomatous polyps is considered for secondary prevention of CRCs. However, the resection of some polyps becomes technically challenging when they are flat or located behind colonic folds. Laparoscopy can help endoscopic polypectomy, known as combined endo-laparoscopic surgery (CELS). It starts with the creation of pneumoperitoneum and abdominal exploration. All necessary adhesiolysis is performed to aid colonoscopy. It can be performed in various ways as described below. The laparoscopic-assisted endoscopic resection (LAER) is laparoscopic manipulation of the colonic segment to facilitate intraluminal exposure of polyp and endoscopic removal. Another method is endoscopic assisted wedge resection (EAWR) where after endoscopic localization of the polyp, excision is performed with a laparoscopic linear stapling device. The endoscopic assisted transluminal resection (EATR) is used for lesions located near the mesentery. In this method, a small colotomy is performed after localization during colonoscopy. The lesion is elevated and divided using a linear stapling device. Closure of colotomy is performed with laparoscopic sutures or staplers. The endoscopic-assisted segmental resection is used for lesions not amenable to LAER, EAWR, or EATR. After colonoscopic localization, laparoscopic segmental resection is performed. Figure 2 shows different types of CELS. Studies comparing surgical resection with CELS reported quicker procedures and fewer complications[107-109]. No long-term studies are reporting the outcome of CELS for colonic malignancy, the upcoming LIMERIC-II trial will help to know the long-term oncological outcome of CELS for malignant lesions[110]. Table 3 shows studies reporting a comparison of CELS with surgical resection.

Table 3 Results of combined endo-laparoscopic surgery, segmental resection and outcome						
No.	Number of patients	Complications (%)	Length of stay (d)	Procedure time (min)	Cost (dollars)/others	Ref.
1	23 SR; 23 CELS	CELS: 13; SR: 47.8	CELS: 4; SR: 7	CELS: 135; SR: 200	-	Golda <i>et al</i> [107], 2022
2	11 CELS; 11 SR	CELS: 0; SR: 9	CELS: 0-3; SR: 2-5	CELS: 66.73; SR: 204.7	CELS: 5523.29; SR: 12626.33	Jayaram <i>et al</i> [108], 2019
3	5 CELS; 9 SR	CELS: 0; SR: 33.3	CELS: 1; SR: 5	CELS: 159; SR: 205	-	Lee <i>et al</i> [109], 2013

CELS: Combined endo-laparoscopic surgery; SR: Segmental resection.

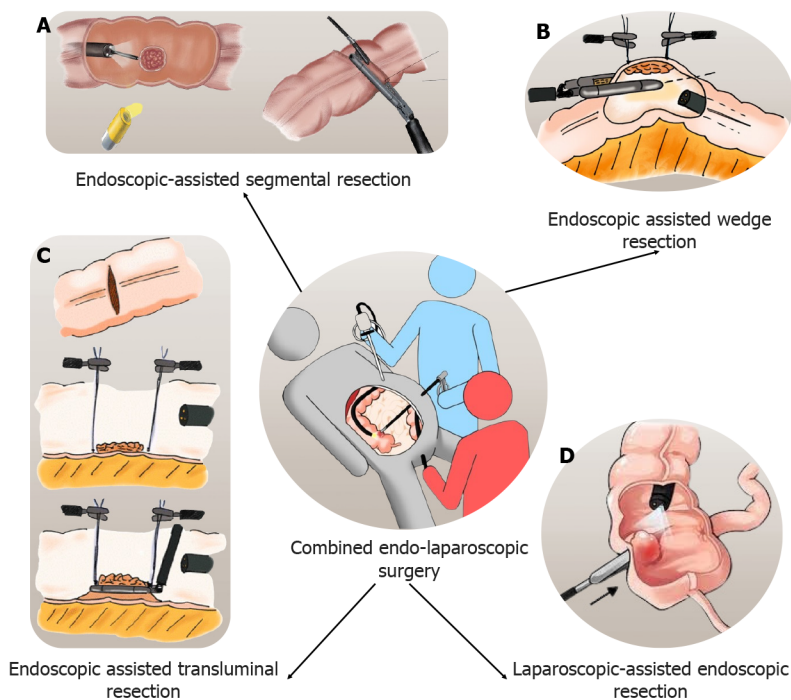


Figure 2 Types of combined endo-laparoscopic surgeries. A: Endoscopic-assisted segmental resection; B: Endoscopic assisted wedge resection; C: Endoscopic assisted transluminal resection; D: Laparoscopic-assisted endoscopic resection.

As we have discussed, many acute, chronic, benign, and malignant conditions of colorectum can be managed endoscopically for which surgery was considered the standard of care, however, it was associated with morbidity. Studies comparing endoscopic *vs* surgical management in colorectal malignancies are shown in Table 4. Overall, the 5-year overall survival is better with surgical resection compared to endoscopic polypectomy, however, in high-risk patients, still endoscopic polypectomy is reasonable considering post-operative complications following surgery. In cases of malignant obstruction, both metallic stenting and emergency surgery had similar survival; however, surgery had more complications. Hence, patient selection is paramount for treatment decision-making.

FUTURE DIRECTION

The twentieth century was credited with the research on the development and refinement of colonoscopes for better efficacy and fewer complications. Therapeutic endoscopy, as a subspecialty, subsequently came up in the later part of the century but with limited application in colorectal diseases. The incorporation of technology, tools, and techniques in the colonoscopes including AI has added another dimension to it. This newer version of scopes has resulted in quicker and more efficient diagnoses as compared to conventional colonoscopy with more accuracy, minimal discomfort, and wide therapeutic applications. Endo cytology is improving day by day, which can quicken the diagnosis of malignant pathology at an earlier stage. Robotic endoscopes, an upcoming tool may be used as a surgical robot to curtail the technical limitations of conventional scopes with broad indications and application in colorectal diseases. These innovations and newer versions of scope may avoid surgical intervention in select colorectal diseases in addition to its role in early and accurate diagnosis.

Table 4 Results of published series on surgery vs endoscopic intervention in malignant colorectal polyps and colonic obstruction

No.	Patients	Diagnosis	Complications (%)	Outcome (surgery vs endoscopy)	Ref.
1	Of 2077 patients: Surgical resection (1340), endoscopic polypectomy (737)	Malignant polyp	Surgery: 8.8. Endoscopy: 1.4	1-yr OS (92% vs 75%); 5-yr OS (88% vs 62%)	Cooper <i>et al</i> [136], 2012
2	Of 13157 patients: Surgical resection (11113), endoscopic polypectomy (2044)	Malignant polyp	-	Right colon polyps: < 20 mm polyp: 94.5% vs 94.3% ($P = 0.9$); 20-39 mm: 91.8% vs 74.2% ($P < 0.01$); > 40 mm: 92.4% vs 60% ($P < 0.01$)	Gangireddy <i>et al</i> [137], 2018
3	Of 31062 patients: Surgical resection (28469), endoscopic polypectomy (2593)	Malignant polyp	-	5-yr OS: 86.1% vs 80.6% ($P < 0.05$)	Lowe <i>et al</i> [138], 2020
4	Of 12 studies (meta-analysis)	Malignant obstruction	SEMS: 32.7. ES: 48.2 (RR = 0.61, 95%CI: 0.41-0.91)	Mortality (RR = 1.06, 95%CI: 0.55-2.04). Successful primary anastomosis (SEMS: 69.75% vs ES: 55.07%) (RR = 1.26, 95%CI: 1.01-1.57)	Cirocchi <i>et al</i> [55], 2021
5	Of 167 patients: SEMS (115), ES (52)	Malignant obstruction	SEMS: 20. ES: 30.8	5-yr OS: 85.6 vs 82.6% ($P = 0.68$)	Kim <i>et al</i> [54], 2023

CI: Confidence interval; ES: Emergency surgery; OS: Overall survival; RR: Risk ratio; SEMS: Self expanding metallic stent.

CONCLUSION

Minimally invasive techniques for the diagnosis and treatment of colorectal diseases are ongoing and allow earlier diagnosis and treatment with better outcomes. Ultra-minimally invasive colonoscopes present today are a result of thinner versions, flexibility, better vision systems, and mucosal enhancement tools. The use of AI has resulted in the minimization of human errors and improvement in the diagnostic yield. Development in smart glass has a further chance of improvement in diagnosis and intraprocedural professional guidance. Due to these newer innovations and newer versions of scope therapeutic colorectal intervention has increased. These minimally invasive colonoscopes loaded with gadgets and multiprong applications are being used both for benign (bleeding, obstruction, perforation) and malignant diseases (EMR, ESD, FTER). The use of robotic endoscopes with flexible instruments can be an emerging alternative to surgery in some selected diseases in the form of endorectal surgeries.

FOOTNOTES

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Role of artificial intelligence in colorectal cancer

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Abstract

The sphere of artificial intelligence (AI) is ever expanding. Applications for clinical practice have been emerging over recent years. Although its uptake has been most prominent in endoscopy, this represents only one aspect of holistic patient care. There are a multitude of other potential avenues in which gastrointestinal care may be involved. We aim to review the role of AI in colorectal cancer as a whole. We performed broad scoping and focused searches of the applications of AI in the field of colorectal cancer. All trials including qualitative research were included from the year 2000 onwards. Studies were grouped into pre-operative, intra-operative and post-operative aspects. Pre-operatively, the major use is with endoscopic recognition. Colonoscopy has embraced the use for human derived classifications such as Narrow-band Imaging International Colorectal Endoscopic, Japan Narrow-band Imaging Expert Team, Paris and Kudo. However, novel detection and diagnostic methods have arisen from advances in AI classification. Intra-operatively, adjuncts such as image enhanced identification of structures and assessment of perfusion have led to improvements in clinical outcomes. Post-operatively, monitoring and surveillance have taken strides with potential socioeconomic and environmental savings. The uses of AI within the umbrella of colorectal surgery are multiple. We have identified existing technologies which are already augmenting cancer care. The future applications are exciting and could at least match, if not surpass human standards.

Key Words: Artificial intelligence; Colorectal cancer; Pre-operative; Intra-operative; Post-

operative; Adjuncts; Colonoscopy

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Core Tip: We reviewed the role of artificial intelligence (AI) in colorectal cancer as a whole. Divided into pre-operative, intra-operative and post-operative, we identified a number of adjuncts that can help the clinician. Endoscopic detection and diagnosis are two of the mainstays of AI in this field, however there are a number of other adjuncts that can help surgeons intraoperatively. These include identification of anatomy, and assessment of blood supply. Moreover, post-operative efficiency improvements with histopathological analysis can aid the clinician. Overall, these adjuncts are aimed at augmenting the clinicians experience to improve outcomes.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the second most common cause of cancer-related deaths worldwide[1,2]. Approximately 21% of CRC cases are diagnosed at stage IV, or with metastatic disease[3]. Of note, the five-year survival rate declines from 80%-90% in patients with local disease compared to 12.5% for those diagnosed with distant-stage disease[4].

Developments in the diagnosis and management of CRC have led to decreases in overall mortality; most notably through screening[5,6]. A recent multi-centre European study of 84585 patients identified the risk of CRC was reduced in screened patients, with a relative risk reduction of 18%[7]. Additionally, further advances have been made regarding novel diagnostic markers and their use for risk stratification and early detection[8].

Surgery is currently the gold standard for deeply invasive CRC, but this remains a management option with significant potential morbidity and mortality[9]. Operative risks include anastomotic leak, ureteral injuries, haemorrhage, injury to surrounding organs, and ileus. The primary treatment for unresectable metastatic disease is systemic therapy; chemotherapy, immunotherapy or biologic therapy[10]. Again, this management option is plagued with potential complications and side effects. These risks need to be ameliorated if patient outcomes are to be improved.

Despite the advent of novel techniques and treatment options, the morbidity and mortality related to CRC remains. Thus, the idiom of “prevention is better than cure” holds true. The digital surgery revolution has enabled a multitude of adjuncts to improve all aspects of surgical care. Artificial intelligence (AI) represents just one of these. AI is defined as the ability of digital computing or a computer-controlled robot to perform tasks commonly associated with intelligent beings [11]. AI first aided in healthcare in the 1950s when physicians first used the technology to improve their diagnoses[12]. This includes but is not limited to: The use of AI in analysing medical imaging, supporting clinician decision making by analysing large quantities of data, tailoring personalised treatment plans and remote monitoring of patient data[13-15]. Since then, several studies have demonstrated its use within the healthcare setting; with many studies reporting AI performance to be comparable, if not exceeding humans[16].

AI is not a singular component but in fact a collection of technologies (Figure 1). Not all forms of AI are relevant to healthcare. The most salient forms are outlined below.

Machine learning

Machine learning is one of the most common forms of AI[16]. The technology aims to marry data models, with the system learning from trained examples. Within healthcare the most common application of machine learning is precision medicine[16]. For example, predicting and tailoring treatment regimens based upon bespoke patient characteristics[17]. More complex forms of machine learning involve deep learning or neural network models.

Deep learning and artificial neural networks

Deep learning is based on models with less assumptions about the raw data; it is therefore more adept at handling complex data[18]. It is composed of a multi-layer neural network architecture which learns representations of data with multiple levels of abstraction, without the need for human-crafted feature extraction[19-21]. An artificial neural network (ANN) is an algorithm that is inspired by human biology. Every ANN contains nodes that communicate with other nodes *via* connections (analogous to cell bodies connecting *via* axons)[22,23]. A convolutional neural network (CNN) is a type of neural network that distinguishes itself with superior performance for image or audio data[21]. Early clinical applications in the translation of CNNs include computer-aided detection (CADe) and diagnosis (CADx) of colorectal polyps during colonoscopy, with multiple regulatory approved algorithms available in the United Kingdom, European and Asian market[21].

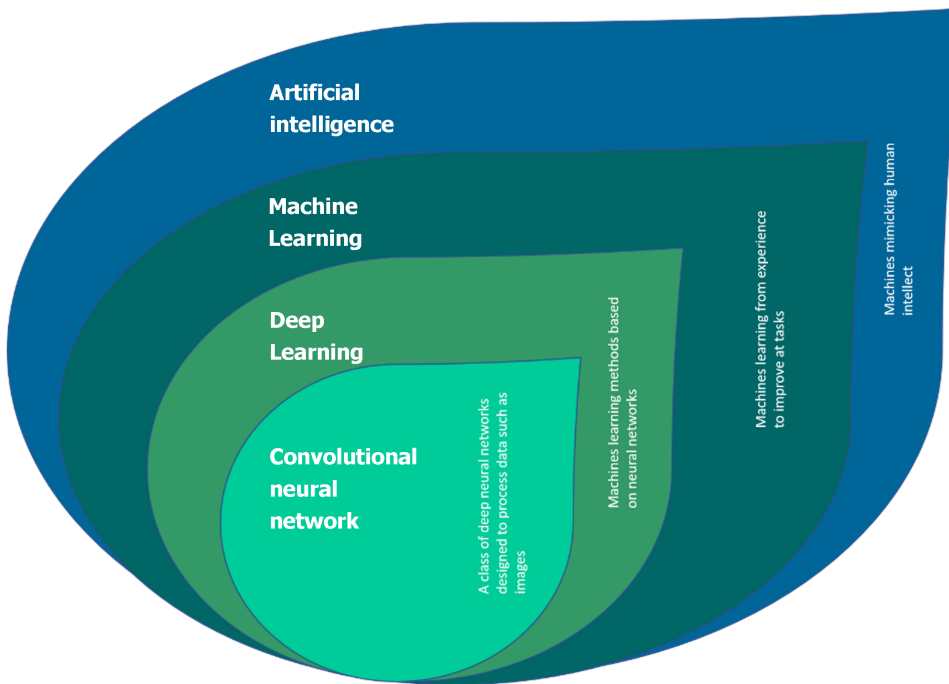


Figure 1 A diagrammatic representation of artificial intelligence technologies[21]. Citation: Kader R, Hadjinicolaou AV, Georgiades F, Stoyanov D, Lovat LB. Optical diagnosis of colorectal polyps using convolutional neural networks. *World J Gastroenterol* 2021; 27: 5908-5918.

Deep learning and ANN models are increasingly being used throughout the field of medicine. The most prominent use being the application within radiology for the detection of basic pathology and pre-cancerous lesions[24,25].

Natural language processing

Natural language processing (NLP) in its simplest form is teaching a computer how to read[26]. Traditional NLP applies grammatical rules to interpret meaning from text. The main applications of NLP in healthcare includes the understanding of clinical documentation. For example, preparing radiology reports, transcribing patient interactions and analysing clinical notes. NLP in combination with machine learning has even been used to help perform systematic reviews[27]. Perhaps the most well-known NLP system is “Chat GPT4” (Generative Pre-trained Transformer 4). This is a generic AI large language model open to public use, providing human-like conversation. Recently, a research team from Copenhagen built upon this model to create a specialty-specific clinical AI model. They were able to demonstrate that “Gastro GPT”, outperforms generic models in overall utility and completing clinical tasks[28].

Developments in all these aspects of AI may aid with ultimately providing the ability to perform autonomous surgery [29]. Nonetheless, presently AI is being utilised in all aspects of surgical care: Pre-operative, intra-operative and post-operative. This article will review the current applications in the field of colorectal cancer.

METHODOLOGY

A series of broad scoping and focused searches were conducted in Medline (*via* OVID), CINAHL Complete (*via* EBSCO), Cochrane Database of Systematic Reviews, and ScienceDirect, Academic Search Index and Directory of Open Access Journals (*via* EBSCO Discovery Service). The search strategy employed controlled vocabulary subject headings pertinent to each database, and free text keyword searches of title and abstract fields. Synonyms, truncation and spelling variations were used to retrieve records relating to colorectal cancer, colonoscopy, artificial intelligence, imaging overlay, pre- and post-operative care, individualised medicine, and prognoses.

Results were reviewed and records meeting the inclusion criteria were selected for full-text retrieval. Inclusion criteria included: English language articles, randomised controlled trials (RCTs), cohort studies, qualitative research and publications after the year 2000.

PRE-OPERATIVE USE OF AI IN CRC

Colonoscopy

The advent of the colonoscopy screening programme in Europe has led to a significant decrease in CRC-related mortality. This is in part due to the earlier detection and resection of neoplastic polyps. Colonoscopy remains the gold standard for both screening and surveillance of CRC[30]. However, detection of polyps during colonoscopy remains user dependent.

A meta-analysis of 43 publications and more than 15000 colonoscopies reported a human miss rate of 26% for adenomas, 9% for advanced adenomas and 27% for serrated polyps[31]. The use of CAdE systems has provided a promising avenue for improving polyp detection rates. A meta-analysis including 5 RCTs reported a significant improvement of pooled adenoma detection rate (ADR) to 36.6% from 25.2% in the control group ($P < 0.01$)[32]. Another RCT of over 600 patients concluded similarly that ADR was improved with use of CAdE, but also additionally commented that this improvement was seen across both expert and non-expert endoscopists[33].

AI in colonoscopy has progressed significantly, with recent improvements in translational aspects. Initial work was centered on using hand-crafted annotations to automated polyp classification using existing human derived classification. One of the first applications of this was for Kudo pit patterns from as early as 2010. Takemura *et al*[34] developed a partially automated software application capable of distinguishing polyps based upon colour differences on borders of polyps and mucosa, with a 98.5% accuracy. However, the main limitation to clinical translation was the computational power required and therefore the program's ability to function in real-time.

The emergence of deep-learning and CNN's addressed issues relating to computational power and processing time. The Paris classification was modelled using deep learning methods from colonoscopy videos to reach a mean 89% accuracy, surpassing all reported rates from the literature[35]. Similar results were achieved for Narrow-band Imaging International Colorectal Endoscopic (NICE) and Japan Narrow-band Imaging Expert Team classifications, whereby CNN's were employed. These are similar to ANN, however focus mainly on image processing. Deep metric learning was used to train the system with approximately 4000 polyp images, which were then tested against two experts. With respect to the NICE classification of type I-III lesions, the system was able to produce a mean accuracy level of 94%[36].

However, a real breakthrough may be on the horizon with novel classification methods. AI has the ability to classify polyps histologically (without human derived classification systems), termed CADx[37]. A recent study comparing CADx to expert endoscopists reported a sensitivity for diminutive polyps of 91% *vs* 42% respectively[38]. Significant improvements were also seen in negative predictive values and overall accuracy indicating the potential to outperform endoscopists.

Multimodal data categorisation has enabled not only surface risk analysis of polyps, but also the incorporation of patient demographic data and colonic location into creating a novel colorectal cancer invasion calculation. This represents significant strides in augmenting real-life practice, as management differs greatly for benign and malignant polyps – namely endoscopic resection versus formal bowel resection. Lu *et al*[39] trained their system with over 300000 images and benchmarked this against two expert endoscopists. More notably, the system has also been trained and tested using real time video data. Accuracy reached up 93.8%, with the system outperforming 5 out of 7 junior endoscopists. Whilst there have been significant technological advances, reviews have reported limitations[40]. This includes the lack of high quality RCT's impact upon the clinical usefulness of this data and the failure to improve non-expert's optical diagnosis performance when supported with CADx. Future work may help to elucidate the aspects which will augment and aid the clinician's practice.

Virtual colonoscopy/colon capsule endoscopy

Despite being the gold standard, colonoscopy is not always possible. As the global population ages, we are faced with increasing demands on healthcare, including the need for non-invasive diagnostic tools. Virtual colonoscopy (VC) or computed tomography colonography (CTC) is a commonly used alternative when colonoscopy is not possible. This is often due to a patient's poor baseline health but can also be used if colonoscopy fails. Common reasons for failure include: Poor bowel prep, stricturing disease or patient discomfort. AI based polyp detection frameworks have also been proposed for VC. Similarly, with respect to colonoscopy, the most promising areas appear to be in the increased detection of smaller polyps[41,42]. A study evaluating 104 CTC records reported their prospective clinical performance data with a computer aided detection system[41]. This had per-polyp sensitivities of 91.5% for adenomas 10mm or larger, and 82.1% for adenomas 6-9 mm. Common reasons for computer-aided system misses include: Adherent contrast medium, flat adenomas and adenomas adjacent to normal colonic folds[41].

Another less invasive alternative to colonoscopy is colon capsule endoscopy (CCE). This involves a patient swallowing a camera capsule, with the device relaying image and video data back to the clinician. There are several limitations to this diagnostic procedure including poor luminal views, inability to perform therapeutic procedures and the subjectivity of image interpretation. However, a key barrier to its use is the length of time it takes for endoscopists to interpret the images. Some studies have shown that AI can aid in the reduction of reading times for CCE. A study of twenty videos reported that their CAdE system reduced expert endoscopist reading time from 12.2 min to 3.1 min in the intervention group, without reducing the pathology detection rate[43].

Lymph node metastasis

Lymph node involvement in CRC plays a key role in management pathways and disease-free survival. Currently CRC is typically staged with contrast enhanced computer tomography (CT), with the addition of magnetic resonance imaging (MRI) in those with rectal cancer. In patients with locally advanced tumours, the current recommendation for rectal cancer is neoadjuvant chemoradiotherapy[44]. However due to the poor accuracy of lymph node staging in CRC, neoadjuvant treatment is not favoured[45]. The accuracy of lymph node staging is affected by multiple factors including poor quality images, experience of radiologist and patient related factors. Two published series reported a 70% or less accuracy for diagnosing lymph node metastasis on both CT and MRI[46,47]. With this significant need for improvement in the accuracy of lymph node staging, the hope remains that AI has a role to play.

Radiomics is a method of extracting regions of interest from diagnostic images. This in combination with deep learning algorithms have shown there to be benefit during pre-operative lymph node staging in CRC. A systematic review and meta-analysis aimed to evaluate the diagnostic accuracy of AI models in the detection of lymph node metastasis on pre-

operative staging imaging for CRC[48]. They concluded that both radiomics models and deep learning models have the ability to predict lymph node metastasis more accurately than radiologists. This meta-analysis reported with regards to rectal cancer, there was a per-patient area under the receiver operating characteristic curve (AUROC) of 0.917 for deep learning models versus the radiologists who had an AUROC of 0.688. Similar results were seen in colorectal cancer with a per-patient AUROC of 0.727 *vs* 0.676 for radiomics and radiologists respectively. Another study of 545 patients evaluated pre-operative MRI imaging with Faster Region-based Convolutional Neural Network; an advanced deep learning system [49]. Again, they were able to show AI models are reliable tools for predicting metastatic lymph nodes pre-operatively[49]

INTRA-OPERATIVE USE OF AI IN CRC

The majority of CRC patients will undergo surgery. This involves surgical resection of the cancer-plagued bowel, often with an anastomosis to re-establish continuity. Inadequate formation or poor healing of this anastomosis can lead to a major complication known as an anastomotic leak (AL). AL rates vary depending on several factors but can be as high as 30%[50].

Sufficient blood supply is a key component of tissue healing including anastomotic healing. Traditionally the perfusion of bowel has been measured *via* human inspection. This may include assessment of bowel discolouration, noting of bleeding edges, identification of palpable vasculature and intestinal peristalsis. This is a highly subjective technique and been proven to be unreliable[51].

The recent advances in visualisation systems have driven the field towards more objective measures which augment the intraoperative views. This includes techniques such as fluorescence imaging and laser speckle contrast imaging (LSCI).

Indocyanine green

Indocyanine green (ICG) is the most widely used fluorescent dye for intraoperative perfusion assessment[52]. ICG binds to plasma proteins and is then eliminated *via* the biliary system (with no enterohepatic recirculation). It fluoresces when activated with near infra-red or laser systems[53]. Intraoperatively, ICG is injected with the visual luminescence used to help assess perfusion of the anastomosis. A meta-analysis including over 3000 patients showed the use of ICG was associated with lower anastomotic leakage rate (OR = 0.31), postoperative complications (OR = 0.70) and reoperation rate (OR = 0.334)[54].

ICG has also been widely studied across other surgical domains including lymph node detection, extrahepatic biliary anatomy identification and ureter identification. As aforementioned, ureteric injury during colonic surgery is a significant risk. The incidence of injury is noted to be as high as 1.95%[55]. They are associated with higher mortality, morbidity and increased hospital stay[56]. Traditionally identification of ureters has been performed *via* visual inspection of peristalsis (Kelly's Sign). However, this can be affected by several factors including; incorrect plane of dissection, adipose tissue and adhesions. In higher risk cases, it is generally accepted that indwelling ureteral stents can be used. The evidence for stenting decreasing ureteric injury remains insufficient[57]. This has led to rise of fluorescence imaging in intra-operative ureter detection. Injection of ICG *via* a cystoscopy-guided ureteric catheter allows ICG to bind to the ureteric epithelium [58]. This technique has been proven to be safe and useful in several small studies[55].

Since the introduction of total mesorectal excision (TME) local recurrence rates have fallen dramatically. Globally TME is the accepted gold-standard treatment in those with rectal cancer[59]. Lateral pelvic lymph node dissection (LPLND) refers to the removal of the nodes along the common iliac, internal iliac and obturator arteries. Management of disease within in this area varies worldwide. Generally, Western nations have adopted neo-adjuvant chemotherapy whilst Eastern countries have opted for LPLND without neo-adjuvant therapy[60]. In fact, the Japanese Society for Cancer of the Colon and Rectum guidelines state that even when pre-operative imaging does not detect lateral lymph node metastasis, LPLND should still be performed[61].

ICG fluorescence imaging has been proven to be a useful tool for identifying lymphatic drainage and colorectal resections are no exception. Zhou *et al*[62] concluded that ICG enhanced imaging is a feasible and convenient to guide LPLND. Additionally, this series of 42 patients showed a significantly lower intraoperative blood loss (55.8 mL *vs* 108.0 mL, $P = 0.003$) and a greater number of harvested lateral pelvic lymph nodes (11.5 *vs* 7.1, $P = 0.017$)[62].

However, the use of ICG fluorescence imaging is not without its limitations. Overall, it is still considered a subjective tool. Furthermore, it requires the use of a fluorophore which has been known to cause anaphylaxis. This has allowed newer visualisation techniques to break through including LSCI.

Laser speckle contrast imaging

'Speckles' refer to the pattern created (with dark and bright areas) when an object is illuminated by laser light[63]. LSCI uses this concept to be able to detect tissue blood flow and therefore tissue perfusion *via* laser scatter. This culminates in a colour heatmap of real-time blood flow. The advantages of LSCI over ICG fluorescence is the lack of fluorophore needed, the ability for repeat use on demand and no delay between contrast injection and perfusion display. The main disadvantage is poor tissue depth perception, with the perfusion visualisation limited to the most superficial 1-2 mm of tissue[64]. A case- control study of 27 patients aimed to validate the use of LSCI in assessing bowel perfusion as well as assessing improvement in patient outcomes with regards to AL rate[65,66]. They reported 0% of patients ($n = 27$) undergoing LSCI perfusion assessment developed an anastomotic leak, however 18.5% ($n = 27$) of the patients in the control group did.

Despite being in its relative infancy, LSCI has potential future applications. Integration with AI to provided objective measurements, and analysis of extracellular matrix stiffness[67] provide an insight into development opportunities. However, a lack of high quality RCT's limit its current clinical application.

POST-OPERATIVE USE OF AI IN CRC

Pathology

CRC cannot be classified as one disease but rather a collection of neoplastic diseases with huge heterogeneity in biology [68]. Therefore, factors such as tumour grade, lymphovascular invasion, and microsatellite status are pertinent in guiding the treatment and therefore prognosis of the disease. AI can be broadly useful in two main domains of pathology: Clinical application and research[69]. AI can support pathologists in quantitative repetitive tasks. An example of this is the detection and quantification of mitotic figures. Mitotic count is a vital histopathological parameter for the prognostication of malignant diseases[70]. However, the quantification is often fraught with discrepancies due to inter and intra-observer bias. A multi-centre study conducted in the United States compared computer-assisted mitotic count analysis to unaided mitotic count analysis[70]. They found that the interobserver consistency for the mitotic count was significantly increased with computer aid (interobserver correlation coefficient 0.92 *vs* 0.70 in the unaided group)[70].

Additionally, AI can be used as a quality control measure to provide a second opinion for pathologists[69]. A multi-centre study of 740 patients found that in second-opinion cases, discrepancies were identified in 14.1% of patients, of which 4.1% had a resulting change in care[71]. In the research domain of pathology, AI can analyse large complex datasets which can lead to individualised treatment. For example, an American study of over 1000 patients evaluated a multistain deep learning model which was used to determine the Almmunoscore[72]. This model outperformed other clinical, immune and molecular based parameters.

Surveillance imaging

Similarly, to pathology, AI has a significant role to play in the reduction of time spent on routine tasks. The amount of radiological data is growing at a disproportionate rate to the amount of trained-readers[73]. In fact, McDonald *et al* calculated that the average radiologist must interpret one image every 3-4 seconds in an 8 h workday to keep up with demands.

AI algorithms, in particular deep learning models have shown remarkable progress in image-recognition tasks[74]. Traditionally, radiologists visually assess images using a combination of education and experience, to report their findings. However, this can be subjective and relies on the ability of the observers' pattern recognition. In contrast, AI is able to utilise vast quantities of data and complex patterns to provide a quantitative assessment[74].

Furthermore, the use of AI models has been shown to increase the accuracy of radiological reports. Jerebko *et al*[75] designed a system with the aim of increasing the sensitivity and reducing the number of false positive findings with computed tomographic colonography. They reported a 36% reduction in false positive rate and improved sensitivity of 6.9%.

Remote patient monitoring

Enhanced recovery after surgery pathways have been shown to reduce the length of hospital stay and post-operative complications in patients undergoing elective colorectal surgery[76]. The protocol encompasses a multi-disciplinary approach with advice for patient management at three key stages: Preoperative, perioperative and post-operative. A key component of the post-operative phase is early mobilisation. Unfortunately, this can often be hindered by simple logistics, such as the need for patient observations in the inpatient setting. The advent of 'wearables' has significantly impacted healthcare by enabling remote monitoring of patients. Examples include rings, wristbands, and body suits that can detect a patient's heart rate, temperature, oxygen saturations, glucose level, motion data and electrocardiography[77]. This will allow patients to be ambulated quicker post operatively, increase the flow of patients through the hospital, and have financial implications. Additionally, data generated from wearables, in combination with machine learning, has been able to predict disease progression in neurological disorder up to 4 times more precisely than traditional methods[74].

CONCLUSION

AI has the potential to augment all aspects of surgery and CRC: Pre-operatively, intra-operatively and post-operatively (Table 1). Comparable and improved results have been seen compared with human recognition of polyps during colonoscopy. Laser speckle contrast imaging in combination with AI has the potential to be a safe and effective method of assessment and diagnosis. Cancer surveillance can be streamlined and become more accurate with pathological and radiological augmentations. We may not have even realised the tremendous potential of this exponentially evolving field. Exciting times for the future of surgery and colorectal cancer exist, with innumerable benefits for the patient journey.

Table 1 Summary of applications of artificial intelligence within colorectal cancer

Pre-operative	Intra-operative	Post-operative
Colonoscopic detection: Human derived classification; Novel computer aided detection/diagnosis	Indocyanine green: Ureteric identification; Perfusion assessment	Surveillance imaging
Virtual colonoscopy	Laser speckle contrast imaging	Pathological quantification
Capsule endoscopy		Remote patient monitoring
Lymph node metastasis		

FOOTNOTES

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Virtual reality tools for training in gastrointestinal endoscopy: A systematic review

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Abstract

BACKGROUND

Virtual reality (VR) has emerged as an innovative technology in endoscopy training, providing a simulated environment that closely resembles real-life scenarios and offering trainees a valuable platform to acquire and enhance their endoscopic skills. This systematic review will critically evaluate the effectiveness and feasibility of VR-based training compared to traditional methods.

AIM

To evaluate the effectiveness and feasibility of VR-based training compared to traditional methods. By examining the current state of the field, this review seeks to identify gaps, challenges, and opportunities for further research and implementation of VR in endoscopic training.

METHODS

The study is a systematic review, following the guidelines for reporting systematic reviews set out by the PRISMA statement. A comprehensive search command was designed and implemented and run in September 2023 to identify relevant studies available, from electronic databases such as PubMed, Scopus, Cochrane, and Google Scholar. The results were systematically reviewed.

RESULTS

Sixteen articles were included in the final analysis. The total number of participants was 523. Five studies focused on both upper endoscopy and colonoscopy training, two on upper endoscopy training only, eight on colonoscopy training only, and one on sigmoidoscopy training only. Gastro-intestinal Mentor virtual endoscopy simulator was commonly used. Fifteen reported positive results, indicating that VR-based training was feasible and acceptable for endoscopy learners. VR technology helped the trainees enhance their skills in

manipulating the endoscope, reducing the procedure time or increasing the technical accuracy, in VR scenarios and real patients. Some studies show that the patient discomfort level decreased significantly. However, some studies show there were no significant differences in patient discomfort and pain scores between VR group and other groups.

CONCLUSION

VR training is effective for endoscopy training. There are several well-designed randomized controlled trials with large sample sizes, proving the potential of this innovative tool. Thus, VR should be more widely adopted in endoscopy training. Furthermore, combining VR training with conventional methods could be a promising approach that should be implemented in training.

Key Words: Virtual reality; Gastrointestinal endoscopy; Systematic review; Virtual reality training; Simulation

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Core Tip: Virtual reality (VR) is a promising tool in endoscopy training. This systematic review assessed VR's effectiveness and feasibility. Sixteen articles were analyzed, with 15 reporting positive results. VR training enhanced endoscopy skills, reducing procedure time and increasing accuracy in both VR scenarios and real patients. Patient discomfort also decreased significantly. VR training is effective and should be widely adopted in endoscopy training. Combining VR with conventional methods could further enhance training.

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INTRODUCTION

The coronavirus disease 2019 pandemic has affected various domains of our lives, such as work, communication and education. In medical training, despite the difficulties it has posed, it has also opened up new possibilities. In addition to conventional methods, alternative forms of training are required to cope with the unprecedented situation of the pandemic. Furthermore, the rising demand for high-quality, safe medical care and the expectation of patient satisfaction have exposed the limitations of traditional medical training. Thus, the necessity of incorporating more innovative approaches to address the unmet need is evident.

Virtual reality (VR) is a simulated experience that can be like or completely different from the real world. It is achieved by using computer-generated images or sounds that create an immersive and interactive environment for the user. VR creates a 3D environment that enables users to explore and interact with virtual surroundings in a way that approximates reality, as it is perceived through the users' senses, with special devices, such as a headset, gloves, goggles, and controllers. The simulated environment is developed with advanced computer hardware and software.

Because of these unique features, VR has its advantages and disadvantages. Firstly, it can provide an immersive experience that can enhance the enjoyment and engagement of the user. For example, VR can be used for gaming, movies, and social networking, where users can feel part of the virtual world. Secondly, VR can increase productivity and efficiency by creating a distraction-free environment for work or learning. Finally, VR offers medical therapy and treatment applications for various conditions and disorders.

However, VR has some disadvantages. One drawback is that it requires expensive equipment and software that may not be accessible or affordable for everyone. Next, it can cause health risks such as nausea, dizziness, eye strain, headaches, and motion sickness, also known as VR sickness. Moreover, if VR is overused, it may lead to social isolation and addiction by reducing the interaction with the natural world and people. This can lead to losing social skills, empathy, and emotional connection.

With its unique features, VR application in medical training is an ideal innovative approach that could be used to meet the urgent needs of medical training lately. VR has been increasingly used in various fields of medical education and training, such as anatomy, communication skills, physical examinations, procedures, surgeries or diagnostic imaging feedback. VR enables learners to practice their skills in realistic and risk-free situations, improve their confidence, and obtain immediate feedback. VR can also reduce the costs and limitations of using physical models, cadavers, or live patients. Furthermore, VR can also facilitate collaborative and adaptive learning, as multiple learners can interact with each other and the virtual environment in real time. According to several studies, VR can enhance the learning outcomes, motivation, engagement and retention of medical students and professionals. Moreover, VR can provide opportunities for practicing complex and rare scenarios in a safe and controlled setting, without risking patient safety or ethical issues [1-4].

VR has emerged as an innovative technology in endoscopy training, providing a simulated environment that closely resembles real-life scenarios and offering trainees a valuable platform to acquire and enhance their endoscopic skills. Several studies have highlighted the potential benefits of VR-based training in gastrointestinal endoscopy[5]. VR simulation training provides a realistic, immersive, controlled, and highly interactive experience, allowing trainees to practice endoscopic procedures[6]. It has been shown to reduce procedural errors, improve polyp detection rates, and shorten the learning curve. Furthermore, VR-based endoscopy training has positively improved adverse events and enhanced patient safety[7].

Furthermore, VR training can boost the psychomotor skills of the trainees, which involve coordination, dexterity, and precision of movements[8]. VR training can also improve the quality of the endoscopic study, which is determined by factors such as bowel preparation, visualization, and documentation[9]. Additionally, VR training can help the trainees to correctly identify pathologies during the procedure, which is essential for diagnosis and treatment[10,11]. VR training can also reduce the adverse events that may occur during or after the procedure, such as perforation, bleeding, infection, or cardiopulmonary complications[8,9]. Finally, VR training can enhance the skill test performance of the trainees, which is a way to assess their technical and cognitive success in performing endoscopy[11,12].

Current American Council for Graduate Medical Education (ACGME) training guidelines mandate incorporating simulation training into gastroenterology fellowship programs. While simulation can potentially reduce training costs as staff endoscopists are more productive when performing procedures independently, there are costs associated with acquiring and maintaining simulators. It is therefore essential to ensure that skills gained through simulation training positively transfer to the clinical environment[13].

According to the current guidelines established by the ACGME, gastroenterology fellowship programs must include simulation training as part of their curriculum[13]. This study aims to evaluate the effectiveness and feasibility of VR-based training compared to traditional methods. By examining the current state of the field, this review seeks to identify gaps, challenges, and opportunities for further research and implementation of VR in endoscopic training.

MATERIALS AND METHODS

This study is a systematic review following the guidelines for reporting systematic reviews set out by the PRISMA statement[14].

Search strategy

A comprehensive search command was designed and implemented to identify relevant studies from electronic databases, including PubMed, Scopus, Cochrane, and Google Scholar, to achieve the stated objectives. A total of 673 articles were found after running the following search on 11 September 2023: ("virtual reality" OR "computer simulation" OR "virtual training" OR "virtual simulation" OR "Cyberspace" OR "simulation training") AND ("training" OR "teaching" OR "learning") AND ("digestive endoscopy" OR "colonoscopy" OR "endoscopy").

Study selection

The search utilized predefined keywords related to simulation-based training, VR, gastrointestinal endoscopy, training, and simulation.

The inclusion criteria encompassed studies published in peer-reviewed journals that evaluate the use of VR for training in gastrointestinal endoscopy and report outcomes related to endoscopic skills or patient outcomes. Studies not available in English and those without relevant outcomes related to endoscopic skills or patient outcomes were excluded.

The screening process involved the reviewers assessing the titles and abstracts of the identified studies for potential eligibility based on the inclusion and exclusion criteria. Full-text articles of potentially eligible studies were retrieved and assessed for final inclusion. The study selection process was documented using a flowchart following the PRISMA guidelines for literature review. This step assessed each paper's administrative information such as titles, authors, the introduction, the research method, study design, risks of biases and confidence in cumulative evidence. In terms of risk of bias assessment, the Application of Cochrane Collaboration's tool for assessing risk of bias was used. Each study was evaluated for seven factors, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. Each factor was categorized as "low risk", "high risk" or "unclear risk" of bias.

Data extraction and synthesis

Microsoft excel version 2016 was used for data extraction. Data extraction involved developing a standardized form to collect relevant information from the selected studies, including study characteristics, participant characteristics, details of the VR intervention, outcome measures, and results related to endoscopic skills acquisition or patient outcomes. The outcome measures included the effectiveness of VR tools in improving technical skills and performance, the feasibility and acceptability of VR-based training programs, the impact of VR training on patient outcomes, the advantages and limitations of VR-based training and other secondary outcomes.

To limit bias, the data collection process was also done under the supervision of the study supervisor.

A narrative synthesis of the included studies summarized their characteristics and findings. Heterogeneity among the studies was assessed by considering the study designs, participant characteristics, VR interventions, and outcome measures.

RESULTS

Study selection

The Search command retrieved 673 references. After applying the exclusion criteria (duplicate records, $n = 1$; non-English records, $n = 1$; “review” records, $n = 128$; meeting abstract without full-text, $n = 5$; not meeting criteria, $n = 522$), 16 articles were included in the final analysis. Figure 1 explains the selection process. Table 1 and Table 2 summarizes the data gathered from each included paper.

The studies were mainly from the United States (6 studies), followed by Canada and Netherlands (2 studies each), and Austria, United Kingdom, Argentina and Portugal (1 study each). The total number of participants was 523. The sample size ranged from 12 to 126 participants, with six studies having more than 30 participants[4,8,9,15-17]. The smallest sample sizes were from Ferlitsch *et al*[10], 2002, and Telem *et al*[18], 2014, with 12 and 13 participants, respectively[10,18]. All participants were physicians of different specialties, including endoscopists, expert endoscopists, gastroenterology fellows, and surgery or internal medicine residents.

Nine of the studies were randomized controlled trials[8,10,12,15,19-23], two were pre and post designs, and two were prospective studies[4,16,11,24]. The study by Hashimoto *et al*[9] in 2018 had two phases[9].

The academic setting was standard for all studies, with nine conducted at academic institutions and seven at academic medical centers. The duration of the studies varied from week to years, with the most extended being Ferlitsch *et al*[12] in 2010, which lasted for four years[12].

Regarding the types of endoscopy, five studies focused on both upper endoscopy and colonoscopy training, two on upper endoscopy training only, eight on colonoscopy training only, and one on sigmoidoscopy training only.

A variety of simulator systems were used for simulation-based training, such as the gastrointestinal (GI) Mentor virtual endoscopy simulator (13 studies), VR sigmoidoscopy simulator[19], VR endoscopy simulator (Grover, 2015)[8] and computer-based colonoscopy simulator[22]. The GI Mentor II was the most commonly used method. The VR platform was mainly used to train fundamental skills, except for one trial that included basic and advanced skills training[17].

The control group was exposed to different types of interventions across the studies. The control group received no intervention in five trials[10,15,18,21,22]. In two trials, the control group underwent conventional bedside teaching training, while the intervention group received VR training[12,19]. In the remaining trials, the control group also used a physical or VR simulator with less time or feedback than the intervention group.

The assessment methods varied across the studies. Three studies used expert ratings based on specific scales and VR platform scores to evaluate trainees[17,18,22]. Eight studies relied on expert ratings only, while five studies used only VR platform scores[4,9,10,16,24]. Van Sickle *et al*[17] study was the only one that also included self-rating as an assessment method[17]. Among studies that used experts' assessment, the Global Assessment of Gastrointestinal Endoscopic Skills (GAGES) scale was the most commonly used.

The measurement of primary outcomes varied among different studies, but the most common primary outcomes were procedure time, procedure skills, and patient discomfort.

Figure 2 shows the risk of bias assessment for the included studies. Two studies had low risk of bias in all domains[3, 10]. Five studies had high risk of bias in one or more domains, such as blinding[12,19] and selection[17,19-21]. Nine studies had unclear risk of bias in some domains, mainly due to insufficient reporting of randomization, allocation concealment, blinding of participants and/or blinding of outcome assessment. Figure 3 summarizes the risk of bias across the studies. Most studies had low attrition bias and reporting bias, while selection bias was the most common source of high or unclear risk of bias.

Yellow circles, green circles and red circles illustrate “unclear risk of bias,” “low risk of bias,” and “high risk of bias,” respectively.

Studies outcomes

The primary outcome in included studies was effectiveness of VR in different circumstances, without comparator, *vs* no training, *vs* conventional patient-based training, *vs* other forms of endoscopy simulation. Most of the studies indicated that that VR-based training was feasible and acceptable for endoscopy learners, including enhance their skills in manipulating the endoscope, reducing the procedure time or increasing the technical accuracy, in VR scenarios and real patients. Some studies assessed the impact of VR training in patient outcomes, advantages and limitations of VR-based training and the feasibility and acceptability of VR-based training program.

VR (without comparator)

Four studies assessed the role of VR in endoscopy training. All of them used the GI mentor as the training tool, and most focused on colonoscopy, with basic endoscopy skills[4,16,17,24].

Buzink *et al*[4] conducted a study to examine the learning curve of novice endoscopists in basic endoscope navigation skills using the GI Mentor II simulator[4]. The study involved 30 participants who had no prior experience in endoscopy, and they completed a VR training session. The task for the VR colonoscopies was to reach the cecum as fast as possible without causing patient discomfort. The result showed that the novices improved significantly, especially in the time needed to complete the tasks. The study implies that VR colonoscopy training significantly enhances novice endoscopists' basic endoscope navigation skills. Piskorz *et al*[16], 2020, reported that trainees who used two GI Mentor™ for 8 h in a clinical simulation center improved their psychomotor skills and endoscopic skills (including cecal intubation time, percentage of examined mucosa, and efficacy of screening) significantly[16].

The quality of the endoscopic study also improved; the proportion of examined mucosa over 85% increased significantly after training with an adjusted OR of 2.72 (95%CI: 1.51-4.89, $P = 0.001$). The authors concluded that the

Table 1 Description of studies included in this systematic review of virtual reality training in gastrointestinal endoscopy

Ref.	Study design	Study setting	Duration	Types of trainees	No. of participants	Types of colonoscopies	Types of VR training
Buzink <i>et al</i> [4], 2007	Pre and post study	Academic medical centers		Novice endoscopists, expert endoscopists	30	Colonoscopy	GI Mentor II
Cohen <i>et al</i> [15], 2006	Multicenter RCT	Academic medical centers	2 yr	Gastroenterology fellows	45	Colonoscopy	GI Mentor
Ferlitsch <i>et al</i> [10], 2002	Single-center RCT	Academic institution	3 wk	Medical residents	13	Upper endoscopy and colonoscopy	GI Mentor
Ferlitsch <i>et al</i> [12], 2010	Single-center RCT	Academic institution	4 yr	Internal medicine residents	28	Upper endoscopy	GI Mentor
Gerson and Van Dam[19], 2003	Single-center RCT	Academic institution	9 months	Internal medicine residents	16	Sigmoidoscopy	VR sigmoidoscopy simulator
Gomez <i>et al</i> [20], 2015	Single-center RCT	Academic institution	1 month	Surgery residents	27	Colonoscopy	GI Mentor
Grover <i>et al</i> [8], 2015	Single-center RCT	Academic medical centers	6 wk	Surgery residents, medicine residents, gastroenterology fellows	33	Colonoscopy	VR endoscopy simulator
Hashimoto <i>et al</i> [9], 2018	Two-phase study	Academic medical centers	6 months	Endoscopists	44	Upper endoscopy and colonoscopy	GI Mentor
Koch <i>et al</i> [11], 2015	Prospective study	Academic institution		Trainees	18	Colonoscopy	GI Mentor II
McIntosh <i>et al</i> [21], 2014	Single-center RCT	Academic institution	1 month	Residents between year 2-4	18	Colonoscopy	GI Mentor II
Park <i>et al</i> [22], 2007	Single-center RCT	Academic medical centers		Surgery residents, internal medicine residents	24	Colonoscopy	Computer-based colonoscopy simulator
Piskorz <i>et al</i> [16], 2020	Pre and post study	Academic medical centers		1 st yr fellows of gastroenterology	126	Upper endoscopy and colonoscopy	GI Mentor
Shirai <i>et al</i> [23], 2008	Single-center RCT	Academic institution	17 months	Residents	20	Upper endoscopy	GI Mentor II
Silva Mendes <i>et al</i> [24], 2021	Prospective, multicenter study	Academic institution	6 months	1 st yr gastroenterology residents	23	Upper endoscopy and colonoscopy	GI Mentor II
Telem <i>et al</i> [18], 2014	Prospective study	Academic institution	6 wk	Novice surgical interns, attending physicians	12	Colonoscopy	GI Mentor
Van Sickle <i>et al</i> [17], 2011	Multicenter pre and posttest study	Academic institution	8 wk	Postgraduate year 1-4	41	Upper endoscopy and colonoscopy	GI Mentor II

RCT: Randomized controlled trial; VR: Virtual reality; GI: Gastrointestinal.

addition of VR endoscopy in the training curriculum enhances trainee endoscopists' performance and psychomotor skills and teaches them how to conduct a quality endoscopic study in a safe and non-patient setting.

A prospective, multicenter study by Silva Mendes *et al*[24] in 2021 examined the effectiveness of GI Mentor II for teaching esophagogastroduodenoscopy (EGD) and colonoscopy. The study measured the technical skills of 21 residents based on the time to reach the D2/cecum (seconds), the efficiency of screening (%), and the time the patient was in pain (%). The residents received theoretical and practical training for 20 h using the GI Mentor II. The results showed that the residents improved their cognitive score and significantly reduced the time the patient was in pain (27% *vs* 10%, $P = 0.005$). The screening efficiency also increased, although not significantly (50% *vs* 68%, $P = 0.062$). The study concluded that VR could be useful for teaching cognitive and technical skills to novice endoscopists[24]. Likewise, the study of Van Sickle *et al*[17], 2011 proved the same patterns. His study used two GI Mentor II flexible endoscopy simulators, and postgraduate years from year 1 to year four participated in this study. This is a multicenter study, with five medical institutions, including the University of Texas Health Science Center-San Antonio, Texas A and M University, Methodist Hospital, and Brooke Army Medical Center, and University of Texas Southwestern. After the training, the procedure time, screening efficiency, and GAGES scores increased significantly. In addition, subjects' endoscopy self-rating scores

Table 2 Training methods, evaluation, comparator and outcomes of studies included in this systematic review of virtual reality training in gastrointestinal endoscopy

Ref.	Training methods	Duration of training and frequency of training sessions	Self-evaluation methods	Evaluation by trainers	Comparator	Main outcomes measured
Buzink <i>et al</i> [4], 2007	Basic skills training	4 sessions, each session: One EndoBubble task and managed multiple VR colonoscopy cases (two in first session and three in subsequent sessions)		Objective metrics		Process skills, procedure time
Cohen <i>et al</i> [15], 2006	Basic skills training	10 h of unsupervised training on the GI Mentor or no simulator experience during the first 8 wk of fellowship		Expert evaluations	No intervention	Procedure completion, global rating of performance, patient discomfort
Ferlitsch <i>et al</i> [10], 2002	Basic skills training	2 h <i>per d</i> , 3 wk		Objective metrics	No intervention	Process skills, procedure time
Ferlitsch <i>et al</i> [12], 2010	Basic skills training	2 h <i>per d</i> , 5 h to 20 h in total		Expert evaluations	Conventional, patient-based training only	Procedure time, patient discomfort
Gerson and Van Dam [19], 2003	Basic skills training	2 wk or ten sigmoidoscopy examination with attending gastroenterologists		Expert evaluations	Bedside teaching	Procedure time, procedure completion, patient discomfort, complication or critical flaw, global rating performance
Gomez <i>et al</i> [20], 2015	Basic skills training	3 modules, 3 wk in total		Expert evaluations (GAGES scale)	Physical simulator group, combination group	Composite score of competency, performance time, visualization of mucosa
Grover <i>et al</i> [8], 2015	Basic skills training	6 h of didactic lectures and 8 h of VR simulation-based training with expert feedback		Expert evaluations (JAG DOPS scale)	VR simulation training only (no experts feedback)	Composite score of competency
Hashimoto <i>et al</i> [9], 2018	Basic skills training	Not limited		Objective metrics	Ten repetitions of each VR simulator	Procedure skills
Koch <i>et al</i> [11], 2015	Basic skills training	50 (group I) or 100 (group II) VR colonoscopies		Expert evaluations	50 (group I) or 100 (group II) VR colonoscopies	Procedure time, procedure completion
McIntosh <i>et al</i> [21], 2014	Basic skills training	16 h of VR simulator training		Expert evaluations, objective metrics	No intervention	The number of proctors 'assists' required <i>per</i> colonoscopy. Procedure time, procedure skills, patient discomfort
Park <i>et al</i> [22], 2007	Basic skills training			Expert evaluations (global rating scale)	No intervention	Procedure completion, complication or critical flaw
Piskorz <i>et al</i> [16], 2020	Basic skills training	8-h worked utilizing two GI Mentor™ in a specialized clinical simulation center		Objective metrics		Procedure time, procedure skills
Shirai <i>et al</i> [23], 2008	Basic skills training	5 h simulation training + bedside training <i>vs</i> bedside training		Expert evaluations	Conventional, patient-based training only	Procedure time
Silva Mendes <i>et al</i> [24], 2021	Basic skills training	Theoretical and a hands-on module (20 h) in the GI Mentor II		Objective metrics		Cognitive score, procedure time, procedure skills, patient discomfort
Telem <i>et al</i> [18], 2014	Basic skills training	2 h a wk, 6 wk		Expert evaluations (GAGES scale), objective metrics	No intervention	Procedure skills, procedure time
Van Sickle <i>et al</i> [17], 2011	Basic skills training, advanced skills		Self-rating score	Expert evaluations (GAGES scale), objective metrics		Procedure time, procedure skills, patient discomfort

GAGES: Global assessment of gastrointestinal endoscopic skills; JAG DOPS: Advisory group direct observation of procedural skills; VR: Virtual reality; GI: Gastrointestinal.

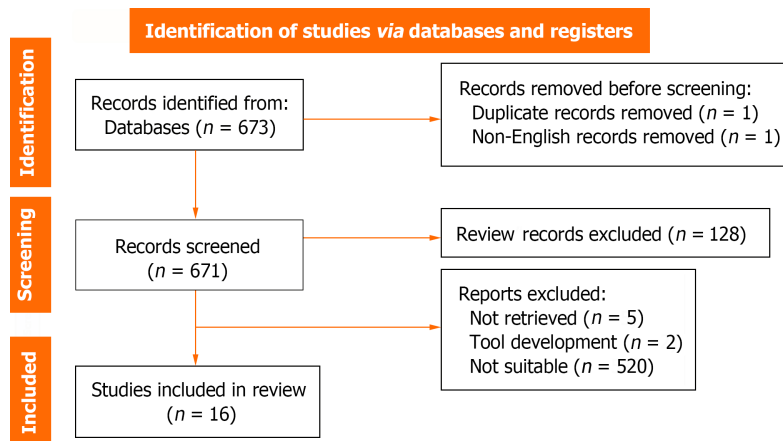


Figure 1 Preferred reporting items for systematic review and meta-analysis protocols for systematic reviews.

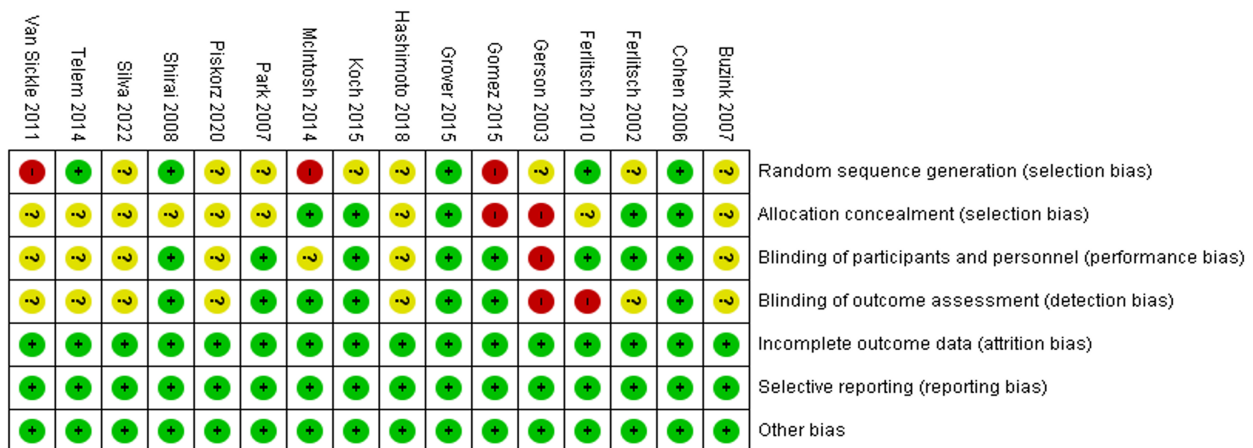


Figure 2 Risk of bias assessment.

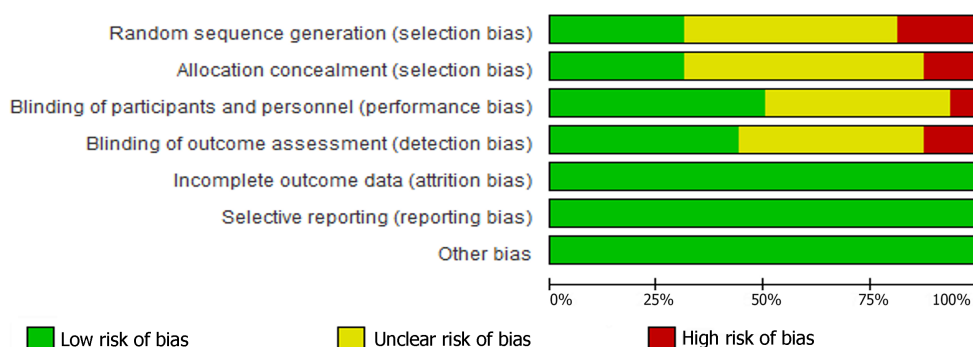


Figure 3 Risk of bias summary.

also show an increase. In conclusion, residents who completed the VR training demonstrated subjective and objective growth in flexible endoscopy skills[17].

VR vs no training

Five studies had the control group did not receive intervention, compared to the VR training group, which included 10 h

for eight weeks[15], 2 h *per* day for three weeks[10], 16 h of VR[21], 2 to 3 h[22] or 2 h a week, six weeks[18] of unsupervised training on the GI Mentor I or II. It can be seen clearly that the VR training group in all five studies significantly improved their endoscopy competency after training.

The intervention group showed better objective and subjective outcomes than the control group in Cohen J's study[15]. The simulator group had higher objective competence, which means they could reach the transverse colon and the cecum without help and recognize and identify abnormalities correctly, with $P < 0.0001$. The difference was more pronounced in the first four blocks than in the last 16 blocks of 20 cases ($P < 0.001$). The simulator group also improved their subjective performance, which was rated on a 5-point scale from 1 (totally unskilled) to 5 (competent and expedient), with $P < 0.001$. The gap between the groups was more significant in the first 40 cases than in the remaining 160 cases ($P = 0.02$). In conclusion, trainees who underwent GI mentor training performed significantly better during the early phase of real colonoscopy training[15].

The study by Ferlitsch *et al*[10] in 2002 shows that intervention improved performance significantly after three weeks of VR training. This could be considered a fast improvement in endoscopic skills. The number of adverse events during endoscopy, the insertion time during colonoscopy, and skill test performance all showed significant improvement. One limit of this study was that the VR-based cases, which cannot interpret the impact of virtual simulator training on real-life endoscopy[10].

According to Ferlitsch *et al*[10] 2002 study, three weeks VR training significantly enhanced the intervention's effectiveness. This suggests a rapid improvement in endoscopic skills. The outcomes of skill test performance, insertion time during colonoscopy, and adverse events during endoscopy all improved considerably. However, this study had a limitation: The VR-based assessment did not reflect real-life endoscopy scenarios, so the influence of virtual simulator training on actual endoscopy needed to be clarified[10].

McIntosh *et al*[21] conducted a study to evaluate the effect of VR simulator training on novice trainees' performance of patient-based colonoscopies. They divided the participants into two groups: The intervention group received 16 h of VR training in GI Mentor II, while the control group did not. The results indicated that the intervention group performed better than the control group regarding procedure time, procedure skill, proctor assists, and competence ratings from the proctors and the nurses. The authors suggested that VR colonoscopy simulation is a valuable tool to enhance the learning curve of beginner colonoscopists, especially in the early training phase[21].

According to Park *et al*[22], 2007, residents who practiced colonoscopy on a simulator before their first live patient procedure performed significantly better than those who did not. The global ratings of performance, which were validated by previous studies, were higher for the treatment group than the control group. This demonstrated that VR skills can be transferred to live patients. However, only 2 out of 8 metrics from the computer-based simulator correlated significantly with the global ratings. This suggests that the simulator's metrics should be refined to match the actual performance level better[22].

Likewise, the Telem *et al*[18], 2014 study suggested that training on the GI mentor simulator improved the colonoscopic skills of novice surgical interns. Before training, only one intern (11%) could reach the cecum in 19.56 min. After training, six interns (67%) could do it in 9.2 min on average ($P < 0.05$). They also improved in four of the five GAGES-C criteria. The interns who reached the cecum after training had better scores on the simulator in efficiency (79% *vs* 67.1%, $P = 0.05$) and time to cecum (3.37 *vs* 5.59 min, $P = 0.01$) than those who did not. There was no significant difference in other GAGES-C categories or simulator parameters. Although the assessment was animal and VR-based, this study still supports training on the GI mentor simulator, improved the colonoscopic skills of novice surgical interns, and used this endoscopic simulator training as an effective supplement to clinical experience for surgical residents[18].

In conclusion, five studies show that VR training helped improve their endoscopy competency significantly, including procedure time, procedure skills, procedure completion, and global performance rating. They also support using endoscopic simulator training as a supplement to clinical experience for surgical residents.

VR vs conventional patient-based training

Three single-center randomized controlled trials (RCTs) from Ferlitsch *et al*[10], 2010; Gerson and Van Dam[19], 2003; and Shirai *et al*[23], 2008 assessed the effectiveness of VR tools for training in gastrointestinal endoscopy, including upper and lower endoscopy. They compared the VR training group with conventional patient-based training. The outcomes were diverse, and there were some controversies[10,19,23].

The trial by Ferlitsch *et al*[10], 2010 demonstrates that VR training positively impacts technical accuracy, such as procedure time and diagnosis of pathological entities. The trial shows that the VR group reached the duodenum faster than the control group in their first ten endoscopic examinations in patients [239 s (range 50-620) *vs* 310 s (110-720)], with $P < 0.0001$, and performed better in technical accuracy with $P < 0.02$. After 60 endoscopic examinations, the VR group's investigation time was still shorter group. However, the VR group no longer had an advantage over the control group in terms of technical accuracy or diagnostic accuracy. In addition, simulator training did not increase the number of pathological entities detected. However, both groups improved their skills and knowledge significantly after 60 live patients' examinations and increased their rate of pathological findings during upper gastrointestinal endoscopy. Therefore, the trial indicates that VR training can be a beneficial component of an endoscopy training curriculum. However, it cannot wholly substitute on-patient training, which is essential for training success[10].

Likewise, Shirai *et al*[23] (2008) conducted a study to evaluate the impact of the GI-Mentor II simulator on residents' EGD skills. They randomly assigned the residents to two groups: One group received simulator training (5 h) and bedside training, while the other group received only bedside training. The residents then performed two EGDs each and were assessed on 11 criteria using a five-point scale. The simulator group showed significantly higher scores on the criteria related to insertion and navigation skills, such as esophageal entry, esophagogastric junction and pylorus crossing, and duodenal bulb and fornix examination. VR training helps residents with manipulation skills[19].

Conversely, an RCT by Gerson and Van Dam[19] in 2003 compared the effectiveness of VR and bedside teaching methods for teaching internal medicine residents how to perform sigmoidoscopy in asymptomatic patients for colorectal cancer screening. The trial involved 16 residents who did five procedures each, and their duration, completion, and skills were measured. The trial found that the VR group had more challenges inserting the endoscope and passing the rectosigmoid junction than the conventional group. VR group also had lower rates of reaching the splenic flexure independently and retroflexing the endoscope. Their average procedure time was longer as well. The trial concluded that a VR-based endoscopy simulator was less effective than conventional bedside teaching techniques when used solely for training residents in sigmoidoscopy[23].

VR vs another form of endoscopy simulation

Among 16 studies, one study from Gomez PP, 2015 assessed VR training compared to physical model training. Participants in this RCT completed a 3-wk flexible endoscopy curriculum. One group was assigned to train with the GI mentor simulator, one with the Kyoto physical simulator, and the last with both simulators. The trial indicates that there is a statistically significant improvement in the GAGES total score ($P < 0.001$). The VR group or combination group showed significant improvement from the pretest to the posttest in terms of GAGES total score ($P = 0.017$ vs 0.024 , respectively). This was not observed for those exclusively using the Kyoto platform ($P = 0.072$). This trial suggests that VR training with the GI mentor platform for colonoscopy training, or in combination with a physical model simulator, improves skill performance in real colonoscopy cases when measured with the GAGES tool[20].

Different methods of VR endoscopy simulation training

Hashimoto *et al*[9], 2018, Koch *et al*[11], 2015 and Grover *et al*[8], 2015 conducted studies that compared different methods of VR application in endoscopy training[8,9,11].

Hashimoto *et al*[9] used the fundamentals of endoscopic surgery (FES) examination, which measures knowledge and skill in flexible GI endoscopy. They randomly assigned participants in pairs to either a repetition curriculum (10 times each task) or a proficiency curriculum (repeated each task until reaching the benchmark twice in a row). They compared both groups' FES scores and pass rates with national and institutional data. The proficiency group outperformed the historical control group significantly ($P = 0.0003$) and had a 100% pass rate (proficiency: 100%, historical control 61.5%, $P = 0.01$). The repetition and proficiency curricula had similar results, but only the proficiency curriculum had a 100% pass rate and a performance that was significantly better than the historical institutional control[9].

Koch *et al*[11] conducted a study with two groups of participants. Group I had 50 VR colonoscopies, and group II had 100 cases. Participants were evaluated on both simulator-based assessment (SBA) and patient-based assessment, and the average cecal intubation time on the SBA for all participants reduced from 9.50 min at the beginning to 2.20 min at the end of the training ($P = 0.002$). Colonic insertion depth during patient-based assessment increased from 29.4 cm to 63.7 cm ($P < 0.001$). The findings indicate a quick improvement in simulator performance during the first 50 VR colonoscopies. After 60 VR colonoscopies, the learning effect of extended training on the simulator diminished. This implies that VR training in colonoscopy can enhance performance on the simulator and, more importantly, patient-based colonoscopy. This study also supports intensive simulator training in the early learning curve of colonoscopy trainees[11].

A RCT by Grover *et al*[8] in 2015 evaluated the effectiveness of a simulation-based structured comprehensive curriculum (SCC) for colonoscopy training. The SCC group received six hours of theoretical lectures and eight hours of VR training with expert feedback, while the control group only received a list of objectives and practiced on the same simulator for eight hours without feedback. The outcome measures showed that the SCC group had better performance, knowledge, communication, and global skills during their first and second clinical colonoscopies than the control group [8].

The potential of VR training in endoscopy was demonstrated by all three studies, which enhanced the skills of trainees in both VR cases and live patients. However, the first two studies differed in their recommendations regarding the timing and duration of VR training. The authors suggested a more extensive, multi-center study to address this limitation. The trial of Grover *et al*[8] showed the importance of incorporating endoscopy simulation into a structured curriculum that includes VR training, instructional feedback, and complementary didactic knowledge as the most effective way to train in colonoscopy.

The impact of VR training on patient outcomes

Many of the 16 studies that were reviewed focused on evaluating the patient outcomes of VR training for endoscopy. In addition to improving endoscopy capacities in live patients from VR training, such as procedure time, procedure skills, some studies also assessed the level of discomfort the patients experienced during the procedure. One such study, conducted by Van Sickle *et al*[17] in 2011, demonstrated that after the VR training, flexible endoscopies of trainees showed that the patient discomfort level decreased significantly, indicating a positive impact on patient satisfaction and safety [17]. However, not all studies found such benefits of VR training on patient outcomes. In the group of studies that compared VR training with no training, the patient's perspectives were also evaluated by Cohen *et al*[15] in 2006 and McIntosh *et al*[21] in 2014. The results of Cohen *et al*[15] study showed that the simulator and the control groups performed similarly overall, and there was no significant difference in the patient comfort level between them[15]. Likewise, McIntosh *et al*[21] 2002 reported no significant differences in pain ratings by proctors, nurses, or patients or attention to discomfort between the VR group and the no-training group[21]. Similarly, according to the studies from Ferlitsch *et al*[12] in 2010 and Gerson and Van Dam[19] in 2003, which compared VR training with conventional patient-based training, there were no significant differences in patient discomfort and pain scores between the two groups. These findings suggest that VR training may not have a consistent or substantial effect on patient outcomes and that other factors may influence the patient experience of endoscopy[12,19].

The advantages and limitations of VR-based training compared to traditional training methods in gastrointestinal endoscopy

VR training has some pros and cons compared to traditional training methods. This is shown by three studies from Ferlitsch *et al*[12], 2010; Gerson and Van Dam[19], 2003; and Shirai *et al*[23], 2008, that compare VR tools and bedside teaching for training in gastrointestinal endoscopy[12,19,23].

The study of Shirai *et al*[23] in 2008 proved other advantages of VR tools. According to this study, the VR simulator helped trainees significantly improve manipulation skills, including insertion and navigation skills, such as esophageal entry, EGJ and pylorus crossing, and duodenal bulb and fornix examination[12].

However, according to the study by Ferlitsch *et al*[10], 2010, the VR group had better procedure time and technical accuracy results than the conventional group. However, this advantage did not last long, and the VR group did not perform better than the control group in technical or diagnostic accuracy after a while. Moreover, the VR group did not detect more pathological entities than the control group. Therefore, this study suggests that VR is beneficial for training technical skills in the early stages of training. However, it has some drawbacks for training the later stages and the pathological entities. These are the areas where bedside teaching is more effective[19].

Similarly, regarding sigmoidoscopy in asymptomatic patients for colorectal cancer screening, the study from Gerson and Van Dam[19] in 2003 found that the VR group had more challenges with inserting the endoscope and passing the rectosigmoid junction than the conventional group. VR group also had lower rates of reaching the splenic flexure independently and retroflexing the endoscope. Their average procedure time was longer as well. The trial concluded that a VR-based endoscopy simulator was less effective than conventional bedside teaching techniques when used solely for training residents in sigmoidoscopy[23].

Gerson and Van Dam[19] (2003) concluded that a VR-based endoscopy simulator was inferior to conventional bedside teaching techniques when used alone for training residents in sigmoidoscopy. Notably, comparing the VR group and the conventional group in sigmoidoscopy for colorectal cancer screening, the VR group had more difficulties inserting the endoscope and passing the rectosigmoid junction than the conventional group. The VR group also had lower success rates of reaching the splenic flexure and retroflexing the endoscope. Their procedure time was longer as well[23].

The feasibility and acceptability of VR-based training programs in gastrointestinal endoscopy

This systematic review included 16 studies that assessed the feasibility and acceptability of using VR as a training tool for gastrointestinal endoscopy. Of these 16 studies, 15 reported positive results, indicating that VR-based training was feasible and acceptable for endoscopy learners. The main reason for this finding was that VR technology helped the trainees enhance their skills in manipulating the endoscope, reducing the procedure time or increasing the technical accuracy both in VR scenarios and in actual patients[4,15-17,24]. VR training was also a promising alternative to no training methods, as it improved the performance of endoscopy learners compared to those who did not receive any training. Furthermore, VR tools were superior to conventional training methods in some aspects, especially for the initial phases of endoscopy training, such as insertion and navigation skills[10,23]. Shirai *et al*[23] also suggested that VR could be used as an effective assessment tool with capabilities similar to expert evaluators[23].

Only one study out of 16 claimed that VR-based training was inferior to conventional teaching and could not replace it (Gerson and Van Dam[19], 2003). This study implied that VR technology did not offer the same benefits as traditional bedside teaching. However, it needed to consider combining the advantages of both teaching methods. A hybrid teaching method involving both VR and patient-based teaching could be a more effective way of delivering endoscopy training [19].

DISCUSSION

This systematic review underscores the efficacy of VR simulator training in instructing gastrointestinal endoscopy, encompassing both gastroscopy and colonoscopy. The findings reveal that VR training surpasses scenarios with no training, lacks comparators, or employs alternative simulations in enhancing trainees' proficiency in endoscope manipulation, procedure duration, psychomotor skills, and technical precision. Consequently, the incorporation of VR-based endoscopy training emerges as an innovative and beneficial approach for practical implementation. Moreover, the review suggests diverse strategies for training endoscopy learners, ranging from utilizing VR cases in isolation to combining them with lectures or incorporating expert feedback.

This systematic review indicates that VR training has some unique benefits, but it also has some drawbacks that prevent it from entirely replacing bedside teaching. Three single-center RCTs from Ferlitsch *et al*[12], 2010; Gerson and Van Dam[19], 2003; and Shirai *et al*[23], 2008 found that VR training can enhance an endoscopy training curriculum, but cannot substitute for on-patient training, which is crucial for success[12,19,23].

This systematic review of VR training's effects on patient discomfort levels reveals that VR training significantly reduced patient discomfort levels, suggesting a positive influence on patient satisfaction and safety. Although the VR and bedside teaching groups had similar overall performance, the VR training improved patient discomfort levels.

These findings are consistent with Singh *et al*[25] in 2014, Qiao *et al*[26] in 2014, Ekkelenkamp *et al*[27] in 2015, and Khan *et al*[28] in 2018.

A systematic review and meta-analysis by Singh *et al*[25] 2014 examined 39 articles on simulation-based training for endoscopy. The result shows that compared with no intervention ($n = 32$ studies), simulation-based training significantly improved endoscopic process skills in a test setting [effect size (ES) = 0.79, $n = 22$], process behaviors in clinical practice (ES = 0.49, $n = 8$), time to procedure completion in both a test setting (ES = 0.79, $n = 16$) and clinical practice (ES = 0.75, $n =$

5), and patient outcomes (procedural completion and risk of significant complications, ES = 0.45, $n = 10$). Only five studies evaluated the comparative effectiveness of different simulation-based training approaches, which provided inconclusive evidence regarding feedback and simulation modalities[25].

According to a systematic review by Qiao *et al*[26] in 2014, fifteen studies met the inclusion criteria of his study. The review compared the outcomes of simulators and conventional training for gastroscopy and colonoscopy. For gastroscopy, simulator training resulted in a significantly higher rate of independent completion of the procedure (87.7% vs 70.0%, 1 study, 22 participants, relative risk (RR) = 1.25, 95%CI: 1.13–1.39, $P < 0.0001$). For colonoscopy, there was no significant difference between simulator training and conventional training in terms of independent completion of the procedure (89.3% vs 88.9%, 7 studies, 163 participants, RR = 1.10, 95%CI: 0.88–1.37, $P = 0.41$, $I^2 = 85\%$)[26].

Ekkelenkamp *et al*[27] 2015 carried out a systematic review of twenty-seven studies on simulator validation. Increased performance on a VR simulator was shown in all studies. Improved performance in patient-based assessment was demonstrated in 14 studies. Four studies reported on the use of simulators for assessment of competence levels. Current simulators lack the discriminative power to determine competence levels in patient-based endoscopy. Eight out of 14 studies on colonoscopy, endoscopic retrograde cholangiopancreatography, and endosonography reported on learning curves in patient-based endoscopy and proved the value of this approach for measuring performance. Ten studies explored the numbers needed for competence, but the proposed thresholds varied widely. Five out of nine studies describing the development and evaluation of assessment tools for GI endoscopy provided insight into the performance of endoscopists. Five out of seven studies proved that intense training programs result in good performance[27].

A 2018 review by Khan *et al*[28] analyzed 18 trials with 3817 endoscopic procedures performed in 2017. The review showed that VR training was better than no training in terms of independent procedure completion (RR = 1.62, 95%CI: 1.15–2.26, moderate-quality evidence), overall rating of performance [mean difference (MD) 0.45, 95%CI: 0.15–0.75, very low-quality evidence], and mucosal visualization (MD 0.60, 95%CI: 0.20–1.00, very low-quality evidence). On the other hand, VR training led to fewer independent procedure completions than conventional training (RR = 0.45, 95%CI: 0.27–0.74, low-quality evidence), and VR training did not improve the composite score of competencies compared to no training or conventional training. Khan *et al*[28] did not find any significant differences between VR training and no training or conventional training for other outcomes and did not find any significant differences between VR training and other simulation training methods based on qualitative analysis. Unlike unstructured curricula, VR curricula that were structured according to educational theory had a positive effect on the composite score of competencies[28].

This systematic review and the above all agreed that VR simulator training is practical for beginners in endoscopy training. Despite minor differences between this review and the other three, the results all suggest that VR-based teaching is effective in endoscopy training, especially in the early training phases. Although there are some debates about whether VR training can fully replace conventional training, it is still a balanced option to consider this method complementary to conventional endoscopy training.

The integration of VR training encounters notable challenges, with a primary obstacle being the substantial cost associated with VR technology for endoscopic training. Acquiring, maintaining, and updating VR simulators demands considerable financial investment, alongside the necessity for dedicated space and personnel. Consequently, the accessibility and affordability of VR training become limiting factors for numerous endoscopic centers, particularly those situated in low-resource settings. Furthermore, the scarcity of long-term studies assessing the impact of VR on clinical outcomes and patient safety raises additional concerns regarding the widespread feasibility of VR training, particularly in resource-constrained environments. Additionally, the development of cases tailored to meet learners' needs and curriculum objectives is a demanding task, requiring in-depth knowledge of the subject matter, learning outcomes, and effective pedagogical strategies.

Moreover, it involves carefully selecting relevant and authentic scenarios, data, and resources to engage and challenge the learners. Furthermore, it necessitates precisely aligning the case with the assessment criteria and feedback mechanisms. Therefore, case development is a complex and time-consuming process that requires careful planning, design, and evaluation. More long-term studies are needed to confirm the cost-effective balance and efficacy of simulator-based training methods for endoscopy learners.

Lately, the field of medicine is undergoing significant changes as a result of the development and application of artificial intelligence (AI) techniques[29,30]. Moreover, AI can also help improve the performance of endoscopists as a cutting-edge training tool[31]. By offering real-time assistance, feedback and evaluation, AI can facilitate the learning process of endoscopy and help endoscopists achieve better outcomes[32].

Endoscopy training can benefit from the integration of AI and VR. While AI can enhance the learning process by providing individualized feedback, tailoring the difficulty level to the learner's needs and generating realistic cases from real-world data, VR can augment and optimize the learning environment that mimic real environments. By combining AI and VR, endoscopy training can offer a more comprehensive and engaging learning experience that improves the trainees' competencies and self-efficacy. Blended learning, which combines conventional methods with cutting-edge technologies such as AI and VR, is a promising approach for endoscopy training. Another potential strategy is mobile health, which involves the use of mobile devices and wireless technologies to deliver health care services and education. Mobile health can enhance the accessibility, quality and efficiency of endoscopy training, especially in remote and rural areas. This strategy can complement blended learning. More studies are needed before implementing these methods to reality.

Regarding limitations, there was the diversity of results, including methodology, types of trainees, interventions and outcomes measured. As a result, head-to-head comparison of individual studies as well as meta-analysis were not conducted.

Additionally, our results were limited by methodological quality of the included studies. About half of them were non-randomized, including several single-group, pre and post, prospective and two-phase studies.

CONCLUSION

In conclusion, this systematic review supports the idea that VR training is practical for endoscopy training. There are several well-designed RCTs with large sample sizes, proving the potential of this innovative tool. Thus, VR should be more widely used in endoscopy training. Moreover, VR training in combination with conventional methods could be a promising approach that should be deployed in training. However, more studies are needed to compare VR training with traditional methods and to design the ideal curriculum for VR or VR and traditional methods.

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Contents

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MINIREVIEWS

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Contents

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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 cholangio-pancreatography, endosonography, esophagoscopy, gastrointestinal endoscopy, gastroscopy, laparoscopy, natural orifice endoscopic surgery, proctoscopy, and sigmoidoscopy.

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Delivering a high-quality colonoscopy service fit for the 21st century

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Abstract

Colorectal cancer (CRC) is the third most prevalent cancer globally. There is a concerning increase in its incidence among younger individuals. Colonoscopy remains the gold standard for CRC diagnosis. With the introduction of population-based bowel screening and increased public awareness, there has been a significant rise in referrals for colonoscopy. Healthcare providers worldwide will need to strategically evaluate how to allocate resources to adequately train the next generation of colonoscopists who will need to provide accurate endoscopic assessment and treatment for premalignant polyps and early CRC. This review outlines the current workload challenges faced by colonoscopists whilst exploring emerging technologies such as artificial intelligence for adenoma detection. Additionally, advanced endoscopic surgical techniques like endoscopic submucosal dissection are discussed.

Key Words: Colonoscopy; Colorectal cancer; Bowel screening; Polyps; Adenoma

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Core Tip: This comprehensive review summarizes the current state of colonoscopy worldwide. We discuss workload, polyp detection and endoscopic management, training, and emerging technologies.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide, and the second leading cause of cancer-related deaths internationally. Worldwide in 2022, more than 1.9 million new cases were diagnosed, and more than 900000 cancer-related deaths were recorded[1]. There is evidence that the incidence of both colon and rectal cancers are increasing in individuals younger than 50 years[2]. When these types of cancer are diagnosed early, survival and quality of life are significantly improved. Stage I colon and rectal cancers have a 5-year survival rate > 90%, whereas the 5-year survival rates for stage IV colon and rectal cancers are 13% and 17%, respectively[3].

The majority of CRCs develop through the 'classical' adenoma-carcinoma sequence, a process that can take 10 years or longer. CRC that developed *via* the relatively accelerated microsatellite instability pathway takes a few years[4]. The long latent phase in disease development means CRC is a potentially preventable and treatable disease.

Globally, over 50 million colonoscopies were performed annually in 2018 and 2019[5]. Colonoscopy involves direct high-resolution visualization of the colonic and rectal mucosa. It provides accurate detection and assessment of premalignant adenomas and carcinomas. In addition, advanced endoscopic resection techniques allow selected premalignant and early malignant lesions to be excised with good oncological outcomes without the need for conventional resection surgery. As a result, global demand for colonoscopy is expected to increase, which will put pressure on healthcare systems to provide this technology. This review summarized contemporary scientific literature to quantify the impact of colonoscopy in reducing disease burden, to evaluate the current quality indicators that define a good colonoscopy examination, to detail current standards in the assessment and endoscopic treatment of premalignant polyps, and to evaluate the current role of artificial intelligence in colonoscopy.

METHODS AND RESOURCES

A list of subtopics related to colonoscopy was compiled with consensus between the authors. A systematic literature search of PubMed, Medline, ScienceDirect, Cochrane Central Register of Controlled Trials databases, and Google Scholar was carried out by the authors. Keywords used included "colorectal cancer," "colonoscopy," "adenoma," "polypectomy," "quality," "training," and "artificial intelligence." A summary of the literature included in the review is presented in Table 1.

BENEFITS AND RISKS OF COLONOSCOPY

When colonoscopy is used as a cancer screening tool in the asymptomatic population the risk of CRC is decreased by 18% compared to no screening at 10 years of follow-up [0.98% *vs* 1.20%; relative risk (RR): 0.82; 95% confidence interval (CI): 0.70-0.93][6]. In the intention-to-treat analysis, the risk of CRC-related death was lower in the screening group (0.84% *vs* 1.2%; RR: 0.69; 95%CI: 0.55-0.83). In the adjusted per-protocol analysis, the magnitude of reduction in CRC-related death was lower in the screening group (0.15% *vs* 0.30%; RR: 0.50; 95%CI: 0.27-0.77). The magnitude of risk reduction appeared to be smaller compared to previous studies[7]. This finding likely reflects a declining risk of CRC and an improvement in the prognosis of CRC due to better treatment options.

In the pooled analysis, the sensitivities of colonoscopy for the detection of adenomas ≥ 10 mm and ≥ 6 mm were 89%-95% and 75%-93%, respectively. The respective specificities are 89% and 95% respectively[7]. Although computed tomography (CT) colonography offers similar performance levels, colonoscopy has several benefits for the management of premalignant and malignant colorectal lesions including direct visualization and characterization of lesion morphology, tissue diagnosis, and the potential to resect the lesion. In addition, CT colonography has several disadvantages including less accurate assessment of distal rectal lesions and detection of 'incidentomas,' which are of no significant clinical consequence but require additional resources for follow-up and can generate unnecessary anxiety for the patient. The risks of colonoscopy are bleeding and perforation, which are < 18 per 10000 and < 6 per 10000, respectively[7].

The potential for pain during colonoscopy is a disadvantage. The endoscopist's ability to assess pain during the procedure is just as important as performing the test itself. In one study examining patients with moderate/severe pain during colonoscopy, factors associated with underestimation of moderate/severe pain by endoscopists included being male [odds ratio (OR): 1.79], normal body mass index (OR: 1.71), no previous abdominal surgery (OR: 1.81), and first colonoscopy (OR: 1.81)[8]. The choice of insufflation technique is also a determining factor. Both carbon dioxide and water insufflation are shown to be superior compared to air insufflation. In one systematic review, use of carbon dioxide insufflation was associated with lower procedural pain [standardized mean difference (SMD): -1.34; 95%CI: -2.23 to -0.45; $Z = 2.96$; $P < 0.003$] and postprocedural pain at 1 h (SMD: -1.11; 95%CI: -1.83 to -0.38; $Z = 2.97$; $P < 0.003$), and at 6 h and 24 h (OR: 0.44; 95%CI: 0.23-0.85; $Z = 2.44$; $P < 0.01$). Carbon dioxide insufflation was associated with faster intubation to the cecum (SMD: -0.20; 95%CI: -0.37 to -0.02; $Z = 2.23$; $P < 0.03$), but the cecal intubation rate was similar ($P = 0.59$) in both colonic insufflation techniques[9]. In another systematic review, water infusion subjects experienced significantly lower pain (mean difference in pain score on a 0 to 10 scale: -1.57; 95%CI: -2.00 to -1.14; $P < 0.00001$). Fewer participants requested on-demand sedation or analgesia or both (RR: 1.20; 95%CI: 1.14-1.27; $P < 0.00001$)[10].

Table 1 Summary of literature reviewed

Ref.	Study format	Level of evidence ¹
Benefits and risks of colonoscopy		
Bretthauer <i>et al</i> [6], 2022	Randomized controlled trial	I
Lin <i>et al</i> [7], 2021	Systematic review	II
Ryhlander <i>et al</i> [6], 2022	Cross-sectional study	III
Sajid <i>et al</i> [9], 2015	Systematic review	II
Hafner <i>et al</i> [10], 2015	Systematic review	II
Quality assurance, training, and human resources		
Rex <i>et al</i> [11], 2015	Systematic review	II
Sawhney <i>et al</i> [12], 2008	Cross-sectional study	III
Chung <i>et al</i> [13], 2010	Cross-sectional study	III
Haycock <i>et al</i> [14], 2010	Randomized controlled trial	II
Khan <i>et al</i> [15], 2012	Systematic review	II
Barton <i>et al</i> [16], 2012	Cross-sectional study	III
Sedlack <i>et al</i> [17], 2011	Observational study	V
Gupta <i>et al</i> [18], 2012	Observational study	V
Hitchins <i>et al</i> [19], 2018	Review	V
Endoscopic assessment and risk stratification of premalignant polyps, with tattoo		
Kaltenbach <i>et al</i> [20], 2022	Guideline	V
The Paris Endoscopic Classification of Superficial Neoplastic Lesions, 2003	Retrospective case series	V
Komeda <i>et al</i> [22], 2017	Retrospective case series	V
Pohl <i>et al</i> [23], 2018	Commentary	V
Kudo <i>et al</i> [24], 1996	Case series	V
Hayashi <i>et al</i> [25], 2013	Case series	V
Hewett <i>et al</i> [26], 2012	Case series	V
Kitajima <i>et al</i> [27], 2004	Case series	V
Ishigaki <i>et al</i> [28], 2020	Retrospective case series	V
Nivatvongs <i>et al</i> [29], 1991	Retrospective case series	V
Ueno <i>et al</i> [30], 2004	Retrospective case series	V
Cooper <i>et al</i> [31], 1995	Retrospective case series	V
Haggitt <i>et al</i> [32], 1985	Retrospective case series	V
Kikuchi <i>et al</i> [33], 1995	Case series	V
Heafner <i>et al</i> [34], 2014	Review	V
Yang <i>et al</i> [35], 2017	Review	V
Artificial intelligence		
Repici <i>et al</i> [36], 2022	Randomized controlled trial	I
Hassan <i>et al</i> [38], 2020	Retrospective case series	V
Bowel preparation		
Lai <i>et al</i> [39], 2009	Case series	V
Mahmood <i>et al</i> [40], 2018	Systematic review	II
Russmann <i>et al</i> [41], 2007	Retrospective cohort study	IV
Parikh <i>et al</i> [42], 2011	Review	V

Spada <i>et al</i> [43], 2017	Randomized controlled trial	I
Chen <i>et al</i> [44], 2020	Meta-analysis	II
Alternatives to colonoscopy		
Lin <i>et al</i> [7], 2021	Systematic review	II
Rex <i>et al</i> [45], 2015	Case series	V

¹Adopted from “Level of evidence hierarchy” published by Elsevier Author Services.

QUALITY ASSURANCE, TRAINING, AND HUMAN RESOURCES

Adenoma detection rate (ADR), cecal intubation rate, and withdrawal time are all commonly used as quality indicators. ADR was initially set at > 20% (25% in males and 15% in females) based on earlier studies but was subsequently raised to 25% by the United States Task Force[11]. The minimal scope withdrawal time was set at 6 min, based on correlation with ADR. The withdrawal time of > 7 min did not improve ADR[12].

Basic competency in performing colonoscopy is achieved by colonoscopists after approximately 200 procedures, although this number varies between 100-500 procedures[13]. Simulation is now widely used to improve training for novices in conjunction with supervised hands-on training. Simulator training significantly improved performance in simulated cases compared to patient-based training. Time to completion and technical finesse were both improved in the simulator group, although such outcomes were not observed when the study groups were assessed in live cases[14].

A Cochrane review in 2012 showed virtual reality endoscopy is useful as an effective supplement to early conventional endoscopy training (apprenticeship model)[15]. However, there was no consensus in the literature for integration into an existing training program, for the duration of training, nor for the level of supervision. The Mayo Colonoscopy Skills Assessment Tool and the Direct Observation of Procedural Skills (DOPS) are used to assess skills. The Mayo Colonoscopy Skills Assessment Tool is generally used for trainees, whereas DOPS is generally used for more senior endoscopists[16, 17]. A separate polypectomy-specific DOPS has also been validated[18]. Non-technical skill domains, such as situational awareness, decision-making, communication, teamwork, and leadership, have been developed but have not been validated. Such skills can potentially improve performance and patient experience[19].

ENDOSCOPIC ASSESSMENT AND RISK STRATIFICATION OF PREMALIGNANT POLYPS

As the quantity and quality of colonoscopies increase, the volume of premalignant and malignant polyp detection will also increase. All colonoscopists should be able to identify and characterize these polyps at the index colonoscopy. The United States Multisociety Task Force on Colorectal Cancer has set out a benchmarking guideline for lesion assessment and description and endoscopic removal[20]. As a minimum, the location, size, and morphology of the polyp and its surface should be carefully documented using the Paris Classifications[21,22]. All polyps should be photographed at the index procedure prior to removal. In particular, all lesions ≥ 10 mm in size should have the post-resection mucosal defect documented photographically. The use of electronic- (*e.g.*, narrow band imaging) or dye (chromoendoscopy)-based image-enhanced endoscopy techniques may help improve morphological descriptions.

All trained colonoscopists should be able to resect small mucosal lesions (< 9 mm) using the cold or hot snare technique for complete resection. The cold and hot snare techniques are acceptable for non-pedunculated (10-19 mm) lesions by colonoscopists with sufficient polypectomy experience. However, endoscopic resection of polyps ≥ 20 mm should be delegated to endoscopists with advanced training. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are both acceptable techniques[23]. ESD has the advantage over EMR due to the en bloc nature of resection, which leads to better lateral and deep margins and more accurate pathological staging. However, the learning curve for ESD is steep, and the perforation rate is higher than in EMR. General anesthesia (and therefore hospitalization) is often needed due to the prolonged nature of the procedure. Therefore, the availability of ESD is limited to selected tertiary referral centers. Even if the index colonoscopy was performed by a colonoscopist with advanced training, EMR and ESD should be deferred to obtain informed consent of the risks.

Recognition of deep submucosal invasion in flat, depressed, or sessile lesions, regardless of polyp size, is key to determining between endoscopic resection and surgical resection. Key endoscopic appearance includes general ulceration of the lesion surface, disruption of the normal vascular, and pit patterns[24]. These findings correspond to type III by the NICE classification and type V/Vn by the Kudo classification[25,26]. Surface ulceration and stiffness of the lesion and colonic wall are also predictive of deep submucosal invasion. In the presence of such a lesion, the risk of lymph node metastasis is higher. Therefore, surgical resection is more suitable for good surgical candidates[27]. Pedunculated polyps can be resected with snare polypectomy with as much stalk as possible for the margin.

Lateral spread tumors (LSTs) are premalignant lesions > 10 mm with an extending horizontal growth pattern[28]. Non-granular LSTs have more potential for deep submucosal invasion and multifocal invasion compared to granular LSTs. Superficial submucosal invasion cannot be reliably identified after piecemeal resection. For lesions > 20 mm, ESD is the only modality that can achieve en bloc resection. Therefore, recognition of this subtype and referral to the appropriate multidisciplinary team to address a complex polyp is recommended.

When submucosal invasion (*i.e.* cancer) is identified in a resected polyp specimen, an assessment of the probability of residual cancer in the bowel wall and lymph node involvement is made. For pedunculated polyps, the presence of one of the unfavorable histological criteria warrants surgery in those who are good candidates. These criteria include poor differentiation[29], tumor budding (defined as separate small groups of cancer cells at the leading edge of the cancer)[30], and < 1 mm resection margin[31]. Haggitt level 4 (cancer invading the polyp stalk) is an alternative factor indicating a poor prognosis[32].

For non-pedunculated polyps, the presence of poor tumor differentiation, lymphovascular invasion, and tumor budding are considered poor histological criteria. A non-pedunculated malignant polyp is generally considered a higher risk for residual disease following endoscopic resection than a pedunculated malignant polyp. However, if the non-pedunculated polyp is resected en bloc and appropriately handled by the colonoscopist and pathologist, low-risk non-pedunculated polyps can be managed without surgery. Historically, the depth of invasion in a non-pedunculated polyp is measured by the Kikuchi Classification[33], which subdivides the mucosa into thirds. However, as full-thickness resection is not achieved for colonic endoscopic resections, the Katajima criterion of greater or less than 1000 μ m of invasion has become the new standard in Japan[29].

For malignant rectal lesions, consideration should be made to perform full-thickness resection using the transanal approach by a trained colorectal surgeon. A baseline endoscopic ultrasound should also be performed. The risk of local recurrence at any stage is higher for rectal cancer compared to colon cancer[34]. Therefore, more intensive endoscopic surveillance is required if endoscopic resection is chosen for low-risk lesions.

It is imperative that lesions ≥ 10 mm or lesions that have high-risk endoscopic features are tattooed at the time of the index colonoscopy (regardless of their resection status). Currently, there is no consensus for the tattoo placement in relation to the polyp/polypectomy site, for the requirement of multiple spots, and for tattooing rectal lesions[35]. In our clinic, we tattoo using Spot® (GI Supply, Camp Hill, PA, United States), which consists of highly purified carbon particles as a tattooing material in an attempt to reduce the mild tissue inflammation caused by traditional India ink. A saline submucosal bleb is created 2 cm distal to the lesion/polypectomy site before injection of the tattoo. At least two spots on opposite sites are injected to easily identify the polyp if the patient proceeds to surgery. Whichever technique is used, it is important that the colonoscopist documents where the tattoo is in relation to the polyp/polypectomy site to aid future follow-up.

ARTIFICIAL INTELLIGENCE

Artificial intelligence, specifically computer-aided detection (CADe) software, has been extensively studied in the context of improving ADRs. In a prospective, randomized controlled non-inferiority trial, CADe (GI Genius™ Intelligent Endoscopy Module; Medtronic, Minneapolis, MN, United States) improved ADR (53.3% *vs* 44.5%; RR: 1.22; 95%CI: 1.04 to 1.40; $P < 0.01$) in non-expert endoscopists (< 2000 lifetime colonoscopies)[36]. Similar results were achieved in another prospective multicenter randomized controlled trial where the overall ADR (39.9% *vs* 32.4%; $P < 0.001$), advanced ADR (6.6% *vs* 4.9%; $P = 0.041$), ADR of expert (42.3% *vs* 32.8%; $P < 0.001$) and nonexpert endoscopists (37.5% *vs* 32.1%; $P = 0.023$), and adenomas per colonoscopy (0.59 ± 0.97 *vs* 0.45 ± 0.81 ; $P < 0.001$) were all significantly higher in the artificial intelligence-assisted colonoscopy (Eagle-Eye; Xiamen Innovision Medical Technology, Xiamen, China)[37].

Deep learning, a subtype of machine learning, uses an artificial neural network comprised of layers of interconnected computing units that mimic biological neural connections and allow for complex interpretation of input data. This allows the computer program to learn from unstructured input data. CADe aids in the detection of small polyps otherwise missed by the human eye. However, further research and development are needed before CADe can be entrusted with full polyp characterization. Currently, there is a high false alarm rate (as high as 27.3 per colonoscopy)[38]. Initially, CADe is being trained to confirm hyperplastic polyps in the rectosigmoid area, which would reduce morbidity and costs for unnecessary polypectomies.

BOWEL PREPARATION

Poor bowel preparation adversely affects completion rate and ADR, and increases the cost due to a repeat examination. The Boston bowel preparation scale has been shown to be a valid and reliable measure of bowel preparation[39]. The quality of bowel preparation is affected by the type of bowel preparation, split-dose regimen, low-fiber diet, comorbidities, concomitant medications, inpatient status, and elderly age[40]. Polyethylene glycol (PEG) is commonly used in 2 L or 4 L preparations. It is safe in patients with renal impairment, although patients with heart disease should exercise caution due to the potential increase in plasma volume[41,42]. Split-dose high-volume PEG has been shown to be more effective than split-dose low-volume PEG. However, high-volume preparations often decrease compliance. As a result, an adjunct to PEG has been added. When 2 L of PEG plus citrate was compared to 4 L of PEG a similar cleansing efficacy (73.6% *vs* 72.3%; 95%CI: -7.5 to 10.1) with greater tolerability (25.4% *vs* 37.0%; $P < 0.01$) and acceptability (93.9% *vs* 82.2%; $P < 0.001$) were observed[43].

A low residue or clear liquid diet at least 1 d prior to colonoscopy are both acceptable. A low residue diet was shown in one study to have better tolerability (OR: 1.92; 95%CI: 1.36-2.70; $P < 0.01$). Patients in the same study had a higher willingness to repeat the bowel preparation (OR: 1.86; 95%CI: 1.34-2.59; $P < 0.01$)[44]. In patients who continue to have inadequate preparation despite compliance, a clear liquid diet for 2 d is usually prescribed, followed by a morning procedure. Other options include the addition of a second laxative if no contraindications exist (*e.g.*, 4 L of PEG followed

by 1 L of magnesium citrate) or repeating the preparation over 2 d (with the exception of sodium phosphate).

ALTERNATIVES TO COLONOSCOPY

CT colonoscopy and capsule colonoscopy are both comparable in diagnostic yield to colonoscopy. The sensitivity for adenomas ≥ 6 mm is 86% for CT colonography and 88% for capsule colonoscopy[7,45]. Whilst both modalities are acceptable for the initial screening of CRC and adenomas, they do not offer therapeutic options. In particular, a CT colonoscopy can result in extracolonic findings that require further follow-up (up to 26.9%)[7]. The interpretation of these images also consumes a significant amount of manpower. The role of colonoscopy as a cost-effective one-stop option to screen and treat premalignant lesions in the same setting remains undisputed.

CONCLUSION

Worldwide demand for colonoscopy is increasing. With a high workload volume, an opportunity exists to streamline and standardize colonoscopy techniques and reporting. In particular, patients with malignant polyps should be stratified by risk to effectively manage treatment through colonoscopy or surgery. To accomplish this, colonoscopists should focus on improving diagnostic yield and quality. Colonoscopists should also participate in multidisciplinary meetings for CRC and counsel patients on the benefits of endoscopic resection. This effectively creates an alternative pillar in the management of CRC, in addition to surgery and chemoradiotherapy.

This article provided a broad and current overview of colonoscopy. It was not intended to be a systematic review but was intended to set the direction for further qualitative and quantitative studies of the subtopics in this growing field.

FOOTNOTES

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