Artificial intelligence and its application in endoscopic diagnosis of digestive disease

Short title: AI in digestive endoscopic diagnosis

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ABSTRACT

Accompanied with increased attention and interests in applying artificial intelligence in medicine, accumulating studies have evaluated application of artificial intelligence in endoscopy to diagnose digestive diseases. This review summarizes current publications on the use of artificial intelligence in digestive endoscopic diagnosis and focuses on the challenges and future of artificial intelligence-aided systems. We expect artificial intelligence to provide an effective and practical method for endoscopists in endoscopy to satisfy the increasing needs of patients.

Keywords: Artificial intelligence, Esophageal, Gastrointestinal, Small-bowel, Pancreatic, biliary diseases

INTRODUCTION

As reported by Global Cancer Statistics 2020, gastrointestinal cancer remains to be the leading cause of death, with a total of 3.5 million new cases and 2.2 million deaths, accounting for approximately 18.5% of incidence and 22.4% of mortality worldwide. Among, esophageal cancer ranks seventh in incidence and sixth in mortality overall, which is comparatively low. Whereas stomach cancer is responsible for over one million new cases and 768793 deaths, ranking fifth for incidence and fourth for mortality globally. More than 1.9 million new cancer cases in colon and rectum and 935,000 deaths were estimated to occur in 2020, representing about one in 10 cancer cases and deaths, which ranked third in incidence, but second in terms of mortality.[1] In China, there had the largest number of colorectal cancer cases and gastric cancer has been the third most common cause of cancer deaths for decades.[2] Due to cancer screening and the control of risk factors, and various advances in the clinical management, it has shown a remarkable decline in mortality.[3,4] But there is a great potential and challenge to improve strategies for diagnosis in order to decrease gastrointestinal cancer incidence rate and mortality.

Endoscopy is the most important tool and gold standard for diagnosis of gastrointestinal cancer.[5] However, most gastrointestinal cancer cases are diagnosed at advanced stages because of insidious and on-specific symptoms, which lead to the poor prognosis. It is believed that the increase and of pre-cancerous adenoma and polyp detection rate is the most important and most closely associated with the decrease in gastrointestinal cancer incidence. Therefore, high quality and standardized endoscopy examinations is essential and widely supported. Currently, the factors that affect adenoma and polyp detection rate include blind spots and physicians error. The first factor is easily overcome and addressed by endoscopic techniques, which developed in many countries.[6-9] But there are differences in physicians' experience, specifications and work intensity. Artificial intelligence (AI) is a branch of computer science capable of analyzing complex medical data, considered to be an assistant and attracting much attention for endoscopists. AI involves multiple facets on artificial neural networks trained on big data,[10] which has provided a new approach in medical imaging analysis and shown potential for assisting humans in medical fields. For example, AI identify melanoma from dermoscopic images of selected lesions.[11] AI also optimized insulin dose based on decision support system in youths with type 1 diabetes.[12] Based on imaging, demographic, and genetic input features, AI was validated to assess the risk of conversion to advanced age-related macular degeneration.[13] In the discipline of gastroenterology, AI has accomplished remarkable advances in endoscopy. The aim of this study was to systematically summarize the application of AI in digestive endoscopic diagnosis.

AI APPLICATION IN ESOPHAGEAL CANCER

Primary esophagus malignancies include esophageal adenocarcinoma (EAC) and squamous cell carcinoma (ESCC). Although the incidence of esophageal cancer is comparatively low with gastric cancer and colon cancer, its prognosis is relatively poor. Identification and treatment at an early stage can achieve above 90% cure rates without esophagectomy.[14] AI-assisted detection and screening of esophageal cancer brought about progress in precancerous lesions and the early detection of esophageal cancer.

AI Identified Early ESCC

ESCC is the most predominant histologic type globally. Currently, chromoendoscopy is considered the gold-standard of screening ESCC. But its specificity is low because of the difficulties in differentiating inflammatory lesions from neoplastic change. Cai *et al.* set up a novel AI system to localize and identify early ESCC under conventional endoscopic white-light imaging, which improved the diagnostic ability of the endoscopists, especially in terms of sensitivity (74.2% vs 89.2%), accuracy (81.7% vs 91.1%), and NPV (79.3% vs 90.4%).[15] Horie *et al.* retrospectively collected white light and narrow band imaging images of esophageal cancer in a single-center and developed deep learning by convolutional neural networks. The system was used to detect esophageal cancer with a sensitivity of 98% and detected the cancer lesions less than

10 mm in size.[16] Guo *et al.* developed a system for computer-assisted ESCC diagnosis with area curve 0.989 using NBI images and validated the system using both endoscopic images and video.[17] The results showed high per-lesion sensitivity for non-magnifying videos, magnifying videos, and unaltered full-range normal esophagus videos. For superficial ESCC detection, the high sensitivity and the sensitivity of AI diagnosis from esophagogastroduodenoscopy videos was confirmed.[18]

AI Identified BE Abnormalities

Barrett's esophagus (BE) is the major risk factor for EAC. Detection of early BE neoplasia mainly depend on usage of high-definition endoscopes, structured BE surveillance protocols, and web-based teaching tools, but do not significantly increase the diagnostic yield of BE neoplasia.[19] Alanna *et al.* developed AI system to differentiate accurately between normal BE and early EAC by capturing random images from the real-time camera livestream.[20] The model was able to detect early esophageal neoplasia in BE images with high accuracy.[21] Also, AI-aided image enhancement interpret a large amount of complex data during volumetric laser endomicroscopy to help detect dysplasia and abnormalities in BE.[22] The novel system used for screening of early esophageal cancer has high accuracy and sensitivity in a short time, and can help endoscopists to detect smaller lesions which were ignored easily under white-light imaging.[23,24] But these studied need to more training in order to facilitate early detection in clinical use, contributing to a better prognosis in the near future

AI and Cancer Invasion Depth

Cancer invasion and metastases are important features of malignant tumor. Accurate assessment of invasion depth is a critical factor for deciding treatment strategy in patients. No matter non-magnified endoscopy, magnified endoscopy or Endoscopic ultrasonography (EUS) is used, these technologies are complicated and require expertise. AI has been shown to exceed endoscopists performance in detection of esophageal cancer. Newly developed AI system by Nakagawa, Tokai, and Shimamoto[25-27] showed favorable performance for differentiating submucosal invasion depth in patients, with high sensitivity, specificity and accuracy than experts. In endoscopic images of barrett's-related cancer, Alanna *et al.* confirmed that AI-based system successfully predicted submucosal invasion.[28] These work are preliminary concept, while ability of an AI system in the prediction of submucosal invasion will improved in the future.

AI APPLICATION IN STOMACH

To date, given the increased implementation of AI-assisted methods, there have been several studies in gastric mainly focus on topics: recognition of Helicobacter Pylori, diagnosis of chronic atrophic gastritis, and detection of early gastric cancers.

AI and Helicobacter Pylori

Helicobacter pylori (H. pylori) infection induces atrophic gastritis and intestinal metaplasia, eventually resulting in gastric carcinogenesis, which plays a central role in the pathobiology of gastric cancer. It has been revealed that the treatment aimed at eradication H. pylori is effective for the reduction of the risk of gastric cancer. Accurate diagnosing H. pylori is the first important step to eradicate H. pylori. The combination of endoscopic impression and gastric biopsies is frequently used for the evaluation of H. pylori. However, the workflow is time-consuming and subjective. An AI diagnostic system developed by Nakashima to diagnose H. pylori infection based on blue laser imaging (BLI) and linked color imaging (LCI) in a single center pilot study showed the area under the curve was 0.96 and 0.95, respectively, superior to 0.66 for white light imaging (WLI).[29] Shichijo used more than 30000 endoscopic images to construct and train AI-based diagnostic system. The sensitivity, specificity, accuracy, and diagnostic time were 88.9%, 87.4%, 87.7%, and 194s, significantly higher accuracy than 23 endoscopists.[30] They also constructed another AI system to evaluate H. pylori infection status using a novel algorithm. The accuracy of 80% was obtained for H. pylori negative status, 84% for post-eradication status, but only 48% for H. pylori positive status, within a lapse time of 261 seconds.[31] Zheng trained AI system and the area under the curve for multiple gastric images per patient was 0.97 (95% CI 0.96–0.99) with sensitivity, specificity, and accuracy of 91.6% (95% CI 88.0%–94.4%), 98.6% (95% CI 95.0%–99.8%), and 93.8% (95% CI 91.2%–95.8%).[32] Given the rapid advances of endoscopic technology, AI-aided different endoscopic images to diagnosing H. pylori infection has been achieved acceptable accuracies in preclinical stage and more efforts in need to promote the real time endoscopic diagnosis directly in clinic.

AI in Chronic Atrophic Gastritis

Chronic atrophic gastritis induced by *H. pylori* leads to mucosal atrophy, which is a common precancerous gastric condition and play a crucial role in the progress of gastric cancer and increases the risk of gastric cancer. Therefore, the early diagnosis of atrophic gastritis is important to prevent the occurrence and development of gastric cancer. Endoscopy is the most powerful tool for diagnosing chronic atrophic gastritis, but its sensitivity in only 42%. Whether patients will require endoscopic biopsy depends on the experience of endoscopists. The accuracy of biopsy is related to the location and depth of the mucosa. The study by Zhang designed and trained a convolutional neural network model with gastroscopic images to diagnose atrophic gastritis. The accuracy, sensitivity, and specificity were 0.942, 0.945, and 0.940, respectively, which higher than three experts. Also, the detection rate for mild, moderate, and severe atrophic gastritis were 93%, 95%, and 99%. The model exhibited AI application will be promising drastically in diagnosing chronic atrophic gastritis and decreasing gastric cancer risk, which significantly relaxed burden on endoscopists and simplified diagnostic routines.[33]

AI Detected Early Gastric Cancer

Several the diagnostic systems were constructed through convolutional neural networks to dramatically improved diagnostic ability of early gastric cancer. Hirasawa *et al.* constructed an AI-based diagnostic system that was trained by 13584 endoscopic images to detect early gastric cancer and had an overall sensitivity of 92.2%.[34] Tang also constructed a real-time deep convolutional neural network system for early gastric cancer detection using 45,240 endoscopic images and validated in multi-center. The performance showed better than endoscopists with diagnosis accuracy (85.1%-91.2%), sensitivity (85.9%-95.5%), specificity (81.7%-90.3%), and AUC (0.887-0.940).[35] The study conducted by Ueyama developed and validated an AI-assisted diagnosis system to diagnose early gastric cancer, based on 5574 magnifying narrow-band imaging (ME-NBI) endoscopy. Its accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 98.7%, 98%, 100%, 100%, and 96.8%, respectively, which could facilitate ME-NBI diagnosis of early gastric cancer in practice.[36] Ling made effort to develop a real-time system for accurately identifying differentiation status and delineating margins of early gastric cancer in ME-NBI images. The ability of differentiation status is significantly better than the five experts. For delineating margins, the system achieved an accuracy of 82.7% and 88.1% in differentiated and undifferentiated early gastric cancer.[37] One advanced AI system was trained by Namikawa using gastric cancer and gastric ulcer images for classifying gastric cancers and ulcers.[38] Horiuchi described the convolution neural network system with ME-NBI images could differentiate early gastric cancers and gastritis in a short time with high sensitivity and negative predictive value.[36] Another multicenter study implemented by Wu compared the number of blind spots and performance with or without AI system. Obviously, AI system had fewer blind spots and longer inspection time.[39] The same group concluded the miss rate of gastric neoplasms was lower in AI-assisted group than in the routine group.[40] Besides, AI-aided during EUS is also used in the diagnosis of gastric stromal tumors.[41-45] Great efforts had been made to perfect the AI diagnosis system for improving early gastric cancer detection and reducing of gastric cancer incidence.

AI APPLICATION IN COLON

AI-aided diagnosis for colonoscopy is the most investigated area in endoscopy. Screening colonoscopy is the ability to detect precancerous lesions in colon and the possibility to remove them in time and is the main contributor of colorectal cancer prevention. Poor colonoscopy could impair colorectal cancer prevention. Therefore, standardizing the quality of the colonoscopy is desirable goal.

AI Detected Colorectal Polyp and Adenoma

The adenoma detection rate is considered the most important quality measure. It is generally believed that the adenoma detection rate is negatively correlated with colorectal cancer incidence and mortality. The number of polyps and adenomas during colonoscopy is affected by bowel preparation and varies significantly between endoscopists. Missed detection is likely to increase the risk of cancer. Several studies have demonstrated that the adenoma detection rate can be increased by using AI for diagnostic colonoscopy. Misawa and colleges designed to analyze a large number of routine colonoscopy videos, showed that AI has the potential to provide automated detection of colorectal polyps.[46] Especially, the prospective and randomized studied by Wang and Luo showed that a significant increase in the number of diminutive adenomas/polyps detected, hyperplastic polyps by AI-assisted colonoscopy, but no difference was found with regard to larger lesions.[47,48] Polyps are easily missed by the endoscopists, which are small and flat, isochromatic, had an unclear boundary, and were partly behind colon folds and on the edge of the visual field, but identified by the AI system were generally.[49] The findings supported AI-aided adenomas/polyps detection as a standardized second observer with high accuracy, fidelity, and consistency, which have been shown to increase adenomas/polyps detection, reduce the overall miss rate and improve performance of endoscopists during withdrawal phase.[50,51] In clinic, we should not only assess the efficacy of AI system, but also the safety of patients and procedures. AI system is readily integrated into routine colonoscopy, processing video at the same frame rate as the standard procedure, which could be a safe and powerful assistant for narrowing variations among endoscopists and improving the quality of everyday colonoscopy.[52,53]

AI in Ulcerative Colitis

Patients with longstanding ulcerative colitis have a higher risk of colorectal cancer than the general population. Advances in AI are increasingly being used for polyps and adenoma detection rate, whereas it also shows a potential in ulcerative colitis. Unlike the polyps and adenoma detection from videos, AI-aided ulcerative colitis is from still images on accounts for accurate, accessible, and low-cost. However, there are the large proportion of non-informative frames in images captured during colonoscopy. AI and conventional feature extraction could distinguish non-informative from informative images with ulcerative colitis. The combination could boost automated analysis and the classification performance.[54] Maeda provided AI system to fully automated prediction persistent histologic inflammation of ulcerative colitis with 74% diagnostic sensitivity, 97% specificity, and 91% accuracy, over conventional endoscopy.[55] Grading severity of ulcerative colitis is critical for evaluating response to therapy. Ryan *et al.* found that the feasibility of deep learning algorithms to grade endoscopic severity of ulcerative colitis and applied it to full-motion video recordings. The convolutional neural network distinguished endoscopic remission from moderate-to-severe disease with an AUROC of 0.966.[56] Several studies support the potential for AI to provide endoscopic disease grading and inflammation severity in ulcerative colitis.[57-59] Besides, AI-assisted could identify patients in remission without the need for mucosal biopsy collection and analysis[60] and determine the clinical prognosis of ulcerative colitis.[61]

AI in Colon Capsule Endoscopy

Colon capsule endoscopy is minimally invasion procedure, which was first introduced in 2006. With the development of imaging function, colon capsule endoscopy could achieve higher sensitivity. But the burden of reading and interpretation slowed the step of clinical practice. Currently, AI-aided automatic diagnosis is under progress and appealing solutions in colon capsule endoscopy. Vidal *et al.* developed a deep learning-based convolutional neural network algorithm for automatic polyp detection and also integrated an algorithm to match colon capsule endoscopy and colonoscopy-detected polyps based on size, location, and morphology. 168 polys were matched in both the colon capsule endoscopy and colonoscopy groups in total by the polyp matching algorithm, which showed accuracy, sensitivity, and specificity of 96.4%, 97.1%, and 93.33%, respectively.[62] Artificial intelligence, in conjunction with colon capsule endoscopy, has been shown to improve the colon cancer screening. However, few prospective clinical trials are conducted, so further randomized controlled studies are needed.

AI APPLICATION IN SMALL BOWEL

Capsule endoscopy is generally used for detecting and diagnosing small-bowel diseases. It observes the entire digestive tract and captures 100000 images per examination and took endoscopists many hours to evaluate lesions.[63] Abnormal findings and lesions only exist in a few images. Therefore, analytical methods based on AI are needed to improve the quality of capsule endoscopy diagnoses, reduce reading time and burden on endoscopists. Great efforts have been made to identify a variety of common abnormal lesions, including polyps, nodules, epithelial tumors, submucosal tumors, and venous structures, respectively.[64-70] The AI-based system for capsule endoscopy videos reduced the reading time of endoscopists without decreasing the detection rate.[71] Besides, Ghosh explored AI-based framework to identify bleeding and non-bleeding capsule endoscopy images.[72] Tsuboi trained a deep convolutional neural network system using 2237 capsule endoscopy images to automatically detect angioectasia.[73] All the above studies reflect the potential of AI in the application of small intestinal capsule endoscopy. Although there are still various challenges in the application of AI, the urgent demand for the improvement of small intestinal capsule endoscopy examination cannot be ignored.

AI IN PANCREATIC AND BILIARY DISEASES

EUS is an essential diagnostic method for pancreatic disease. The diagnostic ability for pancreatic disease is high but the specificity is low. Although various of EUS techniques are emerging, the accuracy is still not adequate for a clinical practice. AI application in EUS is still in the early phase and the studying data is more limited compared to other endoscopy. Kuwahara *et al.* investigated whether AI model used EUS images of pancreatic intraductal papillary mucinous neoplasms (IPMNs) could predict malignancy. The study collected 3970 still images from patients who underwent EUS before pancreatectomy and confirmed IPMNs pathologically in a single cancer center. AI model on prediction of malignancy had a sensitivity of 95.7% and specificity of 92.6%. The accuracy (94.0%) was higher than human diagnosis (56.0%) and mural nodules (68.0%).[74] Marya *et al.* aimed to create an EUS-based AI model to differentiate autoimmune pancreatitis (API) from pancreatic ductal adenocarcinoma (PDAC), chronic pancreatitis (CP) and normal pancreas (NP). The results showed 99% sensitive, 98% specific for distinguishing AIP from NP; 94% sensitive, 71% specific for distinguishing AIP from CP; 90% sensitive, 93% specific for distinguishing AIP from PDAC; and 90% sensitive, 85% specific for distinguishing AIP from all studied conditions.[75] Tonozuka developed an original AI system using EUS images and assessed its diagnosis ability to detect PDAC. A total of 920 endosonographic images were used for the training and 10-fold cross-validation, and another 470 images were independently tested. The AUC was 0.924 and 0.940.[76] Udrіştoiu used two deep learning techniques to detect the focal pancreatic masses in four EUS imaging modalities (gray-scale, color Doppler, contrast-enhancement and elastography).[77] The model predicted the clinical diagnosis with an area under curve index of 0.98 and an overall accuracy of 98.26%. The negative values are 96.7% for PDAC, 96.5% for chronic pseudotumoral pancreatitis (CPP), and 98.9% for neuroendocrine tumor (PNET). The positive predictive values are 98.1% for PDAC, 99.7% for CPP, and 98.3% for PNET. Following further validation were needed to differentiate focal pancreatic masses in real-time.

EUS is also the most accurate diagnostic modality in biliary diseases. Detailed evaluation of bile duct is main focus during EUS. Yao *et al.* built a deep learning-based station classification and a segmentation model with white light images of gastroscopy images and EUS images. The model achieved an accuracy of 93.3% and 90.1% in image set and in video set for classification. The model had a dice of 0.77 in image set, sensitivity of 89.48% and specificity of 82.3% in video set. For external validation, the model achieved 82.6% accuracy in classification. In man-machine contest, the models achieved 88.3% accuracy in classification and 0.72 dice in bile duct segmentation, which is comparable to that of endoscopists. In the crossover study, trainees' accuracy improved from 60.8% to 76.3% ($P < 0.01$, 95% CI 20.9 27.2).[78] For polypoid lesions of the gallbladder, EUS is limited by subjective interpretation. Jang *et al.* evaluated the diagnostic performance of AI in differentiating polypoid lesions of the gallbladder using EUS images, with a performance comparable to that of EUS endoscopists.[79]

Because AI-aided application has been slow in the EUS field compared with other endoscopic fields and there are some limitations for EUS, great efforts are made to increase AI application in further prospective multicenter studies that enable analysis of EUS videos in real time.

CONCLUSIONS

In conclusion, this review summarizes the AI application in the field of digestive endoscopy. Growing evidence indicate that AI has a potential to optimize endoscopy procedures and assist endoscopists in diagnosing digestive diseases. Although it may not be ready for application in clinic worldwide, it is expected that AI use shift from exploratory studies to clinical practice.

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Conflict of Interest

None declared.

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