

Application of Artificial Intelligence in Early Gastric Cancer Diagnosis

Zili Xiao Danian Ji Feng Li Zhengliang Li Zhijun Bao

Department of Gastroenterology, Huadong Hospital Affiliated to Fudan University, Shanghai, China

Keywords

Artificial intelligence · Convolutional neural network · Early gastric cancer · Esophagogastroduodenoscopy · Diagnosis

Abstract

Background: With the development of new technologies such as magnifying endoscopy with narrow band imaging, endoscopists achieved better accuracy for diagnosis of gastric cancer (GC) in various aspects. However, to master such skill takes substantial effort and could be difficult for inexperienced doctors. Therefore, a novel diagnostic method based on artificial intelligence (AI) was developed and its effectiveness was confirmed in many studies. AI system using convolutional neural network has showed marvelous results in the ongoing trials of computer-aided detection of colorectal polyps. **Summary:** With AI's efficient computational power and learning capacities, endoscopists could improve their diagnostic accuracy and avoid the overlooking or over-diagnosis of gastric neoplasm. Several systems have been reported to achieved decent accuracy. Thus, AI-assisted endoscopy showed great potential on more accurate and sensitive ways for early detection, differentiation, and invasion depth prediction of gastric lesions. However, the feasibility, effec-

tiveness, and safety in daily practice remain to be tested. **Key messages:** This review summarizes the current status of different AI applications in early GC diagnosis. More randomized controlled trials will be needed before AI could be widely put into clinical practice.

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Introduction

Gastric cancer (GC) is the fifth most common cancer worldwide [1] and the third leading cause of cancer death. The incidence rate differs in various regions but the highest is among East Asian populations. Successful detection of early GC (EGC) could significantly improve survival up to 90% [2].

Endoscopy is the most powerful tool for detection and diagnosis of GC, but the accuracy of detection depends on the experience of the endoscopists and is complicated by various factors of the gastrointestinal (GI) tract. Accordingly, advanced endoscopic techniques such as image-enhanced endoscopy have been developed to improve the detection of EGC. Still, the false negative rate of GC detected by esophagogastroduodenoscopy (EGD)

was reported to be between 4.6% and 25.8% [3–5]. More accurate and objective methods for EGC detection are desired for clinical practice. As for advanced technics pertaining diagnosis of EGC, such as prediction of invasion depth and differentiation from non-neoplasm, the accuracy differs drastically between experts and trainees.

Recently, artificial intelligence (AI) has caught considerable attention in various medical fields. In the field of gastroenterology, AI applications in capsule endoscopy [6] and in the detection, localization, and segmentation of colonic polyps [7] have been reported as well. Like described by Hsiao et al. [8], AI could be applied in assisting the decision of biopsy and ESD evaluation. Among the different AI models, convolutional neural network (CNN) is a method most commonly used in medical imaging [9].

As an AI algorithm that automatically learns features from the data, CNN has been utilized mainly for image recognition [10]. It is designed to think similarly to the human brain using huge datasets of image to learn certain patterns. That is to say, CNN is ideal for endoscopic image recognition to detect and localize GI neoplasms. Characteristic of neoplasm were learned using endoscopic images previously confirmed by endoscopists. After training, the CNN will be tested on non-labeled external datasets and determine whether the model could correctly identify previously unseen neoplasms. Hopefully, the algorithm can identify what it believes is a gastric neoplasm in a real-time endoscopic video input and predict the invasion depth. We try to review recent developments about the application of AI in the diagnosis of EGC.

Detection

The detection of EGC and precancerous neoplasms is essential for the minimum invasive resection and, thus improves prognosis. Since EGC can only have very subtle differences when compared with surrounding mucosa, detection for inexperienced endoscopists could be challenging. Thus, it is paramount to improve the detection rates of EGC using new methods. Many groups have reported to already started integrating AI into their routine practice to improve the overall detection rates of GC.

Sakai et al. [11] proposed a CNN-based automatic detection scheme to assist the diagnosis of EGC in endoscopic images. Transfer learning was performed using 2 classes (cancer and normal) of image datasets that have detailed texture information on lesions derived from a

small number of annotated images. The accuracy of trained network was 87.6%, while the detection accuracy of external dataset was 82.8%.

Hirasawa et al. [12] constructed an AI-based diagnostic system that was trained by >13,000 images of EGD to detect early and advanced GC (AGC), and then tested the diagnostic accuracy. The CNN had an overall sensitivity of 92.2%, and a positive predictive value (PPV) of 30.6%. Seventy of the 71 lesions (98.6%) with a diameter of 6 mm or more as well as all invasive cancers were correctly detected. The diagnostic ability of the same system was compared by Ikenoyama et al. [13] to that of 67 endoscopists using an independent test dataset (2,940 images from 140 cases). The average diagnostic time for analyzing 2,940 test endoscopic images by the CNN and endoscopists were 45.5 ± 1.8 s and 173.0 ± 66.0 min, respectively. The CNN had a significantly higher sensitivity than the endoscopists (by 26.5%; 95% CI, 14.9–32.5%). This study was limited to early GC lesions smaller than 20 mm and difficult to detect.

One real-time assistance system developed by Wu et al. [14] ensure that the whole stomach is observed during endoscopy without blind spot, thereby providing a prerequisite for the detection of EGC. This system identified EGC from non-malignancy with an accuracy of 92.5%, a sensitivity of 94.0%, a specificity of 91.0%, a PPV of 91.3%, and a negative predictive value (NPV) of 93.8%, outperforming all levels of endoscopists. Later, the same group named this system as WISENSE (a combination of “wise” and ‘sense’) and conducted a randomized controlled trial to test its effectiveness for monitoring blind spots during EGD. WISENSE monitored blind spots with an accuracy of 90.40% in real EGD videos. A total of 324 patients were recruited and randomized, 153 and 150 patients were analyzed in the WISENSE and control group, respectively. Blind spot rate was lower in WISENSE group compared with the control (5.86% vs. 22.46%, $p < 0.001$) [15].

Gastrointestinal Artificial Intelligence Diagnostic System (GRAIDS) is another real-time AI system developed by Luo et al. [16]. 1,036,496 white light images from 84,424 individuals were used to develop and test GRAIDS. The diagnostic accuracy in identifying upper gastrointestinal cancers was 95.5% in the internal validation set and ranged from 91.5% to 97.7% in the 5 external validation sets. GRAIDS achieved diagnostic sensitivity similar to that of the expert endoscopists (94.2% vs. 94.5%; $p = 0.692$) and superior sensitivity compared with competent (85.8%, $p < 0.0001$) and trainee (72%, $p < 0.0001$) endoscopists.

Prediction of Invasion Depth

One of the most important preoperative criteria for curative endoscopic resection is the tumor invasion depth. Curative resection by ESD can frequently be achieved for intramucosal cancer (M) and cancer with submucosal invasion <500 μm (SM1), whereas deep invasive GC was required for radical surgery. Although the efficacy of using macroscopic features [17] and EUS [18] for prediction for invasion depth has been reported, a more accurate method is still warranted.

In this very first study for prediction of invasion depth using AI by Zhu et al. [19], an AI-based CNN system was developed through transfer learning leveraging a state-of-the-art pretrained CNN architecture including 790 images as development dataset and another 203 images as test dataset. The CNN system achieved significantly higher accuracy (by 17.25%; 95% CI, 11.63–22.59) and specificity (by 32.21%; 95% CI, 26.78–37.44) than human endoscopists.

Cho et al. [20] established one algorithm to predict submucosal invasion events of gastric neoplasm based on endoscopic images. In the external validation, the mean areas under the curves (AUC) reached 0.887 (0.863–0.910) which suggested potential clinical relevance during the choice of therapeutic strategy.

For differentiation between M-SM1 and SM2-SI invasive cancer, Nagao et al. [21] used 16,557 images from 1,084 cases of GC to develop an AI system through transfer learning leveraging a CNN architecture, ResNet5. The lesion-based sensitivity, specificity, accuracy, PPV, and NPV of this AI system were 84.4%, 99.4%, 94.5%, 98.5%, and 92.9%, respectively.

Another study from Korea showed AUC of receiver operating characteristic curves for EGC detection and depth prediction were 0.981 and 0.851, respectively. Among the factors affecting AI prediction of tumor depth, only histologic differentiation was significantly associated, where undifferentiated-type histology exhibited a lower AI accuracy [22].

Differentiation of Neoplasm and Non-Neoplasm

An accurate differentiation of gastric neoplasm and non-neoplasm is sometimes difficult with conventional white light imaging endoscopy; nevertheless, it remains the standard endoscopic examination modality. Over the years, several methods have been used for the differentiation of gastric neoplasm including NBI with or without magnification. Efforts were also made to test the efficacy of these methods using AI system. Some results indicate that by using magnifying endoscopy with narrow band

imaging (ME-NBI), AI system could achieve satisfying diagnostic efficacy.

Horiuchi et al. [23] developed a 22-layer CNN system which was pretrained using 1492 EGC and 1,078 gastritis images from ME-NBI. This system achieved high sensitivity and speed for differentiation of EGC and gastritis. The accuracy of the CNN system with ME-NBI images was 85.3%, with 220 of the 258 images being correctly diagnosed. The method's sensitivity, specificity, PPV, and NPV were 95.4%, 71.0%, 82.3%, and 91.7%, respectively. The overall test speed was 51.83 images/s (0.02 s/image).

Ueyama et al. [24] constructed an AI-assisted CNN computer-aided diagnosis (CAD) system, based on 5,574 still ME-NBI images. The overall accuracy, sensitivity and specificity of this system were 98.7%, 98%, and 100%, respectively. All misdiagnosed images of EGCs were of low-quality or of superficially depressed and intestinal-type intramucosal cancers that were difficult to distinguish from gastritis, even by experienced endoscopists.

Comparison between AI systems and experts has been done in several institutes. Zhang et al. [25] constructed a CNN-based diagnostic system based on a ResNet34 residual network structure and a DeepLabv3 structure using 21,217 non-magnified white light images of 5 gastric conditions, peptic ulcer, EGC, and high-grade intraepithelial neoplasia (HGIN), AGC, gastric submucosal tumors, and normal gastric mucosa without lesions. After comparing with experienced endoscopists, the diagnostic specificity and PPV of the CNN were higher than that of the endoscopists for the EGC and HGIN images (specificity: 91.2% vs. 86.7%, by 4.5%, 95% CI, 2.8–7.2%; PPV: 55.4% vs. 41.7%, by 13.7%, 95% CI, 11.2–16.8%) and the diagnostic accuracy of the CNN was close to those of the endoscopists for the lesion-free, EGC and HGIN, peptic ulcer, AGC, and submucosal tumors images.

Li et al. [26] retrospectively reviewed 386 images of noncancerous lesions and 1,702 images of EGC for CNN training and then prospectively enrolled 171 images of noncancerous lesions and 171 images of EGC to test and evaluate the diagnostic capability of CNN. The sensitivity, specificity, and accuracy of CNN system in the diagnosis of EGC were 91.18%, 90.64%, and 90.91%, respectively. No significant difference was spotted in the specificity and accuracy of diagnosis between CNN and experts but those were significantly higher than those of the non-experts.

Besides still images of ME-NBI, using video clips during magnification as pre-training material may also contribute to improve the efficacy of AI system. One CAD system was pretrained using 2,570 still images (1,492 can-

Table 1. Current clinical trials from the NIH Web site

ClinicalTrials.gov identifier	Recruitment status	Official title	Time perspective	Sponsor	Study type	Actual enrollment	Actual study start date
NCT04040374	Completed	A Single-center, Retrospective, Open Label, Randomized Controlled Trial of Artificial Intelligence Versus Expert Endoscopists for Diagnosis of Gastric Cancer in Patients Who Underwent Upper Gastrointestinal Endoscopy	Retrospective	Tokyo university, Japan	Interventional (clinical trial)	500 participants	July 1, 2019
NCT03883035	Completed	Utilization of Real-time Automatic Quality-control System in the Detection of Gastric Neoplasms	Retrospective	Shandong University, China	Interventional (clinical trial)	1,060 participants	March 20, 2019
NCT04384575	Recruiting	Study on the Effectiveness of Gastroscope Operation Quality Control Based on Artificial Intelligence Technology	Prospective	Peking University, China	Observational	700 participants	February 22, 2020
NCT04869618	Recruiting	Validation of an Artificial Intelligence System Based on Raman Spectroscopy (SPECTRA IMDx) for Real Time Diagnosis of Gastric Premalignant Lesions and Early Gastric Cancer in Patients Undergoing Gastric Endoscopic Resection	Prospective	Changi General Hospital, Singapore	Interventional (clinical trial)	100 participants	Estimated study start date: May 2021
NCT04563416	Recruiting	Application of Artificial Intelligence for Early Diagnosis of Gastric Cancer During Optical Enhancement Magnifying Endoscopy	N/A	Shandong University, China	Observational	Estimated enrollment: 80 participants	July 10, 2020
NCT04840056	Recruiting	Prediction of Gastric Cancer in Intestinal Metaplasia and Atrophic Gastritis - Application of Artificial Intelligence in Histology and Clinical Data	Retrospective	Chinese University of Hong Kong	Observational	Estimated enrollment: 1,300 participants	Estimated study start date: April 15, 2021
NCT04675138	Recruiting	Development of a Clinical Decision Support System With Artificial Intelligence for Cancer Care	N/A	National University Hospital, Singapore	Observational	Estimated enrollment: 1,000 participants	August 20, 2020
NCT04015466	Recruiting	Advanced GC Multi-omic Characterization in EU and CELAC Populations	Prospective	Fundación para la Investigación del Hospital Clínico de Valencia	Observational	Estimated enrollment: 800 participants	June 12, 2019
NCT04720924	Recruiting	Computer-aided Real-time Automatic Quality-control System for Detection of Early Cancer and Precancerous Lesions on Upper Gastrointestinal Tract: a Multicenter Randomized Controlled Study	N/A	Shandong University, China	Interventional (clinical trial)	Estimated enrollment: 1,840 participants	January 16, 2021

cerous and 1,078 noncancerous images) and 174 videos (87 cancerous and 87 noncancerous videos) obtained using ME-NBI. Horiuchi et al. [27] used this system to compare with 11 experts who were skilled in diagnosing EGC using ME-NBI with clinical experience. The CAD system demonstrated an AUC of 0.8684. The accuracy, sensitivity, specificity, PPV, and NPV were 85.1% (95% CI, 79.0–89.6), 87.4% (95% CI, 78.8–92.8), 82.8% (95% CI, 73.5–89.3), 83.5% (95% CI, 74.6–89.7), and 86.7% (95% CI, 77.8–92.4), respectively, which were equivalent to or better than that of several experts.

Pathological Diagnosis

The histological examination for large ESD specimen could be time-consuming and requires additional effort for the evaluation of risk factor like lymphovascular invasion. Song et al. [28] reported a clinically applicable system using a deep CNN trained with 2,123 pixel-level annotated H&E-stained whole slide images. This model achieves a sensitivity near 100% and an average specificity of 80.6% on a real-world test dataset with 3,212 whole slide images digitalized by 3 scanners. This system showed some promise for aiding pathologists in improvement of diagnostic accuracy and prevention of misdiagnoses.

Ongoing Clinical Trials and Possible Future Path

Although a bunch of researches on developing CNN systems has been published recently [29], the relatively lacking of RCT has always been a holdback. When searching PubMed for AI and endoscopic procedures, only a limited number of RCT enlisted pertaining EGC could be found, casting a doubt on the future of integrating AI into clinical practice.

To further elaborate this topic, we then performed search on <https://clinicaltrials.gov/> with the term “Artificial Intelligence” and “Gastric Cancer” [30]. Only 9 clinical trials are currently listed, and 7 of them are still recruiting (Table 1). Nation-wise, most of these trials are on far-east Asian, either Japan or China. This is quite reasonable due to high prevalence of GC in these regions.

Among the registered trials, only 3 trials are labeled as prospective. Amongst them 2 trials were still recruiting, while one research in China led by Yanqing Li has prospective RCT in esophagus and colon polyps, instead of EGC. It is possible they have unpublished materials that may emerge in the near future.

In China, Tang et al. [31] reported a retrospective research of a DCNN system for detecting EGC, with an external validation dataset from other institutions. Training of the system was conducted by 35,823 images from 1,085

patients, the system was then validated by 9,417 images from 279 patients. Validation dataset obtained from other institutions was then applied on the system as external validation, showing a promising result of high overall performance, with a PPV of 86.9%, an NPV of 90.7%, and an AUC of 0.906. The system was then applied on OGD videos, showing a real time-based diagnostic ability with decent sensitivity. The authors stated a plan for future prospective RCT and also offered open access to their system.

In Japan, as mentioned earlier, Hirasawa et al. [12] also reported a retrospective RCT, in which the CNN system showed ability to process endoscopic images with a decent diagnostic ability. As an attempt to compare the diagnostic ability of the system, the same group of authors conducted a test to compare it with expert endoscopists [32].

Horiuchi et al. [13] conducted a retrospective research in which they constructed a CAD system that could be compared with expertise of seasoned endoscopists. The system was further tested under a single-center retrospective trial to further elaborate its possible usage under actual clinical usage [27]. It is also mentioned that they were planning a multicenter and prospective study differentiating gastritis and GC through a biopsy of all cases.

However, all of the research works mentioned above are retrospective, which are prone to bias. This means future RCT is required before AI could be put into actual clinical usage.

Another possible holdback hides in the underlining different algorithm. Although most research adapted CNN as their system of choice, different institutions have chosen to develop their own algorithm. This might be beneficial as diversity could bring game-changers to this world, but we must keep in mind that training of these AI system requires relatively large number of inputs, and we might be doing redundant labor during the process.

Conclusion

As described in this review article, many studies have already been published as stepping-stones toward the application of AI in diagnosing EGC. Some systems even showed high accuracy which could be compared with those of experts. However, before AI systems were verified by multicenter RCTs, it seems reasonable to only use AI for auxiliary diagnosis, like determining whether there is a blind spot during the process of EGD. After screening using high sensitivity system, suspicious lesions need to

be further confirmed by experienced endoscopists. False-negative results will be the worst-case scenario in clinical practice because it means either EGC is not successfully detected, or additional surgery is needed. “Eyes can only see what brain knows.” After enough information being inputted into the AI system and validation by multicenter RCTs, we should believe AI will have a better performance for EGC diagnosis.

Conflict of Interest Statement

The authors declare no conflicts of interest regarding this review article.

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