Artificial Intelligence in Gastrointestinal Endoscopy

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Early gastrointestinal cancer: The application of artificial intelligence

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

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

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

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INTRODUCTION

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

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

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

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

LITERATURE SEARCH

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

SEARCH RESULTS

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

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

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

There is also study on AI being involved in preclinical stage. For instance, the diagnostic ability of AI using DL to detect esophageal cancer including superficial and advanced squamous cell carcinoma and adenocarcinoma was characterized as highly sensitive (98%) and efficient based on WLI images. Small cancer lesions less than 10
In terms of EAC, AI using DL to diagnose superficial esophagogastric junctional adenocarcinoma showed favorable sensitivity (94%) and acceptable specificity (42%) of WLI images compared with experts[16]. A CAD using DL (CAD-DL) model was trained by two datasets based on two different kinds of images (WLI and NBI images) used to detect early EAC. The diagnosis of EAC by CAD-DL reached sensitivities/specificities of 97%/88% for WLI images and sensitivities/specificities of 94%/80% for NBI images, respectively (Augsburg dataset) and 92%/100% (another dataset) for WLI images[17]. Additionally, one research compared several AI methods including regional-based CNN (R-CNN), Fast R-CNN, Faster R-CNN, and Single-Shot Multibox Detector. Single-Shot Multibox Detector outperformed other methods achieving a sensitivity of 96% in automatically identify EAC[18].

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

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

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

**AI AND EGC FROM CAG AND DYSPLASIA TO EGC**

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

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

ECC has been defined as a carcinoma with invasion limited to the submucosa regardless of lymph node status and according to the Royal College of Pathologists as TNM stage T1N0M0. If the dysplasia is restricted to the layer of epithelium, it is defined as low-grade or high-grade intraepithelial neoplasia. Mild or moderate dysplasia is the pathological character of low-grade intraepithelial neoplasia, and severe dysplasia is the pathological character of high-grade intraepithelial neoplasia or preinvasive carcinoma. Colonic precancerous lesions include traditional serrated adenoma and sessile serrated adenoma/polyp. The submucosal invasion in clinical practice is considered as the superficial depth of tumor invasion and further as a surrogate for nominal LNM risk. Meanwhile, it can be a general criterion to identify whether patients are eligible for local ER or surgery. Curative ER is indicated for lesions confined to the mucosal layer or invading less than 1 mm into the submucosal layer. Endoscopic screening is proven to decrease the risk of disease-specific morbidity and mortality. Current guidelines recommend screening beginning at age 50 and continuing until age 75 with fecal immunochemical test every year, flexible sigmoidoscopy every 5 years, and/or colonoscopy every 10 years. Early diagnosis and treatment are pivotal. When colon carcinoma is detected in a localized stage, the 5-year relative survival is 91.1%. However, the 5-year relative survival of colon carcinoma patients with regional metastasis or distant metastasis were 71.7% and 13.3%, respectively.
AI has been widely involved in the research of ECC on the aspect of detection, diagnosis, classification, invasion depth, and histopathology as well as inflammatory bowel diseases associated with inflammation-dysplasia-colon cancer pattern. Regarding the detection and diagnosis, a research trained Faster R-CNN with VGG16 based on WLI images and videos covering ECC (Tis or T1) and precursor lesions including hyperplastic polyps, sessile serrated adenoma/polyps, traditional serrated adenoma, low-grade intraepithelial neoplasia, high-grade intraepithelial neoplasia, and submucosal invasive cancer was conducted. It showed the sensitivity and specificity were 97.3% and 99.0%, respectively[58]. Another research used two CNN methods trained by WLI images. ResNet-152 showed a higher mean area under the curve for detecting tubular adenoma + lesions (0.818), and the mean area under the curve for detecting high-grade intraepithelial neoplasia + lesions reached 0.876 by ResNet-2[59]. Regarding the invasion depth, for deeply invasive cT1(SM) (hereafter, cT1) or deeper colorectal cancer (CRC), there is a 10%-15% or higher risk of lymph node metastases. Further surgical resection including lymph node dissection is required[60]. For an accurate depth of invasion diagnosis, the CNN method was used to assist in cT1 diagnosis and demonstrated that cT1 sensitivity, specificity, and accuracy were 67.5%, 89.0%, and 81.2%, respectively[61].

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

In the aspect of histopathology, AI has been used in ECC and precancerous lesions. A systematic review has concluded that AI use in CRC pathology image analysis included gland segmentation, tumor classification, tumor microenvironment characterization, and prognosis prediction[69]. A DL approach was developed to recognize four different stages of cancerous tissue development, including normal mucosa, early preneoplastic lesion, adenoma, and cancer and obtained an overall accuracy more than 95%[70]. Prediction of LNM for early CRC is critical for determining treatment strategies after ER. An LNM prediction algorithm for submucosal invasive (T1) CRC based on machine learning showed better LNM predictive ability than the conventional method on some datasets[71-82].

**PROSPECTS AND CHALLENGES OF AI APPLICATION ON EARLY GI CANCER**

Endoscopy is usually the first choice in the diagnosis and management of early GI cancer. According to the Clinical Practice Guideline, ER is now a standard treatment for early GI cancers without regional LNM. Early GI cancers can completely be removed by en bloc fashion (resection of a tumor in one piece without visible residual tumor) via endoscopic mucosal resection and/or endoscopic submucosal dissection. High-definition white light endoscopy, chromoendoscopy, and image-enhanced endoscopy such as ME-NBI can be used to assess the edge and depth of early GI cancers for delineation of resection boundaries and prediction of the possibility of LNM before the decision of ER. Histopathological evaluation can confirm the depth of cancer invasion and lymphovascular invasion[83]. From this review, we can see AI as a novel technology has been penetrated in early GI cancer detection, diagnosis, boundaries, invasion depth, lymphovascular invasion, and prognosis prediction based on endoscopic images and videos and pathological tissue slides obtained after ER.
Both high-quality endoscopy and high-quality AI model construction research are crucial to ensure better health outcomes and benefits of patients. Some AI methods have been designed to identify and assure the quality of endoscopy to improve the detection rate of early GI cancer. In upper GI tract, missed EGC rates are an important measure of quality. A deep CNN model was built to monitor blind spots, time the procedure, and automatically generate photo-documentation during esophagogastroduodenoscopy. Meanwhile, in colonoscopy, poorer adenoma detection rates are associated with poorer outcomes and higher rates of post-colonoscopy colonic cancer. A deep CNN model was developed for timing withdrawal phase, supervising withdrawal stability, evaluating bowel preparation, and detecting colorectal polyps.

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

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

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AIGE AI and early GI cancer


