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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *Artificial Intelligence in Gastroenterology* (*AIG*, *Artif Intell Gastroenterol*) is to provide scholars and readers from various fields of artificial intelligence in gastroenterology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

AIG mainly publishes articles reporting research results obtained in the field of artificial intelligence in gastroenterology and covering a wide range of topics, including artificial intelligence in gastrointestinal cancer, liver cancer, pancreatic cancer, hepatitis B, hepatitis C, nonalcoholic fatty liver disease, inflammatory bowel disease, irritable bowel syndrome, and *Helicobacter pylori* infection.

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EDITORIAL

Digital histology in celiac disease: A practice changer

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Abstract

Artificial intelligence (AI) has grown tremendously in the last decades and is undoubtedly the future era in medicine. Concerning digestive diseases, applications of AI include clinical gastroenterology, gastrointestinal endoscopy and imaging, and not least pathological diagnosis. Several gastrointestinal pathologies require histological confirmation for a positive diagnosis. Among them, celiac disease (CD) diagnosis has been in the spotlight over time, but controversy is still ongoing with regard to the so-called celiac-type histology. Despite efforts to improve histological diagnosis in CD, there are still several issues and pitfalls associated with duodenal histology reading. Several papers have assessed the accuracy of AI techniques in detecting CD on duodenal biopsy images and have shown high diagnostic performance over standard histology reading. We discuss the role of computer-assisted histology in improving the assessment of mucosal architectural injury and inflammation in CD patients, both for diagnosis and follow-up.

Key words: Celiac disease; Histology; Artificial intelligence; Computer; Digital; Diagnosis

Core tip: Histology in celiac disease (CD) diagnosis is hampered by several pitfalls, from low adherence to biopsy sampling recommendations and reporting of results to significant inter-observer variability. A quantitative, computer-assisted histological assessment of mucosal biopsies could overcome many of the current limitations of conventional histology. We herein discuss the current evidence on artificial intelligence-based histology in CD diagnosis and its role in improving histological measurements in CD.

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DIGITAL HISTOLOGY IN CELIAC DISEASE – A PRACTICE CHANGER

Artificial intelligence (AI) has grown tremendously in the last decades and is undoubtedly the future era in medicine. From optimizing diagnosis to guiding therapy, AI can be a real practice changer in several medical specialties. Concerning digestive diseases, applications of AI include clinical gastroenterology, gastrointestinal (GI) endoscopy and imaging and pathological diagnosis. It is well known that several GI pathologies require histological confirmation for a positive diagnosis. Among them, celiac disease (CD) is a well-recognized systemic autoimmune disorder triggered by gluten ingestion in genetically susceptible individuals, whose diagnosis in adults is based on testing for specific antibodies and histological examination of the small bowel mucosa. CD diagnosis has been in the spotlight over time with several guideline updates, but controversy is still ongoing with regard to the so-called celiac-type histology[1,2]. While significant improvement has been made concerning mucosal sampling techniques, site sampling, number and processing of biopsies and standardization of histopathology reports, there are still many issues and pitfalls associated with duodenal histology reading[3,4]. The issues of bulb biopsies, sampling-associated artifacts, orientation and readability of biopsy samples, inter-observer variability and low adherence to currently available histology reporting systems have all been a matter of debate in recent literature and have set the need for optimizing histological diagnosis in CD[5,6].

With growing medical data and the need to optimize care in a setting of limited human resources, AI has emerged as a breakthrough solution for improving diagnosis, treatment selection and even guiding prognosis in various medical fields. Several AI techniques have been used, such as machine learning, decision trees, support vector machines and artificial neural networks[7]. In gastroenterology, several applications have been validated both for the GI tract and hepato-biliary-pancreatic pathology[8-10].

CD has been a good candidate for AI applications, owing to its clear-cut diagnosis and the validation of endoscopic markers of villous atrophy[11]. At first, most of the interest with AI in CD was oriented on computer-aided detection of villous atrophy[12], but recently there has been a switch in focus on digital histology in CD. Several papers have assessed the accuracy of AI techniques in detecting CD on duodenal biopsy images and have shown high diagnostic performance over the standard histology reading. Using a machine learning–based histopathological analysis model, Syed *et al*[13] showed a 93.4% case-detection accuracy on 3118 images from duodenal biopsies of patients with environmental enteropathy, CD and controls. A deep learning approach on automated detection of CD was described by Wei *et al*[14] in 212 biopsies (1230 slides), which identified CD, normal mucosa and non-specific duodenitis with 95.3%, 91.0%, and 89.2% accuracy, respectively. A novel, quantitative histology algorithm proposed by Das *et al*[15] has been developed on digitized images of duodenal biopsies from a derivation cohort of 261 subjects (137 controls, 124 CD) and then validated on 225 subjects (105 controls, 120 CD), discriminating CD from controls with 90.3% sensitivity and 93.5% specificity; this Q-histology classification system was proven superior to all existing histological classification systems (Marsh, Marsh-Oberhuber, Corazza-Villanacci, Ensari) with regard to intra- and interobserver agreement. Moreover, in a real-world setting, even these qualitative scoring systems are rarely used in pathology reports, which are often just descriptive[5,16].

Computer-assisted histological assessment of duodenal biopsy slides overcomes many of the issues associated with conventional histology. In contrast with the currently available, subjective, qualitative evaluation of slides, digital histology provides a quantitative assessment of duodenal mucosal biopsies and could be of great use in equivocal cases, in measuring changes on follow-up biopsies and in multicentric clinical trials. Besides providing quantifiable measurements, an automated histology image analysis could reduce the burden of pathology departments by prescreening histology slides and saving only those that are preliminarily classified as diseased mucosa to be reviewed by the pathologists[14]. Not least, computer-assisted quantitative histology could provide arguments for cases of mild enteropathy that could otherwise be mislabeled as normal or for cases of refractory CD.

A large European multicentric study with central pathology reading has shown an alarmingly high discordance rate of 7.1% in labelling a case as either CD (Marsh 2/3)

or non-CD (Marsh 0/1)[17]. Considering the implications of either missing a diagnosis of CD or misdiagnosing a normal individual as CD, there is a promising role for computer-assisted histology in CD. AI-techniques can provide objective and accurate histological measurements in CD diagnosis and help avoid all the confounding factors associated with currently used conventional histology. Also, AI-based histology could be used as an alternative to expert pathologists in clinical trials, where small changes of the mucosa may occur with different interventions, and precise measurements are warranted[16].

At a glance, AI-based diagnosis might seem the perfect practice changer in CD management. However, there are some pitfalls with CD diagnostic based on AI techniques. On one hand, there is the issue of correctly labelling a histology image as appropriate for reading; previous studies have shown that bad orientation of samples can require re-cuttings for proper reading and correct diagnosis, and this is currently eyed by the pathologist[18]. Moreover, there is the wide-spectrum of non-celiac villous atrophy, which can pose diagnostic challenges[19].

At present, we are simplifying the continuum of mucosal injury in CD patients with a categorical score, in one of the Marsh-Oberhuber classes. Using computer-assisted histology, we can significantly improve the assessment of mucosal architectural injury and inflammation in CD patients, both for diagnosis and follow-up.

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MINIREVIEWS

Application of artificial intelligence in hepatology: Minireview

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Abstract

With the rapid advancements in computer science, artificial intelligence (AI) has become an intrinsic part of our daily life and clinical practices. The concepts of AI, such as machine learning, deep learning, and big data, are extensively used in clinical and basic research. In this review, we searched for the articles in PubMed and summarized recent developments of AI concerning hepatology while focusing on the diagnosis and risk assessment of liver diseases. Ultrasound is widely conducted for the routine surveillance of hepatocellular carcinoma along with tumor markers. Computer-aided diagnosis is useful in the detection of tumors and characterization of space-occupying lesions. The prognosis of hepatocellular carcinoma can be estimated *via* AI using large-scale and high-quality training datasets. The prevalence of nonalcoholic fatty liver disease is increasing worldwide and pivotal concern in the field is who will progress and develop hepatocellular carcinoma. Most AI studies require a large dataset, including laboratory or radiological findings and outcome data. AI will be useful in reducing medical errors, supporting clinical decisions, and predicting clinical outcomes. Thus, cooperation between AI and humans is expected to improve healthcare.

Key words: Artificial intelligence; Deep learning; Machine learning; Hepatocellular carcinoma; Prognosis; Computer-aided diagnosis

Core tip: Artificial intelligence (AI) plays a significant role in our daily life and the research field. In this review, we summarized the recent findings of AI concerning hepatology. AI will be useful in the detection and diagnosis of liver tumors and the discrimination of high-risk patients for hepatic decompensation and hepatocellular

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carcinoma development. Furthermore, AI can be utilized in basic research, such as in the interpretation of genomics, transcriptomics, and proteomics. We hope that this review will help in future management.

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INTRODUCTION

Recent developments in artificial intelligence (AI)-related techniques have shown a remarkable improvement in the field of healthcare[1]. Among others, AI comprises search algorithms, expert systems, machine learning, and deep learning[2]. Machine learning requires feature characteristics input by a human; however, technical advances achieved by innovation in computer science leads to a more sophisticated deep learning method[3]. Deep learning provides new insight into existing diseases but not into why the chosen parameters cannot be interpreted or understood. The issue of ensuring the balance between white box and black box AI is widely debated among the research community[4]. Nevertheless, exploration and translation of black box AI could lead to a better understanding of the disease mechanism. Moreover, it could pave the way for novel discoveries in their treatment.

Such advances in hepatology can be useful for detecting tumors and screening high-risk populations for hepatocellular carcinoma (HCC) development. A curable treatment for HCC can be adopted when the tumors are found in early stages[5]. Routine ultrasonography is widely accepted as a screening method for HCC[6]. However, an ultrasound (US) is highly dependent on the sonographer's skill. Thus, AI detection systems can be used for efficient detection.

Infections from the hepatitis B virus and hepatitis C virus are well-recognized risk factors for hepatic decompensation and HCC development[7-9]. In addition, nonalcoholic fatty liver disease (NAFLD) has been recently identified as a risk factor. The prevalence of NAFLD is increasing and has been estimated at 24% worldwide. Its incidence is observed to be highest in South America and the Middle East followed by Asia, United States, and Europe[10,11]. Chronic liver diseases cause liver fibrosis and progresses through mild fibrosis to cirrhosis. Liver fibrosis is also one of the well-known risk factors for hepatic decompensation and HCC development[12,13]. Any chronic liver disease could be worse without proper treatments. To determine who is at high-risk for HCC development and disease progression in such a population is a crucial clinical question. The deep learning methods are expected to be useful in identifying high-risk patients. In this review, we summarize the recent advances of AI in hepatology and discuss their clinical implications. In this review, we searched for the literature in PubMed and summarized recent developments of AI concerning hepatology.

CURRENT AI METHODOLOGY

AI systems can be roughly divided into four categories: search algorithm, expert system, machine learning, and deep learning. Machine learning generates a mathematical algorithm from the training dataset and utilizes it to predict outcomes or make decisions[14]. Moreover, machine learning is divided into supervised and unsupervised learning. In a supervised learning model, the algorithm learns from a labeled dataset (individual parameters and outcomes). Conversely, deep learning is based on the neural network structure inspired by the human brain. There are different types of neural networks in deep learning, and representative types are artificial neural network, convolutional neural network (CNN), and recurrent neural network.

Artificial neural network is a computational analysis tool inspired by the biological nervous system[15]. It consists of three layers: input, hidden, and output. Each layer comprises several "neurons," and the hidden layer processes the input and the output

layer produces the result. Through an appropriate training process, the weights among the neural connections are adjusted to optimize the result.

CNN is an image-based machine learning method that is directly inspired by the visual cortex of the brain[16]. A basic CNN consists of convolution layers, nonlinear layers, and pooling layers. CNNs are currently one of the most successful deep learning models because of their unique ability to process spatial information[17].

Recurrent neural network is a type of neural network with feedback connections[18,19]. It exhibits great performance in labeling and predicting sequential data. A prominent example of sequential data is natural language. Recurrent neural network maintains the history of input data within the network, and the output is produced from the past input. In the following sections, we discuss related studies from the literature. The content is summarized in Table 1.

DIAGNOSIS OF LIVER DISEASES AND TUMOR DETECTION

Currently, imaging examinations are displayed and stored as digital images. Furthermore, computer-aided diagnosis/detection (CAD) has already been applied for chest nodule detection[20] and cerebral aneurysm detection[21]. Recently, Mei *et al*[22] reported an AI system that used chest computed tomography along with clinical symptoms, exposure history, and laboratory testing to enable rapid diagnosis of coronavirus disease 19. The results of this AI system depicted an area under the receiver operating characteristics (AUROC) of 0.92[22].

However, the CAD system is costly, and regular maintenance is required for its use. Nevertheless, it can help healthcare workers in diagnosing and detecting tumors. The first CAD system was approved by the Food and Drug Administration for mammography in 1998[23]. Nowadays, the CAD system uses deep learning for the analysis and classification of medical images[16]. Big data availability and increased chip processing capability enable foreseeable advances in deep learning-based systems. The following section summarizes the recent AI research on focal and diffuse liver diseases.

Detection of focal liver diseases

Hassan *et al*[24] used the stacked sparse auto-encoder system to detect HCC, hemangioma, and liver cysts from US images. They used a four-step framework as follows. First, the processing images were enhanced while the background noises were reduced. Subsequently, liver segmentation was conducted using the level set method and fuzzy c-means clustering algorithm. Next, stacked sparse auto-encoder was employed to identify latent features from unlabeled input data in an unsupervised manner. Finally, a softmax layer was used to diagnose different focal liver diseases. The sensitivity and specificity of the proposed deep learning system were 98.0% and 95.7%, respectively[24]. Sato *et al*[25] developed a machine-learning model for predicting HCC in 539 HCC-positive and 1043 non-HCC patients at a tertiary referral center, and the AUROC of the model for HCC was 0.940 compared to 0.766, 0.644, and 0.683 for alpha-fetoprotein, des-gamma-carboxyprothrombin, and Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein, respectively.

Staging of diffuse liver diseases

Biswas *et al*[26] reported that deep learning techniques were superior to conventional machine learning techniques for detecting fatty liver disease through US examinations. The study was based on 63 patients (27 healthy and 36 abnormal), and the AUROCs of the support vector machine, extreme learning machine, and deep learning were 0.79, 0.92, and 1.0, respectively. Byra *et al*[27] employed an Inception-ResNet-v2 CNN pre-trained on ImageNet for NAFLD diagnoses using US examinations in 55 obese patients admitted for bariatric surgery. They used a wedge biopsy liver sample as the reference standard. The AUROC of the approach was 0.9777, compared to 0.9590 for the conventional hepatorenal index. The detection of steatosis is beneficial in the field of hepatology. However, more data are needed for better AI applications, and resources, such as liver biopsy samples, are limited because of their invasiveness.

Recently, US elastography has been widely used in clinical practice for noninvasive diagnosis of liver fibrosis stages and as a surrogate marker for clinical outcomes such as HCC development, liver failure, and rupture of esophageal varices[28-31]. Wang *et al*[32] reported deep learning radiomics for shear wave elastography, and the AUROC of the model for diagnosis of cirrhosis was 0.97 (95% confidence interval: 0.94-0.99), which outperformed the biomarkers. Generally, the stiffness value of US elastography is

Table 1 Clinical applications of artificial intelligence

	Samples	Diagnosis	AI technique	Accuracy, %	AUROC	Ref.
Focal liver disease detection	US	Benign tumors	DL	97.2	NA	[23]
	Serum tests, clinical data	HCC	ML (gradient boosting)/DL	87.34/83.54	0.940/0.884	[25]
Diffuse liver disease staging	US	FLD	DL/SVM/ELM	100/82/92	1.0/0.79/0.92	[26]
	US	NAFLD	DL	NA	0.9777	[27]
	Elastography	Cirrhosis	DL	NA	0.97	[32]
Risk assessment	Clinical, pathohistological data	Poorer survival after HCC resection	2 DL models	NA	0.78, 0.75 (c-index)	[35]
	Sequence data	Poorer survival after HCC resection	DL	NA	0.68 (c-index)	[36]
	Clinical data	HCC development	ML	NA	0.64 (c-index)	[37]
	Clinical, histological data	1-yr and 3-yr clinical outcomes	ML	NA	0.78, 0.76	[38]

AUROC: Area under the receiver operating characteristics; c-index: Confidence interval; DL: Deep learning; ELM: Extreme learning machine; FLD: Fatty liver disease; HCC: Hepatocellular carcinoma; ML: Machine learning; NAFLD: Nonalcoholic fatty liver disease; SVM: Support vector machine; US: Ultrasonography; NA: Not available.

considered to be affected by inflammation, obstructive jaundice, liver congestion, fasting, and steatosis[33,34]. Deep learning methods integrating stiffness values and elastograms with other clinicopathological factors will be powerful tools for the diagnosis of liver fibrosis.

RISK ASSESSMENT OF LIVER DISEASE

The risk assessment of HCC is crucial for the apt management of patients with chronic liver diseases. Saillard *et al*[35] implemented two deep learning algorithms based on whole digitized slides for predicting the survival of HCC patients after hepatic resection. They first created a composite score using clinical, biological, and pathological factors for survival prediction. However, both deep learning models reported higher performance than the composite score. An expert pathologist examined the high-risk and low-risk slides obtained from the models. Subsequently, the pathologist observed that the high-risk group had cellular atypia, vascular spaces, and macrotrabecular architectural pattern. In contrast, the low-risk group had tumoral fibrotic stroma, immune cells, and fibrosis in both tumor and nontumor areas[35]. These findings will lead to further research focusing on the inflammatory reaction against HCC.

The deep learning model proposed by Chaudhary *et al*[36] integrated RNA sequencing (15629 genes), miRNA sequencing (365 miRNA), and methylation data (19883 genes) from The Cancer Genome Atlas. The model detected a critical subgroup that was associated with frequent *TP53* inactivation mutations, higher levels of stemness markers (*KRT19* and *EPCAM*), tumor marker (*BIRC5*) expression, and activated Wnt and Akt signaling pathways[36]. Deep learning models regarding the prognosis of chronic liver disease patients have not yet been fully evaluated. Thus, machine models have been used to determine the prognostic model in several studies[37,38]. A deep learning model requires a considerable amount of data than a traditional machine learning algorithm. Therefore, machine learning sometimes fits in clinical settings with limited datasets. Singal *et al*[37] used a random forest model to predict HCC development in Child A or B cirrhotic patients. The model was validated through the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis cohort and depicted better performance than the traditional regression analysis. Konerman *et al*[38] used the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial cohort to construct a random forest model to predict outcomes of patients with chronic hepatitis C and validated it with 1007 patients during a median of 4.9 years of the observation period. The AUROC for 1 year and 3 years risk of clinical outcomes was 0.78 (95% confidence interval: 0.73-0.83) and 0.76 (95% confidence interval: 0.69-0.81).

LIMITATIONS OF AI TECHNOLOGY

Although the algorithms mentioned above are promising, AI has several limitations[39]. First, it may not be possible to understand how and why the model is created. Second, AI does not conform to personal preferences and legal responsibility. If the AI makes a wrong decision, who will be held accountable for this result? Moreover, a biased AI could affect the outcome of several patients. Therefore, careful attention should be paid to the interpretation of AI's decision. Third, to avoid the overfitting problem, multicenter studies with high-quality datasets to validate the models are required. Fourth, the protection of privacy and security of data is crucial. The personal medical history should be protected and hacking or manipulating the model should be strictly avoided.

CONCLUSION

Digitalization of image examinations and big data availability has resulted in advancements to the AI system represented by deep learning research, especially in the detection of liver diseases. There exists a robust gold standard, *i.e.* histological diagnosis obtained by either biopsy or resection for the detection of liver tumors. However, for the surveillance of NAFLD patients, the gold standard is not just the degree of fat accumulation but also the clinical outcomes of who will develop HCC and who will progress to liver failure. The quality of deep learning models highly depends on the training dataset. A large volume of high-quality data is required to build an accurate and useful AI system for identifying liver diseases.

The application of AI in medical imaging has a good prospect and value. It has been reported that successful applications of AI technologies in endoscopic images for esophageal cancer[40], gastric cancer[41-43], small intestinal cancer[40], colorectal cancer[44,45], analysis of computed tomography for pancreatic cancer[46,47], and others[48-50]. Hepatologists should learn from these other areas.

AI will also be an essential element in the management of liver diseases to reduce medical errors, select the best treatment, and predict outcomes. Nevertheless, even with further advances in computer science, decisions on real clinical practices are affected by the patient's will, treatment availability, and financial issues. Moreover, social rapport plays a vital role in building a patient's trust and satisfaction[51]. Thus, cooperation between humans and AI is expected to improve healthcare in the future.

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MINIREVIEWS

Application of artificial intelligence in the diagnosis and prediction of gastric cancer

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Abstract

Gastric cancer is the second leading cause of cancer deaths worldwide. Despite the great progress in the diagnosis and treatment of gastric cancer, the incidence and mortality rate of the disease in China are still relatively high. The high mortality rate of gastric cancer may be related to its low early diagnosis rate and poor prognosis. Much research has been focused on improving the sensitivity and specificity of diagnostic tools for gastric cancer, in order to more accurately predict the survival times of gastric cancer patients. Taking appropriate treatment measures is the key to reducing the mortality rate of gastric cancer. In the past decade, artificial intelligence technology has been applied to various fields of medicine as a branch of computer science. This article discusses the application and research status of artificial intelligence in gastric cancer diagnosis and survival prediction.

Key words: Artificial intelligence; Gastric cancer; Early diagnosis; Survival prediction

Core tip: Much research has been focused on improving the sensitivity and specificity of diagnostic tools for gastric cancer, in order to more accurately predict the survival times of gastric cancer patients. Artificial intelligence technology has been applied to various fields of medicine as a branch of computer science. This article discusses the application and research status of artificial intelligence in gastric cancer diagnosis and survival prediction.

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INTRODUCTION

Gastric cancer is a common malignant tumor of the digestive system caused by the proliferation of malignant gastric cells. It can spread to every part of the stomach and other organs, especially the esophagus, lungs, and liver. Gastric cancer is the fourth most common cancer in the world after lung cancer, breast cancer, and intestinal cancer[1], and the second leading cause of cancer deaths worldwide[2]. The incidence and mortality rates of gastric cancer in China far exceed those of other countries, both developed as well as developing. By 2020, death due to gastric cancer will become the leading cancer death in China[3]. Due to the lack of specific symptoms and signs of early gastric cancer, most patients are already in advanced stages when they are diagnosed with gastric cancer. Although the diagnosis and treatment of gastric cancer have made great progress, the mortality rate of gastric cancer is still very high. Determining how to improve the diagnosis rate of early gastric cancer and accurately predict the survival of gastric cancer patients is a major problem facing clinicians.

In November 2015, Google DeepMind's AlphaGo artificial intelligence (AI) software program played a best-of-five match against the European Go champion Fan Hui and won easily. Then in March 2016, AlphaGo played another best-of-five match against 18-time Go world champion Lee Sedol. The program won the first three games to win the match. This result made many people realize the impact that AI could have on real life. Today, AI is widely used in various fields of medicine, such as diagnosis and prediction of related diseases, medical image interpretation and classification, drug development, personalized medicine, and genomics. This article focuses on the application of AI in gastric cancer diseases and combines the actual cases to determine the application and research status of AI in the diagnosis and survival prediction of gastric cancer.

ARTIFICIAL INTELLIGENCE

AI is a branch of computer science devoted to enabling machines to perform complex tasks that normally require human intelligence. AI in a broad sense includes machine learning, robots, and computer vision. AI goes through four stages: Inference period, knowledge period, machine learning period, and deep learning period. Using artificial neural network (ANN), support vector machine (SVM), convolutional neural network (CNN), and fully convolutional networks are represented[4,5]. This article focuses on the application of machine learning in the diagnosis and prediction of gastric cancer. Machine learning can be divided into three types of training methods: Supervised learning, unsupervised learning, and reinforcement learning[6]. Supervised learning refers to the training of machines with annotated data and includes random forest, SVM, decision tree linear regression, logistic regression, naive Bayes, K-nearest neighbor, AdaBoost, and neural network. Unsupervised learning refers to directly submitting data lacking manual labeling to a computer for classification. Unsupervised learning includes the K-means method, mean moving method, cluster analysis method, Gaussian mixture modeling method, Markov random field method, and iterative self-organizing data method. Reinforcement learning refers to constructing a computer classifier using artificially labeled datasets and then providing a certain amount of unlabeled data training to the constructed system to optimize the performance of the mode[7].

APPLICATION OF AI IN THE DIAGNOSIS OF GASTRIC CANCER

The prognosis of patients with gastric cancer depends on the stage of the cancer at the time of diagnosis[8,9]. Due to the lack of specific symptoms and signs of early gastric cancer, most patients with gastric cancer are already in advanced stages at the time of diagnosis. Although the prognosis for patients with advanced gastric cancer is poor,

the 5-year survival rate of patients diagnosed with early gastric cancer is greater than 90%[8-11]. Therefore, improving the diagnosis rate of early gastric cancer is the most effective measure to reduce the mortality rate of the disease. Because early gastric cancer lacks characteristic morphological changes, its diagnosis generally depends on the subjective judgment of doctors. The development of AI technology has brought about opportunities to solve these problems.

Application of AI in endoscopic images of gastric cancer

In recent years, CNNs have made great progress in AI image recognition for deep learning and as a result are increasingly used in diagnostic imaging in the medical field (Table 1). Hirasawa *et al*[12] developed a CNN diagnostic system that can automatically detect gastric cancer in endoscopic images and used 13584 gastric cancer endoscopic images as a training set for the CNN diagnostic system. Then, 2296 gastric cancer images were used as a testing set to evaluate the accuracy of the diagnosis. The results showed that CNN analyzed 2296 test images in only 47 s and correctly diagnosed 71 of 77 gastric cancer lesions, with an overall sensitivity of 92.2%. The missing lesions were surface depressions and differentiated intramucosal cancers. Even experienced endoscopists have difficulty distinguishing these from gastritis. The system classified 161 non-cancerous lesions as gastric cancer, with a positive predictive value of 30.6%. The reason for the low positive rate could be that the morphological characteristics of early gastric cancer are fewer and are similar to gastritis.

To solve the above problems, Sakai *et al*[13] proposed a transfer CNN model, using two types of image datasets for transfer learning. A data enhancement method was used to intercept 9587 cancer images and 9800 normal images from the cancer images and the normal images as the training set. Similarly, 4653 cancer images and 4997 normal images obtained from the unused cancer images and normal images were used as the testing set. The network accuracy after training was 87.6%, the detection accuracy was 82.8%, the sensitivity and specificity achieved a good balance, and the candidate regions of early gastric cancer could be presented as heat maps of unknown images to reveal the approximate position.

Zhu *et al*[14] used the most advanced pre-trained ResNet 50 CNN model to construct a set of AI-based CNN computer-aided detection systems to analyze the depth of cancer cell invasion in endoscopic images, with 790 images as the training set of the system and 203 images as the test set. The researchers compared the analysis results of the CNN model with the analysis results of the endoscopy doctor. The CNN model specificity was 95.56%, and the overall accuracy rate was 89.16%. The specificity of the endoscopist was 32.21%, and the accuracy was 17.25%. The study showed that the CNN model performs better than the human eye in judging the depth of cancer cell infiltration in endoscopic images. Because early gastric cancer lacks specific morphological features, even an experienced endoscopist has trouble distinguishing it from chronic gastritis. The diagnosis rate of inexperienced young endoscopists will be even lower, which will easily lead to missed diagnoses and misdiagnoses.

To more accurately determine early gastric cancer and non-cancerous lesions, Li *et al*[15] developed a CNN system based on narrow-band magnifying endoscopy. By observing the microvessels and microsurface structures of the gastric mucosa, the narrow-band magnifying endoscopy-based system was able to establish an average 0.02s/picture speed to screen for early gastric cancer. Comparing the results of CNN with those of experts and nonexperts, the sensitivity of the CNN system in the diagnosis of early gastric cancer was 91.18%, the specificity was 90.64%, and the accuracy was 90.91%. Although there was no significant difference in the specificity and accuracy of diagnosis between CNN and the experts, the diagnosis sensitivity of the CNN system was higher than that of the experts. In addition, the sensitivity, specificity, and accuracy of CNN system diagnosis were significantly higher than those of nonexperts. Horiuchi *et al*[16] conducted a similar study to identify early gastric cancer and chronic gastritis and obtained higher sensitivity and accuracy. The reason may be that researchers have different interpretations and naming rules for histology.

Application of AI in gastric cancer pathology images

The rapid development of AI in the field of pathological images is also a hot topic in current research. Yoshida *et al*[17] first attempted to screen gastric biopsy specimens using an automated image analysis software system called e-Pathologist. They analyzed 3062 gastric cancer pathological images and compared the results of the automatic image analysis software with those of human pathologists. Classification as third grade (positive cancer or suspected cancer; adenoma or suspected neoplastic lesion; or negative neoplastic lesion) had a total coincidence rate of 55.6%. A biopsy negative specimen had a coincidence rate of 90.6%, and a biopsy positive specimen

Table 1 Application of artificial intelligence in endoscopic images of gastric cancer

Ref.	Images	Sensitivity	Specificity	Accuracy
Hirasawa *et al*[12]	Endoscopic images with NBI imaging	92.20%	-	30.60 %
Zhu *et al*[14]	Endoscopic images	76.47%	95.56%	89.16%
Li *et al*[15]	ME-NBI images	91.18%	90.64%	90.91%
Horiuchi *et al*[16]	ME-NBI images	95.40%	71.00%	85.30%

NBI: Narrow band imaging; ME-NBI: Magnifying endoscopy with narrow band imaging.

had a coincidence rate of less than 50%. The sensitivity of the two-level (negative or non-negative) classification of electronic pathology experts was 89.5%, and the negative predictive value was 90.6%. However, the specificity (50.7%) and positive predictive value (47.7%) were low. The results were encouraging at the time. However, at this stage, the tissue slices created by the pathologist cannot be directly used for AI analysis. The lack of well-annotated pathological image data has become a major limitation to the development of AI in the field of pathological images.

To solve this problem, Qu *et al*[18] proposed a gradually fine-tuned new deep learning CNN for gastric pathological image classifications and introduced the concept of target-related intermediate datasets. The research results showed that the use of target-related intermediate datasets significantly improves the classification performance of CNNs. We hope that the effectiveness of the target-related intermediate data applied to deep neural networks can be specifically evaluated in future work.

Lymph node metastasis of gastric cancer has always been regarded as the most important factor affecting the prognosis of patients, which therefore plays a key role in guiding the selection of postoperative treatment options[19]. Traditional pathological examination methods are time-consuming and expensive, and it is easy to miss tiny lesions. In response to this problem, Wang *et al*[20] evaluated the clinical application value of CNN in the pathological diagnosis of gastric cancer metastatic lymph nodes. They divided 124 patients undergoing radical gastrectomy and D2 lymph node dissection into training set (80 cases) and testing set (44 cases). The test group verification results showed that the accuracy rate was 100% in terms of slice-level classification, that 40 normal slices and 38 tumor slices were correctly classified, and that the classification results were completely consistent with the pathologist. In terms of identifying block-level transfers, the accuracy rate was 0.989, the specificity 0.995, the positive predictive value 0.822, and the area under the curve 0.89, which is basically consistent with the diagnosis level of the pathologist.

Application of AI in noninvasive examination of gastric cancer

Endoscopy and pathological examination are the gold standard for the diagnosis of gastric cancer. Because of their invasiveness, high cost, and low compliance, they are generally only suitable for high-risk groups. This is why it is so important to carry out early gastric cancer risk screening and find practical gastric cancer biomarkers. Compared with invasive examinations, these noninvasive examinations have the advantages of simple operation, low cost, and high comfort, and the patient's compliance is relatively high. Huang *et al*[21] made full use of the advantages of machine learning to find a set of microRNA combinations with high accuracy and high sensitivity for noninvasive prediction of gastric cancer in the serum of patients with gastric cancer. From the published miRNA map (GSE23739), we selected miR-21-5p, miR-22-3p, and miR-29c-3p as the training sets to train the three classifiers. The areas under the characteristic curve were 0.9437, 0.9456, and 0.9563, respectively, and the positive predictive value and negative predictive value were both more than 80%. Then it was verified in two maps (GSE26595, GSE28700) of the Gene Expression Omnibus database and the patient's serum. Finally, similar results were obtained. Quantitative reverse transcription polymerase chain reaction confirmed that the level of serum miR-21 in gastric cancer patients was higher than that in healthy controls, whereas the levels of miR-22 and miR-29c were opposite. The results of this study indicate that miR-21-5p, miR-22-3p, and miR-29c-3p can be used as potential biomarkers for detecting gastric cancer. However, the sample size of this study was small, and therefore its predictive value requires more research to be confirmed.

Liu *et al*[3] used data mining methods to establish four classification models for

screening early gastric cancer risk. A questionnaire entailing serological examination and endoscopy plus pathological biopsy was given to 618 patients with gastric disease, with the patients divided into high risk and low risk groups. The accuracy rates of the three data mining models were higher than the logistic regression model. The study also found that 16 factors, such as occupation, *Helicobacter pylori* infection, and drinking hot water can have a significant impact on the risk of early gastric cancer. The discovery of these risk factors helps to evaluate the occurrence of gastric cancer in patients and reminds them of the importance of early prevention and detection. The study also helps clinical researchers select and implement optimal prediction models.

Mortezag *et al*[2] conducted a similar study using data mining methods, using SVM, decision tree, naive Bayes model and k-nearest neighbor to classify gastric cancer patients. A total of 11 features and risk factors were examined, and research showed that the SVMs achieved the highest accuracy in the classification results. Dividing patients into high-risk and low-risk groups, as done in the above research, can help clinicians target high-risk patients for early gastric cancer screening, which can not only lead to the use of fewer medical resources but also reduce the workload of clinicians.

APPLICATION OF AI IN SURVIVAL PREDICTION OF GASTRIC CANCER

The human body is a complex biological system, and most clinical features exhibit a multidimensional, nonlinear relationship. It is difficult to predict the prognosis of gastric cancer patients using traditional statistical methods. AI offers a unique advantage in evaluating the prognosis of gastric cancer patients. Biglarian *et al*[1] used the Cox proportional hazard model and an ANN to predict the survival rate of gastric cancer patients. The accuracy of the ANN model was 83.1%, and the accuracy of the Cox regression model was 75.0%. Another study obtained similar results. The prediction accuracy of the ANN was 85.3%, and the prediction accuracy of the Cox model was 81.9%[22]. Both of the above studies indicate that the neural network model is a better statistical tool for predicting the survival rate of gastric cancer patients. Because the current tumor, nodes, and metastases (TNM) staging system cannot provide enough information to predict the prognosis of gastric cancer and the effect of chemotherapy, we need to build a more accurate classifier to predict the prognosis of gastric cancer patients.

Oh *et al*[23] used ANNs to establish a predictive model for the survival outcome of gastric cancer patients. The survival curve of the prediction model is better than the survival curve of the American Joint Committee on Cancer stage 8, which can differentiate the survival results of gastric cancer patients. The predicted lifetime of the model is in agreement with the actual lifetime. The immune marker SVM classifier established by Jiang *et al*[24] is more accurate than traditional TNM staging in predicting the survival rate of gastric cancer patients and can supplement the prognostic value of the TNM staging system. Furthermore, the classifier can predict which patients with stage II and III gastric cancer can benefit from adjuvant chemotherapy. Therefore, these gastric cancer survival prediction models can be used to classify high-risk gastric cancer patients and allocate necessary treatment and health resources to them. At the same time, it enables patients with gastric cancer to have more effective consultations after surgery. It also helps clinicians design treatment strategies and arrange follow-ups.

CONCLUSION

The mortality rate of gastric cancer in China is high. Due to the lack of specific morphological characteristics and clinical manifestations of early gastric cancer, its early diagnosis mainly depends on the personal experience of the doctor, meaning that it lacks objectivity and is highly time-consuming. In the diagnosis of early gastric cancer, AI has high sensitivity and specificity. Not only can the use of AI reduce misdiagnosis and variability among observers, but it can also save clinicians a great deal of time. It can also help inexperienced doctors. With AI, clinicians can divide patients into high-risk and low-risk groups according to risk factors related to the incidence of gastric cancer and certain serological markers so that the clinicians can focus on the high-risk patients. Compared with traditional TNM staging, AI is more accurate in predicting the survival of gastric cancer patients. This can guide clinicians to formulate follow-up treatment strategies and arrange follow-up times, which can

help to prolong the survival time of patients with advanced gastric cancer.

However, there are still few articles on the use of AI to guide chemotherapy treatment for advanced gastric cancer. We hope that more scholars will engage in related research in the future. Of course, the development of AI in the medical field also faces many challenges. The training of AI models in order to achieve accuracy requires a great deal of manually annotated medical data. Although many scholars have abandoned many poor-quality data to obtain high performance of AI models, it is still impossible to capture many details of AI for feature extraction and the decision-making process. However, we believe that with the development of AI in the world of medicine, this will soon change.

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MINIREVIEWS

Application of artificial intelligence for the diagnosis, treatment, and prognosis of pancreatic cancer

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Abstract

Pancreatic cancer is a complex cancer of the digestive tract. Diagnosis and treatment can be very difficult because of unclear early symptoms, the deep anatomical location of cancer tissues, and the high degree of cancer cell invasion. The prognosis is extremely poor; the 5-year survival rate of patients with pancreatic cancer is less than 1%. Artificial intelligence (AI) has great potential for application in the medical field. In addition to AI-based applications, such as disease data processing, imaging, and pathological image recognition, robotic surgery has revolutionized surgical procedures. To better understand the current role of AI in pancreatic cancer and predict future development trends, this article comprehensively reports the application of AI to the diagnosis, treatment, and prognosis of pancreatic cancer.

Key words: Pancreatic cancer; Artificial intelligence; Robotic surgery; Artificial neural network; Machine learning

Core tip: There are few unified reports on the use of artificial intelligence (AI) with regard to pancreatic cancer. By collating information on AI's application in this field in recent years, this article systematically reports the use of AI for the diagnosis, treatment, and prognosis of pancreatic cancer. Accordingly, this article fully depicts the current status of AI in this field and predicts future development trends.

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INTRODUCTION

Pancreatic cancer has a high degree of malignancy. Given the difficulty of early diagnosis, pancreatic cancer often metastasizes after diagnosis. Despite significant progress in pancreatic cancer research in the past decade, treatment and prognosis still tend to be unsatisfactory[1,2].

Artificial intelligence (AI) has greatly progressed in recent years. AI can avoid the influence of subjective thinking; deal with large data volumes; and support diagnosis, treatment, and prognosis[3]. Therefore, medical AI is a topic of considerable interest. AI is also widely used in the field of pancreatic cancer. Applications include diagnosing cancer by processing image data[4] and using machine learning to accurately distinguish cancer subtypes[5]. Robotic surgery is also widely applied to make up for the shortcomings of traditional laparoscopic surgery[6]. Artificial neural networks (ANNs) are able to predict the maximum probability of survival of patients with pancreatic cancer 7 mo after surgery[7]. Therefore, AI has great prospects for further application in the diagnosis, treatment, and prognosis of pancreatic cancer. This article summarizes the current role and application of AI in medical work related to pancreatic cancer.

AI'S ROLE IN PANCREATIC CANCER DIAGNOSIS

Application of AI to the molecular diagnosis of pancreatic cancer

In bioinformatics research, researchers often need to collect, screen, process, and summarize large amounts of data. As such, the question of whether machine learning can simplify the process and achieve good results has been a hot research topic[8]. There are many specific molecules related to pancreatic cancer such as microRNA (miRNA) 10b[9], cell-free DNA[10], and ZIP4[11]. Research on the molecular mechanism and diagnosis of pancreatic cancer has become a mature, standardized field, with a large number of relevant articles in recent years[11,12]. However, the need to collect and process data manually can consume a great deal of time and energy.

Machine learning helps researchers spend less time on data processing through one-time modeling. The steps for using machine learning typically include the following: Collecting the basic data, dividing data into an experimental group and a verification group, establishing a screening and processing model, inputting the experimental group data into the model, calculating the output results, and verifying the model's feasibility using the verification group. The verification group can be used to test the specificity and sensitivity of the experimental group while the experimental group can make the model more intelligent[10]. The steps are illustrated in Figure 1.

Using network representation learning and convolutional neural networks, the correlation between miRNA and pancreatic cancer disease can be analyzed, and the potential disease miRNA can be found[13]. Machine learning has been used to process large exocrine RNA data and generate predictive templates that can identify cancer in individuals[14]. An ANN can imitate the human neural meridian system. It is divided into three parts: Input layer, hidden layer, and output layer. "Deep learning" (Figure 2) refers to an ANN with multiple hidden layers. Using this technique, cyst tumor markers, amylase, cytology, and other information are inputted and then combined with two data; the output layer outputs whether the pancreatic cystic lesions are benign or malignant[15]. Some researchers have also proposed an extensible supervised classifier technical framework that can diagnose pancreatic cancer provided the expression profile of a single cell can be input to reveal its identity[9].

Although machine learning can save researchers a lot of time on data processing, machine learning still has many limitations. The first concerns data collection and processing. Specific input projects at the beginning of modeling are needed for machine learning and neural network analysis. However, for researchers who have not carried out data analysis, it is unknown which raw data are necessary and

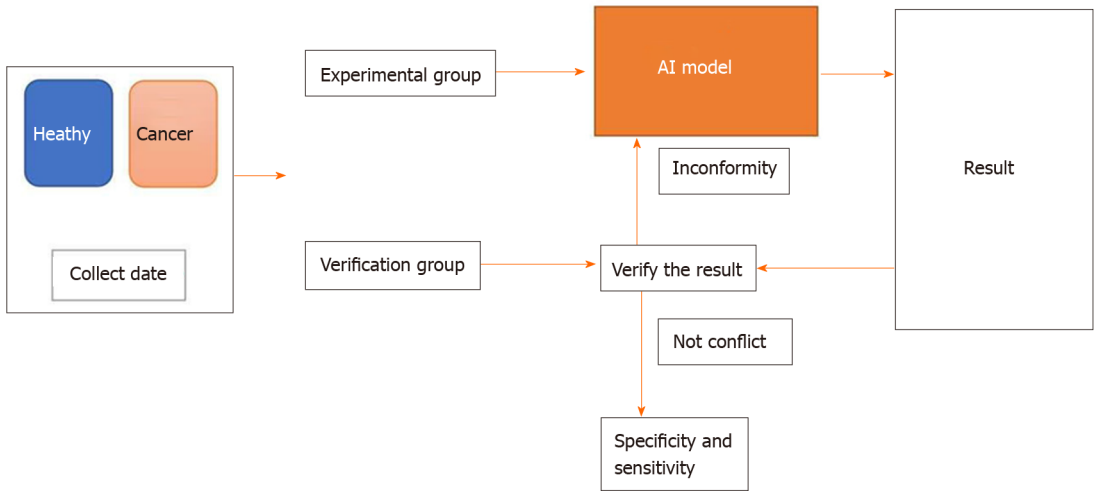

Figure 1 The common steps in machine learning. A similar pattern was used for prognostic analysis of pancreatic cancer.

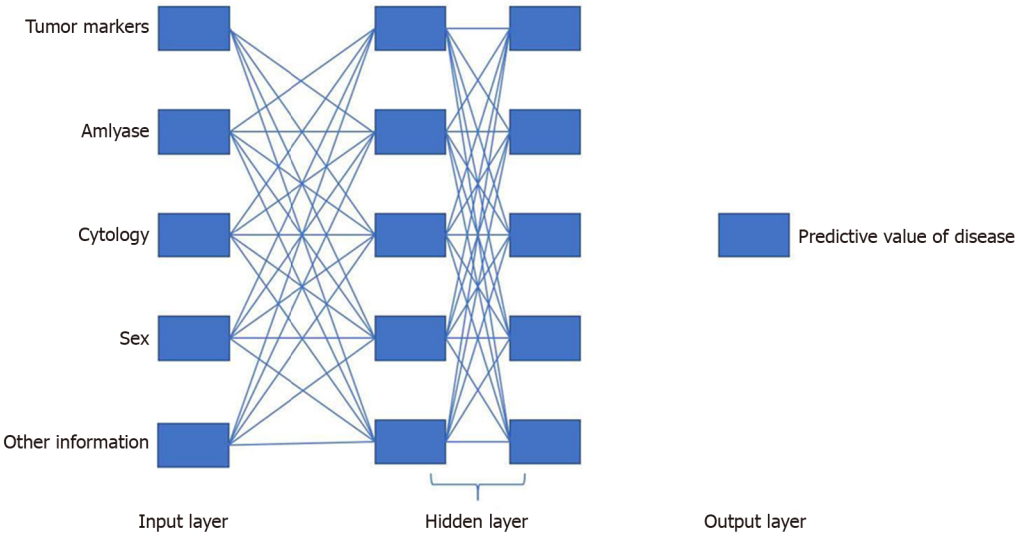

Figure 2 Algorithm of deep learning. Data were passed from layer to layer: from the input layer to the output layer.

unnecessary. Useless data simply increase the workload and can also become the specificity and sensitivity of the model. Meanwhile, editing the model also poses a significant problem. Although AI can save time, the threshold and workload in the establishment of AI programs are prohibitive for nonprofessionals who lack a foundation in math and programming.

The occurrence and development of pancreatic cancer is complex and changeable, and the patient's condition has a large degree of variability. In this regard, AI can be applied to the molecular diagnosis of pancreatic cancer and can obtain objective data processing results. However, AI is not independent and mostly can only be used as an auxiliary tool. Yet, with continuous development and improvement, AI might eventually have a more universal application.

Application of AI in the imaging diagnosis of pancreatic cancer

AI algorithms (especially deep learning) have made great progress in medical image recognition; convolutional variational autoencoders and other methods have numerous applications in this field[16]. In fact, as early as 2001, neural networks were used to analyze endoscopic ultrasound images to distinguish pancreatic cancer from focal pancreatitis. A program was designed that could distinguish pancreatitis from pancreatic cancer by extracting pixel features from images, showing a high accuracy rate of 89%[17]. Given the state of image diagnosis technology at that time, the images were relatively simple, but with the help of computer neural networks, differential

diagnosis became easier and achieved higher accuracy. Since then, neural network analysis images have been used in research to differentiate pancreatic cancer from chronic pancreatitis. This method involves collecting image data into a vector form and then converting it into a hue histogram. The sensitivity, specificity, and accuracy of this method in the differential diagnosis of benign and malignant pancreatic lesions were 91.4%, 87.9%, and 89.7%, respectively[18].

Pancreatic cystic lesions are often considered an important sign of pancreatic cancer. Machine learning is used to extract the imaging features of these cystic lesions, select and classify those features, and then use them to predict benign or malignant pancreatic cystic lesions. In this process, first, image acquisition is conducted uniformly, the edge of the suspected lesion object is delineated, and the three-dimensional (3D) shape of the variant is obtained. Then the features of suspected diseases in the image are extracted including the structure, density, and shape. AI software is used for in-depth learning, the features are screened and analyzed, and the imaging output results are obtained. The obtained results, proteomics, and patient data are entered into the machine learning model as the input layer to generate a predictive model, which can help clinicians in the differential diagnosis of benign and malignant pancreatic cysts[19].The entire process is shown in Figure 3.

Over the past 20 years, with the popularization and development of computed tomography (CT), magnetic resonance imaging, and positron emission tomography-CT, medical staff has been able to obtain more clear imaging data. However, because of human limitations, they cannot achieve zero errors, and diagnostic efficiency is not high. Furthermore, it is time consuming to train professional radiologists. Moreover, the image itself can only reflect the internal structure of the patient at a certain time and from a certain angle; thus, slight changes can be difficult to be detect with the naked eye. As such, reliable AI can improve the accuracy of image diagnosis.

As mentioned above, manual diagnosis has shortcomings such as subjective judgment, a lack of repeatability, and low accuracy. Recent research on using convolutional layer neural networks to recognize CT in pancreatic cancer diagnosis may provide a way to overcome such shortcomings. An AI designed for one related study consisted of two parts: training and verification. First, a patient data database is established, image data are collected, and an image database is established. Then the feature extraction, area generation (RPN), and classification and regression networks are established. In the AI network, the input image is first converted into a convolutional feature graph, and the RPN parameters are adjusted through the feature map to generate the ROI feature vectors. Then the RPN parameters are put into the convolutional layer, and a certain model is used for regression and classification. Next, the regression parameters are generated into new RPN parameters, and the two RPN parameters are updated only for the unique network layer of RPN through machine learning. The RPN parameters are then generated by the regression parameters to fine-tune the unique convolutional layer. Using a reserved verification group input model, the Secure Global Desktop network is trained by back-propagation and random gradient descent, and the network weights and parameters can be constantly updated and optimized. Finally, the final model is obtained as an AI diagnosis system. The receiver operating characteristic curve of the experimental results reached 0.9632. The AI in that study needed only 20 s to identify images and was more objective and effective than traditional diagnosis methods. It was noted, however, that while this method showed high accuracy in the diagnosis of pancreatic cancer, it does not mean AI can replace specialists; rather, it provides an auxiliary tool for diagnosis[20].

Although AI has good prospects for image diagnosis, it also has limitations, and the process of model training is inseparable from the assistance of artificial diagnosis. In theory, the ultimate goal of diagnostic accuracy is infinitely close to the imaging doctor. Therefore, how to make good use of this to make AI more intelligent may be an important problem to be solved in future research. In fact, the application of AI in imaging has been investigated by experts in many fields, and it also requires knowledge from many fields. Such projects create a platform for imaging experts to communicate with computer experts. The result is that an AI system is established that uses a deep learning algorithm to collect and analyze CT images of the pancreas. The experimental group image data and the normal control image data are imported into the program. Through two matrices and the application of a filter, statistics, texture, shape, and other data are obtained. Then the pancreatic ductal adenocarcinoma and the normal control are distinguished by data processing, statistical analysis, and the random forest model.

The relationship between AI and imaging involves knowledge from various fields such as pathology, radiology, oncology, and computer science. Thus, a more intelligent AI system may be built through the combined work of experts from multiple fields[21].

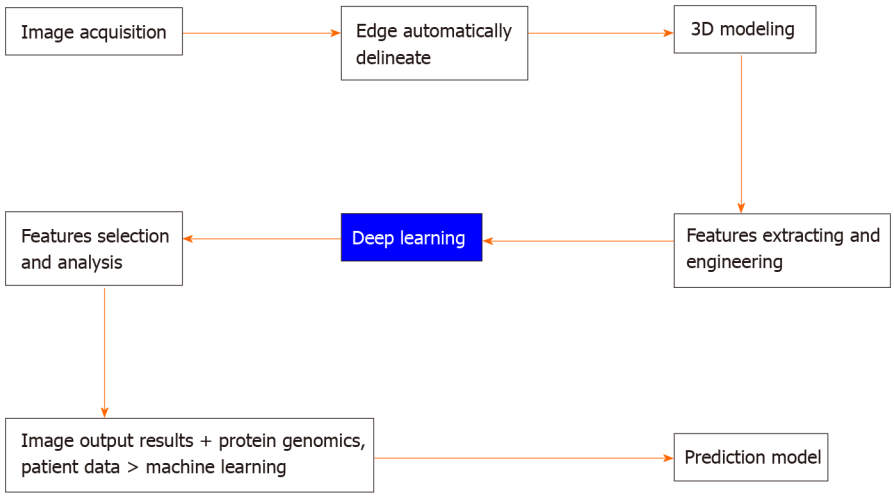

Figure 3 The entire process. Machine learning is used to extract the imaging features of these cystic lesions, select and classify those features, and then use them to predict benign or malignant pancreatic cystic lesions. In this process, first, image acquisition is conducted uniformly, the edge of the suspected lesion object is delineated, and the three-dimensional shape of the variant is obtained. Then, the features of suspected diseases in the image are extracted, including the structure, density, and shape. AI software is used for in-depth learning, the features are screened and analyzed, and the imaging output results are obtained. The obtained results, proteomics, and patient data are entered into the machine learning model as the input layer to generate a predictive model, which can help clinicians in the differential diagnosis of benign and malignant pancreatic cysts.

The AI image acquisition discussed above is based on segmenting the pancreas from the image. The traditional segmentation method is a top-down simulation fitting method based on a large amount of map input and fixed pancreatic label fusion. However, there is also a bottom-up pancreatic segmentation method that subdivides the aggregated image region into a pancreatic region and a nonpancreatic region. The segmentation is based on the visual features of the image itself, which can improve the accuracy of pancreatic segmentation. It has been reported that the bottom-up pancreas segmentation method has been optimized. With the improvement of deep convolutional neural networks, this method can deal with the highly complex appearance of the pancreas in CT images[22].

Based on the above, we can see that the application of AI in the imaging diagnosis of pancreatic cancer has made considerable advances and is constantly improving.

Application of AI in the pathological diagnosis of pancreatic cancer

Pathologists need to identify diseased tissues in different tissue sections, which is a time-consuming and laborious process. Even experienced professionals may have the risk of subjective judgment. As with the application of AI in imaging diagnosis, AI is also important in the field of pathology, wherein tissue sections are digitized by a computer[23]. First, the AI system divides the lumen and nucleus from tissue fragments and extracts feature vectors from tenfold epithelial nuclei. Different cells have different feature vectors. An epithelial nucleus algorithm is used to identify epithelial nuclei. Then, the morphological features of the diseases that can be diagnosed are extracted. Finally, AI classifiers are used for classification. These classifiers include Bayesian classifiers, k-nearest neighbors, support vector machines, and ANNs[24]. Based on an automatic learning framework, cells can be segmented more accurately by combining bottom-up and top-down information. After collecting patient tissue samples, the tissue photographs are uniformly collected. A convolutional neural network model of a deep convolutional neural network is used to generate a probability map of tissue nuclear distribution. Then the iterative region merging method is used to initialize the shape of the probability graph. Next, combining a sparse shape model with stable selection and a local repulsive deformation model, a new segmentation algorithm is proposed to separate a single nucleus.

A significant advantage of this framework is that it is suitable for different stained histopathological images. Because of the feature-learning characteristics of deep cellular neural networks and the characteristics of high-level shape prior modeling, this proposed method is sufficiently universal and can be applied to different staining specimens and various types of histopathological identification. This model is not only less affected by the overlap of pathological tissues and cells but is also relatively insensitive to image noise and uneven intensity. Different tissue-staining datasets are

tested, which can identify and label the concentrated area of the nucleus[25].

In addition to AI classifiers, neural networks also play an important role in image analysis to determine whether the pathology is benign or malignant. After collecting a certain amount of fine-needle aspiration pathology of the pancreatic tumor, a pathological image is captured for preprocessing (image gray conversion and noise reduction). Then, the K-means clustering algorithm is used to extract the highest value of pixels until all of the pixels are equal. The part of the image that needs to be identified is segmented so the tissue can obtain the basic nuclear features, which can be used to evaluate cellular morphological features. These features are input into the AI multilayer perceptron (a feedforward nonlinear neural network) as input vectors, and the decisions made by this perceptron are sent to the second layer perceptron using image evaluation. Because there are a certain number of validated cases, the diagnostic accuracy of benign and malignant lesions can be evaluated using statistical methods (logistic regression, multiple regression, area under the curve, and R-squared)[26]. Different from imaging diagnosis, pathological diagnosis pays more attention to accuracy. Thus, AI has a lot of room for improvement in the accuracy of auxiliary diagnosis, which will inevitably take a long time to develop.

APPLICATION OF AI IN THE TREATMENT OF PANCREATIC CANCER

Application of AI in radiotherapy for pancreatic cancer

It takes a long time to accurately delineate the target area of pancreatic cancer in radiotherapy. A recent study used machine learning to target unlabeled pancreatic cancer. The deep learning neural network included the following steps. Input of the complete X-ray image obtained by the vehicle imager, after which the image was processed by the computer. Then changes were simulated between the target tissue and normal tissue. Finally, the accuracy of the model was reevaluated through a retrospective study of patients with pancreatic cancer. The output was the position of the verified plan target in the projected image[27]. Target planning can also be conducted by imitating the human brain through AI. This AI is based on abdominal magnetic resonance (MR)-ART for automatic contour rendering through two steps. The first step is to compare the patient's MR image with a normal MR image. Because of the high MR resolution, it can roughly outline the object. In the second step, information is directly obtained from the pixel data through a supervised, adaptive, active, learning-based support vector machine, and the target is sketched out from the features of the pixels. The information obtained through these two steps is then integrated by the AI, resulting in the final output. This approach can obtain data science institute values of more than 0.86[28].

Since the pancreas is located deep in the abdomen, radiation therapy requires not only a standard and accurate location but also an appropriate dose. An ANN dose model can be used to determine the appropriate dose. The data are processed by the input + the hidden layer + the output, which is continuously weighted. After training, errors are understood, and the weight distribution of the hidden layer is adjusted. The inputs in ANN data mining are geometric planning parameters [including CT images, treatment plans, structures, and dose distribution calculated by treatment planning systems (TPS)]. A single output is a prediction of the dose calculated by TPS for the voxel[29].

Application of AI in chemotherapy for pancreatic cancer

Different subtypes of pancreatic cancer cells are sensitive to different chemotherapy regimens[30]. The best way to determine cell subtypes is to make a diagnosis through pathology. However, invasive access to pathology will undoubtedly cause some pain for the patient. Due to the heterogeneity and cystic structure of pancreatic cancer tumors, the puncture results are often not ideal, sometimes even producing false-negative results. Machine learning has been applied for the noninvasive determination of pancreatic cancer cell types, including revealing the disease subtypes and molecular characteristics of pancreatic cancer. Using machine learning, pancreatic cancer-related protein expression, mRNA transcription, DNA methylation, and miRNA are integrated. Pancreatic cancer is divided into two categories. The determined subtypes have a clear response to the corresponding drug therapy and can therefore guide chemotherapy[5].

In a retrospective observation cohort study matched with histopathological tumor subtypes, after collecting the patients' clinical and imaging data, the images were classified using a double-blind method. After image processing, feature extraction,

feature preprocessing, feature engineering, and machine learning modeling, 70% of the queues were used for training, and 30% of the queues were tested. This study showed that radiological analysis combined with machine learning modeling can make high-sensitivity, high-specificity distinctions between the two groups of pancreatic ductal adenocarcinoma (PDAC) molecular subtypes defined by histomorphology. The analysis of radiological characteristics through machine learning can predict the subtypes of PDAC. This is highly related to responses to chemotherapy and patient survival[31]. AI can also simulate the effect of tumor targeted therapy drugs on tumor targeted genes. By combining machine learning, pharmacogenomics, and metabolomics, the efficacy of targeted drugs does not depend solely on the status of individual genes. It is also related to the degree of quantification of the Wahlberg effect, which leads to the emergence of the treatment window *in vivo*[32].

Application of AI in the surgical treatment of pancreatic cancer

The first reports of laparoscopic pancreatectomy were published in the early 1990s[33], and the first laparoscopic pancreaticoduodenectomy was reported in 1994[34]. Laparoscopic distal pancreatectomy (LDP) is feasible and safe. Compared to open distal pancreatectomy, LDP has the advantages of less bleeding, shorter hospital stays, lower postoperative complication rates, and short-term oncology effects. LDP is also increasingly used for patients with high BMI, a history of abdominal surgery, complications, and large tumors[35]. Compared to open surgery for pancreatic cancer, laparoscopic surgery also has some limitations, such as a two-dimensional surgical field of vision, a limited range of motion, the fulcrum effect, and the enhanced tremor of effectors[6]. However, robot-assisted pancreatic cancer surgery (RDP) can make minimally invasive surgery more effective while maintaining the advantages of laparoscopic surgery (*e.g.*, less trauma, rapid postoperative recovery, and little bleeding).

There is a question of whether robot-assisted surgery for pancreatic cancer can optimize laparoscopic surgery without increasing the side effects. Some studies have found that RDP is as safe and feasible as laparoscopic DP. The intraoperative blood loss, hospital stay, incidence of postoperative complications, perioperative mortality, and incidence of postoperative pancreatic fistula in RDP were similar to those in LDP[36-38]. Compared to open distal pancreatectomy, the probability of pancreatic fistula in RDP was not increased, and the probability of operative complications, readmission rate, mortality, and hospitalization days were similar. Robot-assisted distal pancreatectomy and pancreatectomy are comparable to traditional surgery in terms of safety and almost all outcome indicators[39,40]. RDP is relatively safe, but compared to traditional surgery and laparoscopic minimally invasive surgery, it improves the preservation rate of splenic vessels and reduces the risk of conversion to open surgery[38,41].

The Da Vinci robotic surgery system has unique characteristics, reflecting the main advantages of laparoscopic surgery. There is a stable 3D view, a wrist-like movement of the effector instrument (seven degrees of freedom), no fulcrum effect, no tremor, and no proportional adjustment of instrument motion[41]. Although robot-assisted distal pancreatectomy has potential benefits for spleen preservation, the cost of robotic surgery is very high, which is one of the obstacles to its widespread use[42]. Robotic surgery also lacks tactile sensory feedback and has a higher learning curve. Studies have shown that it takes 80 cases for a chief surgeon to reach a skilled level, and the experience of laparoscopic surgery can shorten this process[41,43]. In some complex cases, robotic surgery performs better than traditional laparoscopic surgery, such as spleen-preserving surgery with the preservation of splenic vessels[37,44]. For example, for patients with high BMI, robotic surgery may reduce intraoperative blood loss and shorten hospital stay[45]. The summary is revealed in Table 1.

APPLICATION OF AI IN PANCREATIC CANCER PROGNOSIS

Pancreatic cancer is highly malignant. Although it can be cured through radical resection, the 5-year survival rate is still very low[46]. One study used population models and machine learning algorithms to predict the risk of recurrence in patients with pancreatic cancer 2 years after surgical resection. After collecting features considered having the most influence on recurrence, the most representative feature variables were selected, which were then used to train the machine learning algorithm. After repeated training, logistic regression was found to be the best prediction algorithm after cross-validation. This model had high accuracy in predicting the

Table 1 Comparison of advantages and disadvantages of open distal pancreatectomy, laparoscopic distal pancreatectomy, and robot-assisted pancreatic cancer surgery

Class	ODP	LDP	RAP
History	Oldest	Modern	Recently
Bleeding	More	Less	Less
Hospital stay	Long	Short	Short
Postoperative complication rates	High	Low	Low
Short-term oncology effects	Normal	Litter	Litter
Trauma	More	Less	Less
Application prospect	Patients with high BMI, a history of abdominal surgery, complications, and large tumors	Approach to ODP	Preserve splenic vessels, for patients with high BMI
Vision	3D	2D	3D
Tactile sensory feedback	Good	Worse	None
Learning curve	Low	High	Higher

ODP: Open distal pancreatectomy; LDP: Laparoscopic distal pancreatectomy; RAP: Robot-assisted pancreatic cancer surgery; BMI: Body mass index.

recurrence probability for a patient 2 years after surgery, suggesting that the machine learning algorithm may be helpful for identifying high-risk patients and developing adjuvant treatment strategies[47]. However, the sample size of that study was small, and there was no unified standard for treatment. Thus, this machine learning algorithm could be improved in future research by using larger samples and unified treatment.

Machine learning can also be used to develop prognostic classifiers to predict the survival of pancreatic cancer patients by integrating multiple DNA methylation statuses of pancreatic cancer–related mucin genes[48]. As a nonparametric machine learning method, ANN is also used to evaluate the survival rates of patients with pancreatic cancer. Similar to the working mode of the brain, patient variables are collected as processing elements, and interrelated processing elements are arranged and connected layer upon layer. Each connection has a related weight, each weight value can be transferred to the next ganglion layer, each lower layer can aggregate the input values of the upper layer, and the last layer is the output value. The output value is generally binary and can be used to determine whether the patient survives after 7 mo[7]. The malignancy degree of pancreatic cancer is closely related to the invasiveness of its tumor cells. Mathematical modeling represents the growth process of the tumor as a physiological and biomechanical model and personalizes the model according to the clinical measurements of target patients. The volume of the whole tumor, including its size, shape, and involved area, can be predicted[49].

CONCLUSION

Pancreatic cancer is a major cancer that threatens human health. Although there are systematic treatment plans, the effect of radiotherapy is poor because of the deep location of the pancreas and the tissue characteristics of the cancer. The special characteristics of pancreatic cancer also lead to drug resistance after chemotherapy, and surgical treatment is difficult because of the large number of important organs around the pancreas and its anatomical complexity. AI has the ability to replace or assist people in clinical work. It has great application prospects for the diagnosis, treatment, and prognosis of pancreatic cancer. Regarding molecular diagnosis, imaging diagnosis, and chemotherapy, machine learning can help researchers process data, perform analysis, and obtain experimental results. In radiotherapy, AI is mainly used for the automatic planning of radiation targets and radiation dose prediction. The development of robotic pancreatic surgery has increased the accuracy of pancreatic surgery and reduced complications, but automation cannot be fully achieved without continuous training and verification. Therefore, for a long time in the future, most AI applications for pancreatic cancer will continue to be used as practical auxiliary tools.

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ORIGINAL ARTICLE

Retrospective Study

Machine learning better predicts colonoscopy duration

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Abstract

BACKGROUND

The use of machine learning (ML) to predict colonoscopy procedure duration has not been examined.

AIM

To assess if ML and data available at the time a colonoscopy procedure is scheduled could be used to estimate procedure duration more accurately than the current practice.

METHODS

Total 40168 colonoscopies from the Clinical Outcomes Research Initiative database were collected. ML models predicting procedure duration were developed using data available at time of scheduling. The top performing model was compared against historical practice. Models were evaluated based on accuracy (prediction – actual time) ± 5, 10, and 15 min.

RESULTS

ML outperformed historical practice with 77.1% to 68.9%, 87.3% to 79.6%, and 92.1% to 86.8% accuracy at 5, 10 and 15 min thresholds.

CONCLUSION

The use of ML to estimate colonoscopy procedure duration may lead to more accurate scheduling.

Key words: Machine Learning; Colonoscopy; Endoscopy; Artificial intelligence; Practice outcomes; Operations

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Core tip: Machine learning has been utilized to predict surgical procedure duration and enhance operating room proficiency, however its usefulness for predicting colonoscopy procedure duration has not been examined. Procedure duration predictions from a machine learning algorithm trained on data from the Clinical Outcomes Research Initiative database outperformed historical practice.

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INTRODUCTION

Current colonoscopy scheduling models utilize either historical averages or predetermined time allotments (usually 30-45 min). Scheduling has not evolved to incorporate patient information, case complexity, procedure environment, or operator proficiency. Failure to assess for these variables can lead to significant misjudgments of procedural duration. These errors can result in both under- and overutilization of endoscopy room time leading to increased cost, misappropriation of endoscopy resources, delays, and decreases to patient and provider satisfaction[1]. Machine learning (ML) has been utilized to predict surgical procedure duration and enhance operating room proficiency, however its usefulness for predicting colonoscopy procedure duration has not been examined[2,3].

Our aim was to assess if ML and data available at the time a colonoscopy procedure is scheduled could be used to estimate procedure duration more accurately than the current practice.

MATERIALS AND METHODS

The Clinical Outcomes Research Initiative (CORIv.4) database was queried for all colonoscopies with complete procedural duration times from 2008-2014 following approval from our institutional review board.

The CORI database is a national central repository of endoscopic procedures from a physician network of academic, community and veteran administration hospitals/practices. The details of the repository can be found in previous publications[4]. ML models were trained on variables with < 20% missing values and variables available prior to the procedure. Procedures with duration < 5 and > 280 min were excluded. All statistical analyses were performed in R-studio version 3.5.3 (Boston, Massachusetts). 80% of the cases were used for training data and the remaining 20% used to compare the performance of these models. To reduce skew in the data, the target variable (procedural duration), was logarithmically transformed in line with previous publications[3,5].

Following established methodology[3,5,6], several models were tuned to predict procedure-time duration using cross-validation. The various models included random forest, gradient boosting machine, least absolute shrinkage and selection operator or LASSO, and extreme gradient boosting models (xgboost). The best performing model was selected based on lowest root mean squared error of the model and trained using historical data (2008-2013) to predict "current" data (2014). Predictions derived from the best performing model were compared with the current standard of using historical means. Models were evaluated based on accuracy (prediction – actual time) within thresholds of 5, 10, and 15 min to account for operational considerations.

RESULTS

Total of 40168 colonoscopies from 75 different sites from 2008 to 2014 with procedural duration information were obtained. 32136 (80%) of the cases were used for training

the algorithm, with the remaining 8032 (20%) used to compare the performance of these models. A total of five patient (age, gender, race, ASA class, pediatric status), eight provider (endoscopist ID, degree of performing provider, degree year of performing provider, specialty of provider, gender and race/ethnicity of the provider, fellow involvement) and twelve procedure specific [(procedure year, procedure order, site ID, site type (University *vs* Community), location of procedure/facility type, duration of procedure, primary indication of procedure, depth intended of the procedure, sedation type used, state, and region)] variables were all selected for model analysis and training.

Table 1 demonstrates background characteristics of the final cohort. The best performing machine learning algorithm was the xgboost model. Figure 1 depicts the final models accuracy. The percentages of procedures for which the xgboost and the historical models generated forecasts within the 5, 10 and 15 min threshold were 77.1% *vs* 68.9%, 87.3% *vs* 79.6%, and 92.1% *vs* 86.8% ($P < 0.001$). The most important features of the model were: Patient age, procedure year, and the degree year of provider year (Figure 2).

DISCUSSION

We demonstrated that machine learning predicts colonoscopy procedure duration more accurately than the currently accepted standard practice and the improvement was greater as the tolerance for error decreased.

Our results mimic similar applications of machine learning algorithms. Bartek *et al*[6] compared the standard practice of using average historical procedure duration and surgeon estimates of procedural duration compared to predictions derived from a machine learning model. Using a 10% accuracy threshold, the machine learning algorithm outperformed both traditional practices (39% ML *vs* 32% surgeon derived and 30% historical means). In an analysis of feature importance, the authors noted that fundamental case information, such as mean duration of the last ten procedures, was the most important predictive feature, with patient health metrics having a smaller total impact. However, our results suggest that patient specific factors may play a greater role in determining colonoscopy procedure duration. While again provider and procedural factors demonstrated high importance, patient specific factors (such as age, female sex) factored substantially into our model's final predictions.

There are several strengths to our analysis. A large number of colonoscopies from a national repository of endoscopic procedures composed of a wide array of procedures, patients, and providers from an assortment of practice environments were analyzed. Inclusion of a national database increases generalizability by limiting regional or practice related biases.

However, there are several limitations to our analysis. Procedure reporting to the CORI database is voluntary and there may be an inherent selection bias in which easier colonoscopies were more likely to be reported to the database. This is supported by the relatively short overall procedural duration in our cohort. While the effects of a longer average procedure duration on our model are unknown, we anticipate more resiliency to increased error in the ML model compared to historical means, further enhancing the overall accuracy of the model compared to traditional practice.

While the algorithm was successful, it largely represents a rudimentary proof of concept option. Several variables that have been associated with difficult or lengthy colonoscopies in previous reports[7] and were either not available or too incomplete in this current data set to allow for inclusion into our analysis. Addition of variables associated with difficult colonoscopies including body mass index, previous abdominal or pelvic surgeries, bowel habits, weight, height *etc*. would potentially improve the models accuracy.

The use of an algorithm trained on prospectively collected data with greater provider, environmental, patient, and procedural information may lead to improvements in colonoscopy procedure scheduling. Such improvements may contribute to improved efficiency, patient and provider satisfaction, and reduced costs. Further study is necessary to examine the implications of the deployment of such a model in a clinical setting, and assess if such models can be used in other gastrointestinal procedures.

Table 1 Cohort background characteristics

Demographic information		
Total patients	40168	
Mean age	58.95	
Sex	Female	17682
	Male	22485 (56.0%)
ASA Class	I	7071
	II	27699
	III	5237
	IV	158
	V	3
Race	Caucasian	32031
	Hispanic	2219
	Black	2193
	Asian	1140
	Native American	679
	Other	1906
Procedural information		
Median procedure year	2012	(2008-2014)
Total No. of sites	75	
Fellow involved	3575	
Indication for procedure	Average risk screening	12687
	Surveillance of adenomatous polyps	8213
	Hematochezia	3795
	High risk screening	3272
	Anemia	1508
	Diarrhea	1469
	Other	9224
Procedure order	1st	37864
	2nd	2056
	Other	248
Mean duration of procedure	23.4 min	
Depth intended	Cecum	31745
	Terminal Ileum	6798
	Ascending colon	570
	Ileum	424
	Anastomosis site	447
	Other	163
Location of the procedure	Hospital endoscopy suite	15589
	Ambulatory surgery center	14730
	unknown	5739
	Office	2501
	Endoscopy suite	1450

	ICU	88
Region	North Central	3490
	Northeast	11156
	Northwest	12329
	South Central	776
	South East	1466
	South West	10947
Site type	Community	25133
	HMO	1000
	University	5676
	VA	8359
Sedation	None	241
	Moderate/Conscious sedation	28009
	"Deep" Sedation	7289
	General Anesthesia	2510
	Anxiolytic Sedation	78
Provider information		
Gender of provider	Female	9881
	Male	30287
Median degree year of provider	1989	(1962-2009)
Degree of performing provider	DO	1253
	MD	38851
	PA	64
Provider specialty	Gastroenterology	33059
	Surgery	2976
	Colorectal surgery	995
	Internal medicine	1589
	Family medicine	581
	Other	968
Ethnicity of provider	Hispanic	419
	Non-hispanic	37148

ICU: Intensive care unit; HMO: Health maintenance organization.

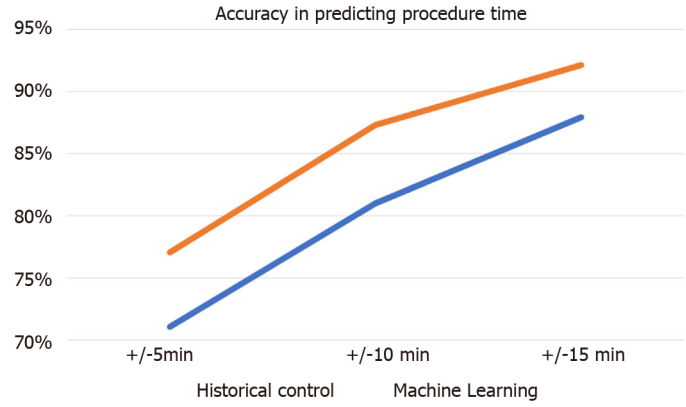

Figure 1 Accuracy of machine learning model *vs* historical average.

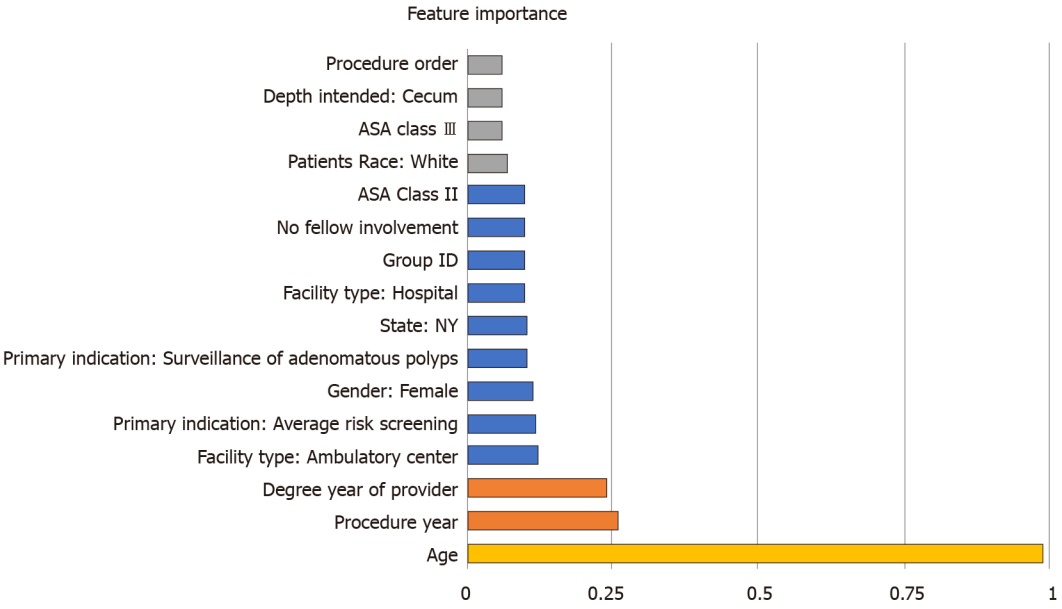

Figure 2 Feature importance of machine learning model.

ARTICLE HIGHLIGHTS

Research background

The usefulness of machine learning (ML) for predicting colonoscopy procedure duration has not been examined.

Research motivation

A ML algorithm trained on endoscopic data derived from the Clinical Outcomes Research Initiative database predicted colonoscopy procedure duration more accurately than the currently accepted standard practice and the improvement was greater as the tolerance for error decreased.

Research objectives

The aim of this study was to assess if ML and data available at the time a colonoscopy procedure is scheduled could be used to estimate procedure duration more accurately than the current practice.

Research methods

Total 40168 colonoscopies were collected. ML models predicting procedure duration were developed using data available at time of scheduling. The top performing model was compared against historical practice.

Research results

ML outperformed historical practice with 77.1% to 68.9%, 87.3% to 79.6%, and 92.1% to 86.8% accuracy at 5, 10 and 15 min thresholds, and the most important features of the model were: patient age, procedure year, and the degree year of provider year.

Research conclusions

The use of ML to estimate colonoscopy procedure duration may lead to more accurate scheduling.

Research perspectives

Further study is necessary to examine the implications of the deployment of such a model in a clinical setting, and assess if such models can be used in other gastrointestinal procedures.

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MINIREVIEWS

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ABOUT COVER

Associate Editor of *Artificial Intelligence in Gastroenterology*, Dr. Xu Zhu is Chief Physician, Professor, and Doctoral Supervisor leading the Department of Interventional Therapy at Peking University Cancer Hospital (China). His over 20 years of research involve image-guided minimally invasive interventional and targeted therapies in tumoral diseases, investigating effects of transcatheter arterial chemoembolization, hepatic arterial infusion chemotherapy, and ablation therapy. He is currently Vice Chairman of the Oncology Interventional Professional Committee of the Chinese Anti-cancer Association, having won the association's second prize Award for Science and Technology Progress in 2019; he is also Vice Chairman of the Liver Tumor Branch, China International Exchange and Promotive Association for Medical and Health Care, Vice Chairman of the Interventional Radiology Professional Committee, Chinese Society of Clinical Oncology, and Chairman of the Cryoablation and Targeted Therapy of Tumor Professional Committee, National Strategic Alliance of Industrial and Technology Innovation for Minimally Invasive Tumor Therapy of China. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of *Artificial Intelligence in Gastroenterology* (*AIG*, *Artif Intell Gastroenterol*) is to provide scholars and readers from various fields of artificial intelligence in gastroenterology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

AIG mainly publishes articles reporting research results obtained in the field of artificial intelligence in gastroenterology and covering a wide range of topics, including artificial intelligence in gastrointestinal cancer, liver cancer, pancreatic cancer, hepatitis B, hepatitis C, nonalcoholic fatty liver disease, inflammatory bowel disease, irritable bowel syndrome, and *Helicobacter pylori* infection.

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MINIREVIEWS

Diagnostic advances of artificial intelligence and radiomics in gastroenterology

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Author contributions: Feng P, Wang ZD, and Pan JJ guaranteed the integrity of entire study; Liu H and Pan JJ designed the research study; Feng P, Wang ZD, and Pan JJ drafted the manuscript; Feng P, Liu H, and Pan JJ revised the manuscript; all authors acquired and interpreted the data, studied the cited literature, agree to ensure that any questions related to the work were appropriately resolved, and have read and approved the final manuscript.

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Abstract

Traditional medical imaging, including ultrasound, computed tomography, magnetic resonance imaging, or positron emission tomography, remains widely used diagnostic modalities for gastrointestinal diseases at present. These modalities are used to assess changes in morphology, attenuation, signal intensity, and enhancement characteristics. Gastrointestinal tumors, especially malignant tumors, are commonly seen in clinical practice with an increasing number of deaths each year. Because the imaging manifestations of different diseases usually overlap, accurate early diagnosis of tumor lesions, noninvasive and effective evaluation of tumor staging, and prediction of prognosis remain challenging. Fortunately, traditional medical images contain a great deal of important information that cannot be recognized by human eyes but can be extracted by artificial intelligence (AI) technology, which can quantitatively assess the heterogeneity of lesions and provide valuable information, including therapeutic effects and patient prognosis. With the development of computer technology, the combination of medical imaging and AI technology is considered to represent a promising field in medical image analysis. This new emerging field is called "radiomics", which makes big data mining and extraction from medical imagery possible and can help clinicians make effective decisions and develop personalized treatment plans. Recently, AI and radiomics have been gradually applied to lesion detection, qualitative and quantitative diagnosis, histopathological grading and staging of tumors, therapeutic efficacy assessment, and prognosis evaluation. In this minireview, we briefly introduce the basic principles and technology of radiomics. Then, we review the research and application of AI and radiomics in gastrointestinal diseases, especially diagnostic advancements of radiomics in the differential diagnosis, treatment option, assessment of therapeutic efficacy, and prognosis evaluation of esophageal, gastric, hepatic, pancreatic, and colorectal diseases.

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Key Words: Artificial intelligence; Radiomics; Texture analysis; Gastroenterology; Esophageal disease; Gastric diseases; Hepatic disease

Core Tip: This minireview summarizes the research and application of artificial intelligence (AI) technology, radiomics, and texture analysis in gastrointestinal diseases in detail and focuses on the diagnostic advances of AI and radiomics in lesion detection, differential diagnosis, decision of treatment plans, assessment of therapeutic efficacy and tumor response to treatment, and prognosis prediction of gastrointestinal diseases. This technology can provide more valuable information to allow clinicians and radiologists to understand and perform AI and radiomics in their clinical practice.

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INTRODUCTION

In the 1980s, with the application of artificial neural network and computer-aided diagnosis and detection system software, artificial intelligence (AI) has gradually been integrated into the daily workflow of various fields[1]. Since the beginning of the 21st century, advances in computer technology have led to the rapid development of AI in medical applications. With the rapid development of AI, the combination of medical imaging and AI is considered a promising field in medicine and is primarily used for image data mining, extraction, searching, and applications, as well as image recognition and deep learning[2]. Currently, AI technology has been widely used in lung nodule, lung cancer, and breast cancer screening as well as prostate cancer, colorectal cancer, and head and neck cancer imaging[3-8]. In terms of gastroenterology, the main applications of AI are radiomics and texture analysis. The concept of radiomics was formally proposed in 2012 and refers to the process of converting digital medical images into mineable high-dimensional data by high-throughput extraction and analysis of innumerable quantitative imaging features from medical images obtained with imaging modalities, including ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET)[9,10]. Radiomics is a technology that combines multiple images and interdisciplinary techniques and primarily includes the following five imaging steps: (1) Image acquisition: Acquirement of high-quality, standardized medical images for diagnosis and evaluation; (2) Image segmentation: Manual, automatic, or semiautomatic segmentation and reconstruction of the image; (3) Feature extraction and quantification: This is the core process of radiomics to extract region of interest (ROI) texture feature parameters, including shape or size, first-order histogram or spherical statistical features, second-order histogram or texture, and higher-order statistics features and other special image features; (4) Feature selection: Screening of features based on repeatability, correlation with other features, and relationship with staging, prognosis, and gene expression; and (5) Model establishment: Incorporation of the selected radiomics features into a suitable prediction model[1,2,11]. By extracting high-throughput quantitative features, radiomics based on quantitative imaging can reflect not only certain components within the tumor but also intratumoral heterogeneity by providing supplementary information, thus helping to assess disease characteristics in detail[12]. The application of radiomics in gastroenterology is mainly focused on lesion recognition, clinical staging, and prognosis analysis. The purpose of this minireview is to provide a descriptive overview of diagnostic advances of AI and radiomics in gastroenterology.

DIAGNOSTIC ADVANCES OF AI AND RADIOMICS IN ESOPHAGEAL CANCER

Esophageal cancer (EC) is the eighth most frequent malignant disease and the sixth most prevalent cause of disease-associated deaths worldwide[13]. The selection of a therapeutic approach and prognosis of EC are closely associated with preoperative tumor stage[14]. Therefore, accurate preoperative staging is of great importance for selecting an appropriate treatment plan and predicting prognosis. Traditionally, CT is a widely used modality for diagnosis and preoperative staging of EC; however, due to limited contrast resolution, CT cannot accurately identify early stage EC (T1-2) and is mainly used in the evaluation of regional spread and distance metastasis[15-17]. Recently, some studies have reported that radiomics and text analysis can improve the accuracy of preoperative tumor staging classification. In a study enrolling 73 patients with esophageal squamous cell carcinoma (ESCC), CT texture parameters based on unenhanced and contrast-enhanced CT images, kurtosis, entropy, and skew showed great potential in differentiating T stages (T1–2 *vs* T3–4), lymph node metastasis (N- *vs* N+), and overall stages of ESCC[18]. In a study of 154 patients with ESCC, the radiomics signature extracted from CT images was significantly associated with ESCC staging, yielding a better performance for discrimination of early stage (T1–2) and advanced stage (T3–4) ESCC compared to tumor volume, indicating the potential of radiomics in staging ESCC preoperatively[19]. F-18-fluorodeoxyglucose (^{18}F-FDG) PET image-derived characteristics, including image textural features, standard unit value (SUV), and shape features, also allowed for better stratification of American Joint Committee on Cancer and tumor-node-metastasis (TNM) than F-18-fluorothymidine (^{18}F-FLT) PET in ESCC patients[20]. Radiomics based on MR images (T_2-TSE BLADE and contrast-enhanced Star VIBE) also more accurately distinguished metastatic lymph nodes compared with nonmetastatic lymph nodes, yielding an area under the receiver operating characteristic curve (AUC) of 0.821 (95%CI: 0.7042 to 0.9376) and 0.762 (95%CI: 0.7127 to 0.812), respectively[21].

In addition to tumor staging, radiomics and textural analysis have also shown significant importance for efficacy and prognosis evaluation. Tixier *et al*[22] extracted gray level cooccurrence matrices (GLCM), gray-level size zone matrix, entropy, long-run matrix, and other texture features from PET images and found that these texture features were more effective (AUC: 0.82-0.89) than SUVmax and SUVmean (AUC: 0.59-0.7) in predicting the clinical response of chemoradiotherapy for patients with EC. In a study on prediction of response after chemoradiation for EC, an integrated model combining CT radiomic features and dosimetric parameters for 94 patients with EC permitted a prediction accuracy of 0.708 and AUC of 0.689, while using radiomic features alone permitted the best prediction accuracy of 0.625 and AUC of 0.412[23]. In total, 138 radiomics features extracted from MR T_2WI in 68 patients with ESCC exhibited potential in distinguishing complete response (CR) from stable disease (SD), partial response (PR) from non-response (SD), and response (CR and PR) from SD. Moreover, using neural network and support vector machine prediction models, features extracted through spectral attenuated inversion-recovery T_2WI exhibited better performance than those extracted from T_2WI in predicting the response to chemoradiotherapy in EC[24].

Radiomics also shows potential in the evaluation of disease prognosis. In a study of 239 patients with EC, a random forest (RF) model based on pretreatment CT radiomics features was used to predict 3-year overall survival (OS) following chemo-radiotherapy. Compared to the model using standard clinical variables that yielded an AUC of 0.63 (95%CI: 0.54–0.71), the radiomics-based RF model yielded an AUC of 0.69 (95%CI: 0.61–0.77), demonstrating better prognostic power of the radiomics model compared with traditional clinical variables[25]. Yip *et al*[26] also analyzed the radiomics features extracted from enhanced CT images of 36 patients with T2 or above EC pre- and posttreatment of chemoradiotherapy and found that a posttreatment medium entropy of less than 7.356, a coarse of less than 7.116, and a median uniformity greater than 0.007 were associated with improved survival time. Moreover, the combination of pretreatment texture parameters (entropy and uniformity) with maximal wall thickness assessment in survival models performed better than morphologic tumor response alone with AUCs of 0.767 *vs* 0.487 and 0.802 *vs* 0.487[26]. In a study on the prediction of therapy response to neoadjuvant chemoradiotherapy in 97 EC patients, Beukinga *et al*[27] constructed a response prediction model based on pretreatment clinical parameters and ^{18}F-FDG PET/CT–derived textural features. Compared with the current most accurate prediction model with SUVmax, the constructed model had higher AUC (0.78 *vs* 0.58) and discrimination slope (0.17 *vs* 0.01). In another study of

31 patients with primary EC, a significant decrease in entropy and CT tumor heterogeneity and increase in uniformity were observed following neoadjuvant chemotherapy, indicating that CT texture analysis has the potential to assess prognosis and survival of patients with primary EC[28]. In another study of 61 ESCC patients who received radical radiation therapy, the survival rate was significantly correlated with the change of coarseness (P = 0.0027) and strength (P = 0.0001), which indicated that CT features (such as coarseness and strength) could be selected as outstanding imaging biomarkers for prediction of RT prognosis of ESC[29].

DIAGNOSTIC ADVANCES OF AI AND RADIOMICS IN GASTRIC DISEASE

Radiomics and texture analysis potentially aid radiologists in differential diagnosis of gastric tumors. In a study on the utility of texture features of CT images in differential diagnosis of gastric tumors, textural features derived from the arterial phase exhibited improved accuracy of differentiation between gastric adenocarcinoma (GC) and gastric lymphoma as well as gastric stromal tumor (GIST) and lymphoma; however, the textural features derived from the venous phase adequately distinguished between GC and GIST[30]. Similarly, in a study on the discrimination of Borrmann type IV gastric cancer and primary lymphoma, objective feature models including CT objective features (stomach wall thickness, infiltration degree, *etc*.) and clinical features (age, gender, *etc*.), texture feature models, and a combination of these two models were established to distinguish these two types of gastric malignancies. A sensitivity of 86.67% and specificity of 82.5% were found in the texture feature model, and a specificity of 100% was noted in the combination model with the highest AUC value (0.903), indicating the ability of radiomics in distinguishing gastric tumors from gastric primary lymphoma[31].

In addition, radiomics and texture analysis are also helpful for detection of local and peritoneal metastases. In a study of 554 patients with advanced gastric cancer (AGC) who were initially diagnosed as having no peritoneal metastasis by CT, a nomogram of radiomics signatures was developed that reflected primary tumor phenotypes and peritoneum region metastasis and demonstrated the best diagnostic accuracy for occult peritoneal metastasis[32]. In another study, texture analysis of CT imaging was also verified as a useful predictor of occult peritoneal carcinomatosis in patients with AGC[33].

Similar to its application in esophageal cancer, radiomics has also been reported to be helpful for tumor staging in many studies. CT texture parameters in the arterial phase and portal vein phase positively correlated with T stage, N stage, and overall stage (P < 0.05) of GC and identified lymph node metastasis of GC[34]. All the entropy-related parameters derived from whole-volume ADC texture analysis exhibited a significant correlation with T, N, and overall stages. Furthermore, significant differences in these parameters were found between GCs with and without perineural invasion[35].

Regarding preoperative prognosis evaluation, texture analysis has also demonstrated good application prospects. Giganti *et al*[36] analyzed the preoperative textural features based on multiple detector CT images of 56 patients with pathologically confirmed GC and found that texture parameters, namely, energy, entropy, maximum Hounsfield unit value, skewness, root mean square, and mean absolute deviation (filter 2), negatively correlated with the prognosis of GC. Moreover, these parameters could be used for risk stratification in GC and aid in assessment of aggressiveness of GC[36]. A radiomics signature based on CT imaging in the portal venous phase was used to predict survival of GC, add prognostic information to the TNM staging system, and predict patient benefit from chemotherapy[37]. Moreover, in another study of 26 patients with human epidermal growth factor receptor 2-positive AGC who received trastuzumab-based combination chemotherapy, heterogeneous texture features on contrast-enhanced CT images were associated with better survival, demonstrating the potential of an imaging biomarker to provide prognostic information on patient selection[38].

DIAGNOSTIC ADVANCES OF AI AND RADIOMICS IN HEPATIC DISEASE

Studies on radiomics in hepatic diseases mainly focus on the staging of hepatic fibrosis, differential diagnosis of tumor and nontumor lesions, treatment selection, and prognosis evaluation. Echegaray *et al*[39] performed enhanced CT texture analysis in 29

patients with hepatocellular carcinoma (HCC) and found that texture features of images obtained in the portal venous phase exhibited the lowest misdiagnosis rate (13.57%) in the differential diagnosis of focal liver lesions, demonstrating the superiority of radiomics compared with traditional imaging in distinguishing hepatic disease characteristics[39]. In a study of 164 hepatic lesions, Huang *et al*[40] extracted the autocovariance texture features of lesions and proposed a support vector machine classifier system to identify benign lesions from malignant lesions. The system had an accuracy of 81.7% in identifying malignant hepatic lesions with a sensitivity of 75.0% and specificity of 88.1% and was useful in reducing the needs for iodinated contrast agent injection in CT examination[40]. Oyama *et al*[41] assessed the accuracy for classification of HCC, metastatic tumors (MT), and hepatic hemangioma (HH) by characterization of non-contrast-enhanced fat-suppressed three-dimensional (3D) T_1-weighted images by using texture analysis and topological data analysis using persistent homology. In the classification of HCC and MT, HCC and HH, and HH and MT, accuracies of 92%, 90%, and 73% were obtained by texture analysis, showing the potential application for computer-aided diagnosis with MR images[41]. In a study on the differential diagnosis of neoplastic or bland portal vein thrombosis in 109 patients, the mean value of positive pixels (without filtration), entropy (with fine filtration), and mean thrombus density values were helpful in the identification of neoplastic and bland thrombi with AUCs of 0.97, 0.93, and 0.91, yielding optimal cutoff values of 56.9, 4.50, and 54.0 HU, respectively ($P < 0.001$); these findings indicated that CT texture analysis and CT attenuation values based on images obtained in the portal venous phase could be helpful in differentiating neoplastic thrombi from benign thrombi[42].

In the evaluation of hepatic fibrosis and other nontumor lesions, radiomics also has shown good prospects. In a study on staging of hepatic fibrosis in 289 patients, CT texture parameters (mean gray-level intensity, kurtosis, and skewness) were helpful in the detection and staging of fibrosis[43]. In total, 41 texture features extracted from enhanced CT images of 83 patients with pathologically proven hepatic fibrosis offered a noninvasive assessment of liver fibrosis[44]. In a study on the texture features of non-contrast-enhanced CT images of 88 patients with pathologically confirmed nonalcoholic steatohepatitis (NASH), the mean texture parameters without a filter and skewness with a 2-mm filter were selected for the NASH prediction model for patients without suspected fibrosis, yielding an AUC of 0.94 and accuracy of 94% in the predictive model for the validation dataset. These results reveal the ability of the model to predict NASH[45].

In addition, imaging texture analysis also shows good prospect in the evaluation of prognosis, optimization of treatment plans, and prediction of tumor response to treatment. Texture analysis exhibited potential in the assessment of prognosis and selection of appropriate patients with intermediate-advanced HCC treated by transcatheter arterial chemoembolization (TACE) and sorafenib[46]. In another study on the prediction of therapeutic response of HCC to TACE, textures derived from pretreatment dynamic CT imaging were analyzed in 96 patients with 132 HCCs, and increased arterial enhancement ratios and GLCM moments, smaller tumor size, and reduced tumor homogeneity were significant predictors of complete response (CR) after TACE[47]. A radiomics scoring system based on ^{18}F-FDG PET was generated in a study of 47 patients undergoing transcatheter arterial radioembolization using Yttrium-90 for unresectable HCC, and statistically significant differences in progression-free survival (PFS) and overall survival (OS) between low-risk patients and high-risk patients were detected, indicating that pretreatment ^{18}F-FDG PET-derived radiomics features served as an independent negative predictor of patient prognosis[48]. Similarly, preoperative skewness derived from images obtained in the portal venous phase was independently associated with OS in patients with resectable HCC and might be useful in the selection of patients for resection[49]. In a study focused on the prediction of OS and time to progression of 92 patients with advanced HCC treated with sorafenib, pretreatment CT texture feature entropy derived from images obtained in the portal venous phase was also identified as an independent predictor of OS in patients[50].

DIAGNOSTIC ADVANCES OF AI AND RADIOMICS IN PANCREATIC DISEASES

At present, the applications of radiomics analysis in pancreatic diseases mainly focus on the diagnosis and differential diagnosis of pancreatic tumors, biological stratification and grading of tumors, prognosis prediction, therapeutic assessment, and

efficacy evaluation. Radiomics analysis also aids in preoperative diagnostic accuracy and proper management decisions. In a study that enrolled 260 surgically resected pancreatic cystic neoplasms, the accuracy rate for serous cystic neoplasms (SCNs) before surgery was only 30.4% (102/260), indicating that greater than two-thirds of patients with SCN underwent unnecessary surgery. However, using a diagnostic model established based on dual-phase pancreatic CT imaging features, the accuracy rate of diagnosis significantly improved with an AUC of 0.767, sensitivity of 68.6%, and specificity of 70.9%[51]. In clinical practice, imaging findings of pancreatic neuroendocrine carcinoma (PNEC) and pancreatic ductal adenocarcinoma (PDAC) usually overlap, and the misdiagnosis of these two entities is common. In addition to traditional CT imaging features of tumor margin, parenchymal atrophy, and contrast ratio in the arterial and portal phases, Guo *et al*[52] confirmed that texture parameters of entropy and uniformity were also valuable for distinguishing PNEC from PDAC. CT features and texture analysis were also useful for the classification of pancreatic neuroendocrine tumors (PNETs). In a study enrolling 101 patients with PNETs, entropy was predictive of Grades (G) 2 and 3 tumors with an accuracy of 79.3% for classifying G1, G2, and G3 tumors[53]. D'Onofrio *et al*[54] also reported that parameters of kurtosis and entropy extracted from 3D CT-texture imaging analysis could predict the grade of PNETs, distinguishing G1 from G3, G2 from G3, and G1 from G2 tumors.

Promising results of radiomics and texture analysis were reported in the field of therapeutic assessment and prognosis prediction of PDAC. Texture parameters from preoperative CT images of pancreas head cancer in patients who underwent curative resection significantly differed between patients with and without recurrence, and this method could be used as an independent imaging tool for predicting prognosis[55]. In another study on patients with unresectable PDAC treated with chemotherapy, pretreatment CT quantitative imaging biomarkers based on texture analysis were associated with PFS and OS, and the combination of pretreatment texture parameters and tumor size performed better in survival models than imaging biomarkers alone[56]. Cozzi *et al*[57] also reported that a CT-based radiomics signature correlated with OS and local control of PDAC after stereotactic body radiation therapy and allowed for identification of low- and high-risk groups of patients.

DIAGNOSTIC ADVANCES OF AI AND RADIOMICS IN COLORECTAL DISEASES

At present, research on colorectal tumors mainly focuses on the extraction of texture features, identification of neoplastic and nonneoplastic lesions, preoperative staging of colorectal cancer (CRC), and evaluation of lymphatic metastasis. In a study on the efficiency of texture features by CT colonography in the differential diagnosis of colon lesions, combining high-order CT images with CT volumetric texture features yielded a significantly increased AUC of 0.85 in distinguishing neoplastic colon tumors from nonneoplastic lesions compared with the exclusive use of the parameter of image intensity[58]. A CT-based radiomics signature of patients with CRC before surgery might be a useful method for preoperative CRC tumor staging given its ability in the discrimination of stage I-II from stage III-IV CRC, yielding an AUC of 0.792 with a sensitivity of 0.629 and specificity of 0.874[59].

The application of radiomics also showed efficacy in therapeutic evaluation of rectal cancer (RC). In a study on the response to neoadjuvant chemoradiation therapy (NCRT) in 51 patients with local advanced RC, radiomics based on pretreatment and early follow-up MRI could provide quantitative information to differentiate pathologic CR (pCR) from non-pCR and good response (GR) from non-GR[60]. Texture parameters derived from T_2WI of RC also exhibited potential to assess the tumoral response to NCRT[61].

Radiomics and texture analysis are also valuable for treatment decisions. In a study that enrolled 95 patients with T2-4 N0-1 RC treated with NCRT, a deep neural network was proposed to predict the CR of tumor to treatment. The model predicted CR with an increased accuracy of 80% compared with the linear regression model (69.5%) and support vector machine model (71.58%) after NCRT, demonstrating the potential of radiomics in the selection of patients for NCRT rather than radical resection[62]. In another study of 326 pathologically proven CRC patients, a radiomics nomogram incorporating both the radiomics signature and clinicopathologic risk factors for individual preoperative prediction of lymph node metastasis in patients with CRC was developed and facilitated the preoperative individualized prediction of lymph node metastasis[63].

CONCLUSION

In conclusion, AI and radiomics have been applied in routine clinical practice, including lesion detection, differential diagnosis, therapeutic assessment, prognosis prediction and so on (Figure 1). The incorporation of AI into current clinical radiology workflow has shown potential to help radiologists improve accuracy of diagnosis, evaluate therapeutic effect, and predict prognosis (Tables 1-3). However, at present these applications in clinical practice remain in their infancy, and many details of workflow need to be improved. First, there is no uniform standard for image acquisition at present. Different types of scanners and imaging acquisition protocols vary across institutions, and the image quality and stability of features also need to be improved. Second, although a majority of models could be built for radiomics analysis, it is still difficult to decide the best one for different clinical issues. Third, till now, most studies were retrospectively designed and the reliability of these research conclusions still needs to be tested. In order to overcome these barriers, it is of great importance to establish a unified labeling database, develop automatic standardized ROI mapping software, and select multiple machine learning methods for optimization. Moreover, for more applications and development of AI and radiomics in gastroenterology, multicenter cooperation is also an inevitable trend to verify large sample data from various institutions. Given the continuous accumulation of data, standardization of work processes, and continuous improvement of computer technology, AI and radiomics will make a major breakthrough in the field of precision medicine for gastroenterology in the future.

Table 1 Application of radiomics in qualitative diagnosis in gastroenterology

Classification of disease	Imaging modality	Features evaluated and methods	Outcomes	Ref.
Gastric disease				
AC; GIST; lymphoma	CECT	RLM; GLCM; absolute gradient; autoregressive model; wavelet transformation	Texture-based lesion classification in arterial phase differentiated between AC and lymphoma, and GIST and lymphoma, with misclassification rates of 3.1% and 0%, respectively Texture-based lesion classification in venous phase differentiated between AC and GIST, and different grades of AC with misclassification rates of 10% and 4.4%, respectively	[30]
Borrmann type IV GC; PGL	CECT	A total of 485 3D features, divided into four groups: First order statistics, shape and size based features, texture features, and wavelet features	The subjective findings model, radiomics signature, and combined model showed a diagnostic accuracy of 81.43% (AUC, 0.806; sensitivity, 63.33%; specificity, 95.00%), 84.29% (AUC, 0.886; sensitivity, 86.67%; specificity, 82.50%), and 87.14% (AUC, 0.903; sensitivity, 70.00%; specificity, 100%), respectively, in the differentiation of Borrmann type IV GC from PGL	[31]
Hepatic disease				
Neoplastic and bland portal vein thrombus	CECT	Mean; entropy; SD of pixel intensity; kurtosis; skewness	In the discrimination of neoplastic from bland thrombus, the AUCs were 0.97 for mean value of positive pixels, 0.93 for entropy, 0.99 for the model combining mean value of positive pixels and entropy, 0.91 for thrombus density, and 0.61 for the radiologist's subjective evaluation	[42]
HCC; MT; HH	MRI	GLCM; GLRLM; GLSZM; NGTDM	Texture analysis in differential diagnosis: HCC and MT: accuracy 92%, sensitivity100%, specificity 84%, AUC 0.95 HCC and HH: accuracy 90%, sensitivity 96%, specificity 84%, AUC 0.95 MT and HH: accuracy 73%, sensitivity74%, specificity72%, AUC 0.75	[41]
Pancreatic disease				
PSCN	CECT	A total of 385 radiomics high-throughput features: Intensity; wavelet; NGTDM	The accuracy rate of SCNs before surgery was only 30.4% (31/102) while the diagnostic model established based on dual-phase pancreatic CT imaging features had an improved accuracy rate of diagnosis, showing an AUC of 0.767, sensitivity of 68.6%, and specificity of 70.9%	[51]
PNEC; PDAC	CECT	Filtration-histogram approach and Laplacian-of-Gaussian band-pass filters (sigma values of 0.5, 1.5, and 2.5) were used and texture parameters under different filters, including: Kurtosis, skewness, entropy, and uniformity	PNEC showed a lower entropy and a higher uniformity compared to PDAC in the portal phase with an acceptable AUC of 0.71-0.72	[52]
Colorectal disease				
Neoplastic and non-neoplastic lesions	CECT	78 features for each lesion in total	Combining high-order CT images with CT volumetric texture features allowed a significantly higher AUC of 0.85 in distinguishing neoplastic colon tumors from non-neoplastic ones than only using the image intensity (AUC of 0.74)	[58]

CECT: Contrast-enhanced computed tomography; AC: Adenocarcinoma; GIST: Gastrointestinal stromal tumors; PGL: Primary gastric lymphoma; MT: Metastatic tumor; HH: Hepatic hemangioma; AUC: Area under the curve; GLCM: Grey level cooccurrence matrices; GLSZM: Gray-level size zone matrix; PSCN: Pancreas serous cystic neoplasms; SCN: Serous cystic neoplasm; PNEC: Pancreatic neuroendocrine carcinoma; PDAC: Pancreatic ductal adenocarcinoma.

Table 2 Application of radiomics in disease staging in gastroenterology

Classification of disease	Imaging modality	Features evaluated and methods	Outcomes	Ref.
Esophageal disease				
ESCC	Unenhanced CT and CECT	Six parameters based on HU values: Mean; 10^{th} percentiles; 90^{th} percentiles; kurtosis; entropy; skew	Kurtosis and entropy based on unenhanced CT were an independent predictor of T stages, lymph node metastasis (N- *vs* N+), and overall stages Skew and kurtosis based on unenhanced CT images showed significant differences among N stages as well as 90th percentile based on contrast-enhanced CT images; entropy and 90th percentile based on CECT images showed significant correlations with N stage and overall stage	[18]
ESCC	CECT	A total of 9790 radiomics features were extracted including the following four categories: First-order histogram statistics, size and shape-based features, texture features, and wavelet features	The radiomics signature significantly associated with ESCC staging and yielded a better performance for discrimination of early and advanced stage ESCC compared to tumor volume	[19]
Gastric disease				
GC	MRI	Entropy-related parameters based on ADC maps including: (1) First-order entropy; (2–5) second-order entropies, including entropy$(H)_0$, entropy$(H)_{45}$, entropy$(H)_{90}$, and entropy$(H)_{135}$; (6) entropy$(H)_{mean}$; and (7) entropy$(H)_{range}$	All the entropy-related parameters showed significant differences in gastric cancers at different T, N, and overall stages, as well as at different statuses of vascular invasion Entropy, entropy$(H)_0$, entropy$(H)_{45}$, and entropy$(H)_{90}$, showed significant differences between gastric cancers with and without perineural invasion	[35]
GC	CECT	Mean; maximum frequency; mode; skewness; kurtosis; entropy	Maximum frequency in the arterial phase and mean, maximum frequency, mode in the venous phase correlated positively with T, N, and overall stage of GC; entropy in the venous phase also correlated positively with N and overall stage; skewness in the arterial phase had the highest AUC of 0.822 in identifying early from advanced GCs	[34]
Hepatic disease				
Hepatic fibrosis	CECT	Mean gray-level intensity; entropy; kurtosis; skewness	Mean gray-level intensity, mean, and entropy increased with fibrosis stage; kurtosis and skewness decreased with increasing fibrosis	[43]
Pancreatic disease				
PNET	CECT	Positive pixels; SD; kurtosis; skewness; entropy	Entropy was predictive of Grades 2 and 3 tumors with an accuracy rate for classifying G1, G2, and G3 tumors of 79.3%	[53]
PNET	CECT	Mean value; variance; skewness; kurtosis; entropy	Kurtosis was significantly different among the three G groups, giving an AUC value of 0.924 for the diagnosis of G3 with a sensitivity and specificity of 82% and 85%, respectively; entropy differed significantly between G1 and G3 and between G2 and G3 tumors, giving an AUC value of 0.732 for the diagnosis of G3 with a sensitivity and specificity of 82% and 64%, respectively	[54]
Colorectal disease				
CRC	CECT	The 16-feature-based radiomics signature was generated using LASSO logistic regression model	The 16-feature-based radiomics signature was an independent predictor for staging of CRC and could categorize CRC into stage I-II and stage III-IV Compared with the clinical model, the radiomics signature showed significantly better performance either in the training dataset (AUC: 0.792 *vs* 0.632; $P < 0.001$) or in the validation dataset (AUC: 0.708 *vs* 0.592; $P = 0.037$)	[59]

ESCC: Esophageal squamous cell carcinoma; CECT: Contrast-enhanced computed tomography; GC: Gastric carcinoma; PNET: Pancreatic neuroendocrine tumor; CRC: Colorectal cancer; AUC: Area under the curve.

Table 3 Application of radiomics in evaluation of therapeutic efficacy and prognosis in gastroenterology

Classification of disease	Imaging modality	Features evaluated and methods	Outcomes	Ref.
Esophageal disease				
EC	^{18}F-FDG PET	A total of 38 features (such as entropy, size, and magnitude of local and global heterogeneous and homogeneous tumor regions) extracted from 5 different textures	Tumor textural analysis provided non-responder, partial-responder, and complete-responder patient identification with a higher sensitivity (76%-92%) than any SUV measurement	[22]
ESCC	MRI	138 radiomic features were extracted from each image sequence based on three principal methods: Histogram-based (IH, GH), texture-based (GLCM, GLRLM, and NIDM), and transform-based (GWTF)	Radiomic analysis showed that CR *vs* SD, PR *vs* SD, and responders (CR and PR) *vs* non- responders could be differentiated by 26, 17, and 33 features, respectively; the prediction models (ANN and SVM) based on features extracted from SPAIR T2W sequence (SVM: 0.929; ANN: 0.883) showed higher accuracy than those derived from T2W (SVM: 0.893; ANN: 0.861)	[24]
Gastric disease				
GC	CECT	Histogram features: Kurtosis, skewness; GLCM: ASM, contrast, entropy, variance, correlation	Contrast, variance, and correlation showed fair accuracy for the prediction of good survival with all AUCs being over 0.7, and all were statistically significant	[38]
Hepatic disease				
HCC	CECT	21 textural parameters per filter were extracted from the region of interests delineated around tumor outline by application of a Gabor filter and wavelet transform with 3 band-width responses (filter 0, 1.0, and 1.5)	Texture analysis was observed to have potential in assessment of prognosis and selection of appropriate patients with intermediate-advanced HCC treated by TACE and sorafenib	[46]
HCC	CECT	First order statistics; geometry; texture analysis; GLCM	Textures derived from pretreatment dynamic CT imaging were analyzed, higher arterial enhancement ratio and GLCM moments, smaller tumor size, and lower tumor homogeneity were significant predictors of CR after TACE	[47]
Pancreatic disease				
Pancreas head cancer	CECT	Laplacian of the Gaussian band-pass filter was applied to detect intensity changes within the images smoothened by Gaussian distribution based on the filter sigma value of 1.0 (fine texture, filter width 4 pixels), 1.5 to 2.0 (medium texture, filter width 6-10 pixels), and 2.5 (coarse texture, filter width 12 pixels)	Texture parameters of average, contrast, correlation, and standard deviation with no filter, and fine to medium filter values, as well as the presence of nodal metastasis were significantly different between recurred and non-recurred patients; lower standard deviation and contrast and higher correlation with lower average value representing homogenous texture were significantly associated with poorer DFS, along with the presence of lymph node metastasis	[55]
PDAC	CECT	Mean gray-level; intensity; entropy; MPP; kurtosis; SD; skewness	Tumor size, tumor SD, and skewness were significantly and independently associated with PFS, while tumor size and tumor SD were significantly and independently associated with OS	[56]
Colorectal disease				
LARC	MRI	18 features extracted using the Haralick's GLCM and 12 parameters calculated for the histogram-based analysis	Radiomics based on pre-treatment and early follow-up MRI could provide quantitative information to differentiate pCR from non-pCR, and GR from non-GR.	[60]
Rectal cancer	MRI	Kurtosis; entropy; skewness; MPP	The change in kurtosis between midtreatment and pretreatment images was significantly lower in the PR + NR subgroup compared with the pCR subgroup; pretreatment AUROC to discriminate between pCR and PR + NR, was significantly higher for kurtosis (0.907, $P < 0.001$)	[61]

EC: Esophageal cancer; ESCC: Esophageal squamous cell carcinoma; PET: Positron emission tomography; MRI: Magnetic resonance imaging; CR: Complete response; SDs: Stable diseases; PRs: Partial responses; GLCM: Gray level cooccurrence matrices; GC: Gastric carcinoma; ASM; Angular second moment; AUC: Area under the curve; HCC: Hepatocellular carcinoma; CECT: Contrast enhanced computed tomography; TACE: Transcatheter arterial chemoembolization; DFS: Disease free survival; PFS: Progression-free survival; OS: Overall survival; PDAC: Pancreatic ductal adenocarcinoma; LARC: Local advanced rectal cancer; GR: Good response; MPP: Mean value of positive pixels.

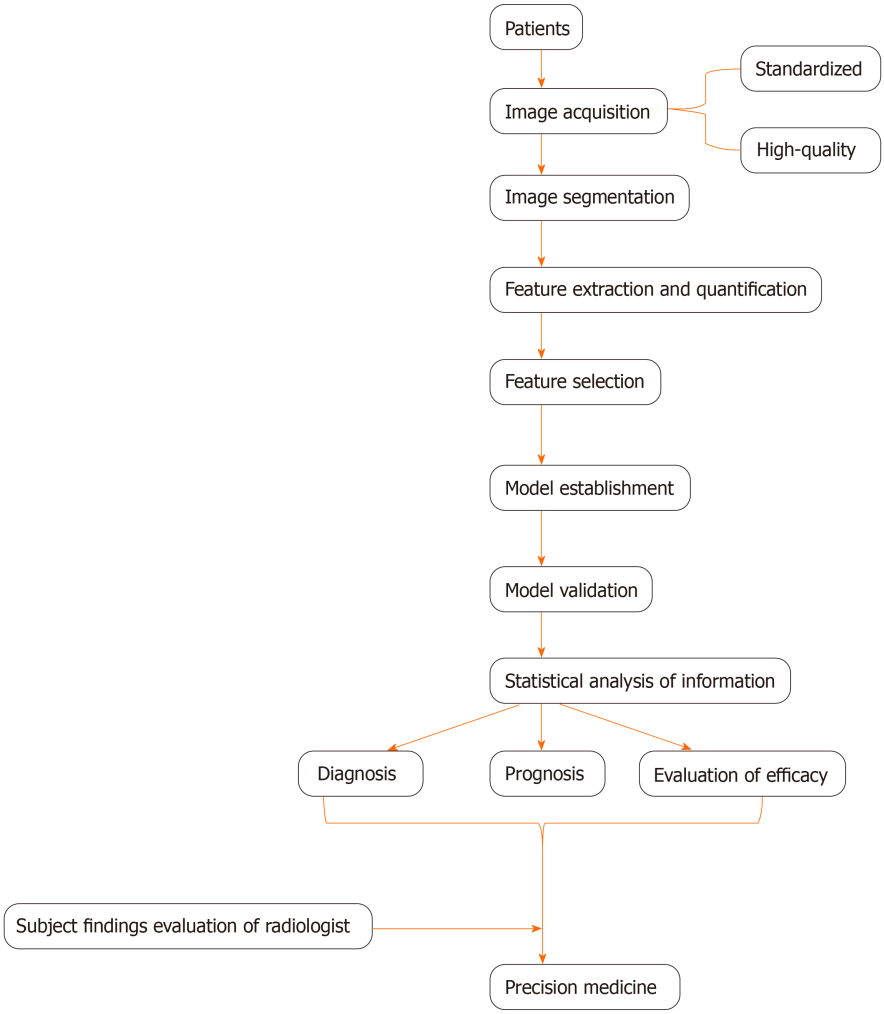

Figure 1 Overview of the workflow of artificial intelligence and radiomics in clinical practice.

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ABOUT COVER

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The primary aim of *Artificial Intelligence in Gastroenterology* (*AIG*, *Artif Intell Gastroenterol*) is to provide scholars and readers from various fields of artificial intelligence in gastroenterology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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MINIREVIEWS

Artificial intelligence for the study of colorectal cancer tissue slides

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Abstract

Artificial intelligence (AI) is gaining incredible momentum as a companion diagnostic in a number of fields in oncology. In the present mini-review, we summarize the main uses and findings of AI applied to the analysis of digital histopathological images of slides from colorectal cancer (CRC) patients. Machine learning tools have been developed to automatically and objectively recognize specific CRC subtypes, such as those with microsatellite instability and high lymphocyte infiltration that would optimally respond to specific therapies. Also, AI-based classification in distinct prognostic groups with no studies of the basic biological features of the tumor have been attempted in a methodological approach that we called "biology-agnostic".

Key Words: Artificial intelligence; Colorectal cancer; Digital pathology; Deep learning; Machine learning; Tumor-infiltrating lymphocytes

Core Tip: Artificial intelligence (AI) is gaining incredible momentum as a companion diagnostic in a number of fields in oncology. In the present mini-review, we summarize the main uses and findings of AI applied to the analysis of digital histopathological images of slides from colorectal cancer patients.

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INTRODUCTION

Artificial intelligence (AI) refers to any form of machine activity that attempts to mimic human intelligence. The main abilities of the human intelligence objective of AI research are performing complex tasks and achieving goals through processes that are typical of the human cognitive functions, such as "learning" [which in this case is termed "machine learning" (ML)] and "problem solving"[1-4].

"Deep" learning (DL) is a basic method of ML. It is based on specific computer algorithms that recall neural networking and that try to model data-rich input for the identification of general and meaningful features/patterns or for the prediction of specific outcomes[5]. The term "deep" refers to the organization in layers of the artificial neural network, with deep layers of analysis being crucial to infer more complex and higher-level characteristics up to the final layer of the label/output that is pursued (Figure 1 and Figure 2).

ML has been successfully applied in the so-called digital pathology[6-8], where histological images are deeply analyzed in every single pixel for color and light intensity by computer algorithms, to deduce a final diagnosis or prognostic/predictive feature.

The use of AI in cancer histopathology has been possible since the advent of histologic images digitalization[6]. Widely available image scanners are currently used in clinical practice, also for the acquisition of initial hematoxylin and eosin (HE) stained slides. Mukhopadhyay *et al*[9] performed a comparison between digital pathology and classical microscopy in a large multi-center cohort of patients and confirmed the exceptional utility of the digital support. Early studies were based on the analysis and segmetation of specific slide regions, such as the tumor center, margins, stroma or others, mainly in order to recognize specific objects and structures[10]. More recently, with the ability of the computational analysis of higher digital dimension, automated analysis of whole HE-stained tumor tissue slides has been possible and inference of patient outcome and prognosis has been attempted[11,12]. In the present mini-review, we summarize the latest findings for the application of AI tools for the digital pathology of colorectal cancer (CRC). In general, two research fields have been identified: AI instruments for identification of specific biologic features and AI instruments for prediction of patient outcome independently of the cancer biology.

ML FOR DETECTION OF SPECIFIC BIOLOGIC FEATURES

One typical approach of AI in pathology is to use pre-defined key image features as building block for AI-algorithm development. These are usually termed "hand-crafted" features and are engineered based on biological insights. Typical examples of "hand-crafted" features are shape and orientation of the cell nuclei[13], that can be used to recognize cancer cells or tumor infiltrating lymphocytes or other cell types.

Assessment of shape and organization of cancer cells

Shape and orientation of cancer cells are among the most commonly assessed variables to predict patient outcome[14]. A predictive, ML-based algorithm for lymph node metastasis (LNM) on whole slide images in early CRC with pathological submucosal invasion (pT1) has proven useful when using data from cancer cell morphology[16]. After delineating cancer cell regions by using immunohistochemistry for cytokeratins, Takamatsu *et al*[15] analyzed tissue slides from over 300 CRC patients diagnosed as pT1, looking for predictors of LNM. They used the popular ImageJ software, released by the United States' National Institutes of Health, and JPEG images. Digital parameters extracted from the slides essentially referred to shape, circularity, orientation and organization of cancer cells (*e.g.*, Feret's diameter), and these were used to feed a supervised ML algorithm based on random forest classifier. AI prediction was proved to be superior to human conventional assessment, with a discriminatory power of area under the curve (commonly known as AUC) 94% *vs* 83%, respectively.

Sailem *et al*[16] proposed a data-rich integrated platform that utilized a ML approach to conjugate high-throughput gene perturbation analysis with morphological features of CRC and, in particular, single cell morphology and cell population organization. After identification of TGFβ and WNT signaling genes and olfactory receptors genes as key altered genes in CRC, they validated their association with single cell and cell population morphology and grade of differentiation in CRC. Those specific gene alterations were associated to abnormal organization of HCT116 CRC cell cultures and

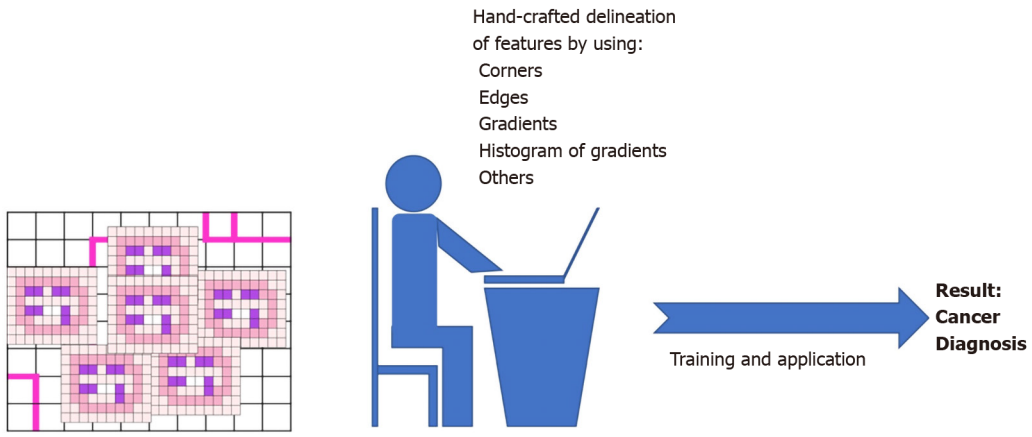

Figure 1 Exemplified representation of hand-crafted feature-based machine learning.

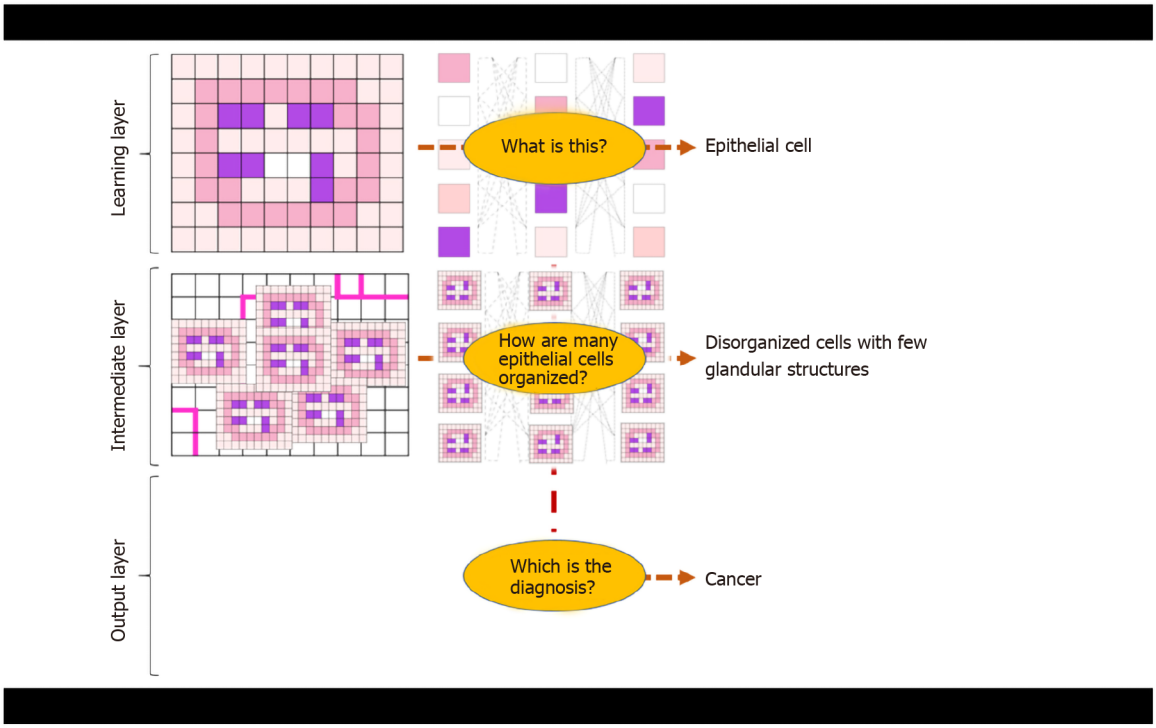

Figure 2 Exemplified explanation of deep learning for tumor tissue slide analysis.

also to specific CRC molecular subtypes (the well-known consensus molecular subtypes – CSM[17]) in over 550 patients from The Cancer Genome Atlas (referred to as TCGA) database.

Assessment of tumor infiltrating lymphocytes

In recent years, the development of immunotherapy has revolutionized the care of cancer[18], and great attention has been placed upon assessment of the immune response surrounding the tumor tissue[19]. Most reports are focused on specific immune cells and chiefly on tumor-induced cytotoxic T cells. Indeed, a high T-cell infiltration appears to be associated with a decreased risk of tumor dissemination and improved survival in most solid tumors. Väyrynen *et al*[20] have recently proposed an AI-based assessment of CRC slides, simultaneously evaluating different cell populations involved in immune response against the tumor. Scanned HE-stained images of CRC cases from two United States' prospective cohorts [the Nurses' Health Study (referred to as NHS), and the Health Professionals Follow-up Study (referred to as HPFS)] were analyzed with an open source software (QuPath v0.1.2), enabling the

recognition of cancer epithelial cells and four immune cell types with distinct morphological features: lymphocytes, plasma cells, eosinophils, and neutrophils. Moreover, QuPath v0.1.2 was able to distinguish between two tissue regions: the intraepithelial region and stromal region[21]. Densities of immune cells in the intraepithelial and stromal regions, together with a function (G-cross function) measuring the proximity of immune cells to cancer cells (expressed as AUC within a distance of 20 μm) were calculated. Findings from NHS and HPFS cohorts were validated in a set of 570 CRC from TGCA with available digitalized pathological images in the data portal. Automated quantification of immune cells was compared to manual count by pathologists.

A high correlation between measurement of immune cell densities performed by automated AI classifiers and manual counts performed by experienced pathologist was found (Spearman's rho 0.71-0.96). Moreover AI-determined stromal density of lymphocytes and eosinophils were independently correlated with survival in a multivariable Cox regression analysis, with higher densities associated with longer cancer-specific survival (*P* for trend across quartiles of density < 0.001 for both cell types). The multivariate analysis included very important molecular factors which were available for the post-hoc analysis of NHS and HPFS populations and partly associated with immune response, such as microsatellite instability (MSI), CpG island methylator phenotype, *KRAS*, *BRAF*, and *PIK3CA* mutations, and LINE-1 methylation level. High G cross function for Tumor: Lymphocyte and Tumor: Eosinophil proximity was also associated with longer cancer-specific survival (P_{trend} 0.002 and < 0.001, respectively). High stromal eosinophil density was associated with better cancer-specific survival also in the TGCA cohort (P_{trend} < 0.001).

AI can also improve CRC cancer staging and, consequently, patient prognosis. Reichling and co-workers[22], using a LASSO algorithm, DGMate (DiGital tuMor pArameTErs), combined the analysis of tumor stroma and tumor cell intrinsic variables, in association with immune cell infiltrate of tumor samples from stage III CRC patients of the PETACC8 study cohort, and were able to detect digital parameters within the tumor cells related to patients' outcomes[23]. Similarly, clinically relevant information were gained in the study of Yoo *et al*[24], in which ML-based analysis was applied to study the quantitative parameters of immune infiltrate within the tumor immune microenvironment. By quantifying intraepithelial tumor-infiltrating lymphocytes, stromal tumor-infiltrating lymphocytes, and the tumor-stroma ratio from CD3 and CD8 immunohistochemical stained whole-slide images, the authors classified five CRC subgroups with distinctive biological features and different prognostic behaviors. Indeed, the CD3+ and CD8+ T-cell infiltration is considered an important independent prognostic factor predicting CRC patient survival[25]. An automated image analysis–based workflow quantifying the tumor-infiltrating immune cells and tumor budding, at the invasive front, combined with a ML approach, demonstrated that the spatial association of lymphocytes and tumor buddings could provide a high prognostic significance in stage II CRC patients[26].

AI for identification of peculiar molecular subgroups

MSI-high (MSI-H) tumors are a peculiar molecular subgroup of CRC characterized by deficient expression of mismatch repair proteins (dMMR phenotype)[27]. MSI-H is associated with the inherited Lynch syndrome and found to be a marker of increased tumor mutational burden, neoantigen generation and exceptional sensitivity to immune checkpoint inhibitors[28]. It accounts for 4%-5% of metastatic CRC and its early recognition is now crucial to avoid useless treatment with conventional chemotherapy and to tailor adequate and effective immunotherapy. Kather *et al*[29] have recently built an AI-classifier of conventionally HE-stained slides of gastric and CRC for the detection of MSI-H. The model used Resnet18, a residual learning convolutional neural network (CNN), which was trained and validated, both internally and externally, in a very large cohort of gastrointestinal cancer. In particular, Resnet18 was initially trained to automatically identify tumor areas within the normal tissue background in common histological slides. In a second step, it was trained to define the degree of MSI using TCGA bank, and specifically 315 and 360 formalin-fixed paraffin embedded gastric and CRC specimens, respectively, and 378 snap-frozen CRC samples. TGCA of stomach cancer was 80% from non-Asian patients, and authors tested the possible influence of ethnicity on the model performance by validating the AI classifier in an external cohort of 185 Japanese patients.

The discriminatory power of the AI tool for the MSI-H status identification was impressively high (AUC around 80% in almost all experiments) across all the different sets: gastric *vs* CRC tissues, Asian *vs* non-Asian patients, and formalin-fixed paraffin embedded *vs* snap-frozen samples. Moreover, it was found that minimal required

number of histological "tiles" on which to train and interrogate the algorithm (the ML process starts by fragmenting the entire histologic digital image in multiple elementary color-normalized slide tiles) was as small as those encompassed in a common core needle biopsy (performance plateaued at approximately 100 "slide tiles" of 256 μm edge length). The logical next step in this field will be to test the predictive value of AI-based MSI-H diagnosis for immunotherapy efficacy.

In another study by the same research group, a DL model for MSI definition was trained and validated in a cohort of nearly 9000 patients from Germany, Netherlands, United Kingdom and United States by using standard HE-stained slides and immunohistochemistry for mismatch repair proteins or conventional genetic test of microsatellite regions as ground truth for MSI status. In the validation step, the DL tool demonstrated an impressively high ability to correctly classify MSI-H patients with a discriminatory power > 95% (AUROC 0.95-096)[30].

AI for the quantification of stromal tissue

In CRC, the so-called desmoplastic reaction, *i.e.* a pronounced stromal tissue growth within the tumor mass, has been associated with reduced prognosis[31]. Desmoplastic reaction is driven by differentiated cells responsible for the deposition of extracellular fibrotic material, the cancer-associated fibroblasts (CAFs). Kather *et al*[32] have used DL for automatic quantification of stromal tissue proportion in CRC tissues and set up a "deep stroma score". They first trained the DL instrument with over 100000 digital image patches of HE-stained tumors from 86 CRC patients where stromal and non-stromal areas were hand-delineated. The DL tool so obtained was then tested in an independent set of over 7000 images from 25 patients, where it demonstrated an accuracy of > 94%.

The tool, that was able to recognize tissue-specific features, was finally used to produce the "deep stroma score" which was calculated for a cohort of 500 colorectal patients from the TCGA repository and correlated with survival. The stroma score significantly and independently associated with overall survival with a hazard ratio of 1.99, P = 0.003. In the same patient group, manual stroma quantification by experienced pathologists or stromal assessment by means of gene expression profiles attributable to CAFs had an inferior performance in terms of survival prediction across the different tumor stages (from I to IV). The DL stroma score yielded similar prognostic efficacy in an independent validation cohort of over 400 patients from Germany: hazard ratio for overall survival 2.29, P = 0.0004.

BIOLOGY-AGNOSTIC ML

DL is a novel type of ML that uses a more "blind" approach to analyze the input data with no pre-definition of hand-crafted features to train the model. An extreme way to apply DL is the direct correlation of the digital input data to the final outcome, for example risk of disease relapse *vs* definitive care after surgical removal of the tumor, with no specific "biological insights" fed into the machine. Skrede *et al*[33] have applied an advanced DL method to analyze whole-slide image, using CNN. CNN makes use of mathematical convolutions, *i.e.* resulting mathematical functions obtained by combining more primary functions reversed and shifted in time. In Skrede *et al*[33]'s experiment, no clinical or biological information (such as grade of histological differentiation, neurovascular invasion, depth of tumor infiltration within the colon wall, or others) was fed into the model, and the final objective was to identify "biology-agnostic" digital image profiles (purely based on patterns of pixel color or intensity of the digital images) predictive of CRC specific survival in surgically-resected patients (stages II and III). Four large cohorts of approximately 1000 patients each were used (training, tuning, test and validation cohorts). The CNN-based automatic prognostic classifier, that authors called DoMore-v1-CRC, was initially trained for outcome prediction in a cohort of patients constituted of two subgroups with "pre-labeled" distinct outcomes: good (survival > 2 years) *vs* poor (relapse within 6 mo) outcome. DoMore-v1-CRC was then tuned, tested and validated in cohorts with non-prelabeled outcome to define its prognostic ability. The DoMore-v1-CRC had an output of three possible classes, good *vs* uncertain *vs* poor prognosis. The DoMore-v1-CRC–based classification had an independent prognostic value in a multivariable survival analysis that included and adjusted for well-known and broadly-used clinical and biological factors, such as pN stage, pT stage, lymphatic invasion, and venous vascular invasion (hazard ratio for DoMore-v1-CRC-defined poor *vs* good prognosis 3.04, P < 0.0001). Accuracy in predicting cancer-specific survival was around 70% in all

cohorts. The prognostic power remained high for both stage II and stage III tumors, and for groups of slides prepared in different laboratories, thus confirming its robustness against inter-laboratory variability in tissue preparation and staining. Moreover, the prognostic yield remained high when two different image scanners were compared (NanoZoomer XR *vs* Aperio AT2 scanner). Interestingly, even though derived from a biology-agnostic approach, DoMore-v1-CRC significantly correlated with clinical and biological markers, such as age, pN stage, pT stage, histological grade, tumor sidedness, BRAF mutation, and microsatellite instability.

CONCLUSION

Even if still at the early stages, AI in digital pathology is increasingly gaining momentum, for a number of reasons: (1) worldwide transferability; (2) high-dimension of analyzable data; and (3) automated procedural approaches. Far from being conceived as substitutive of human intelligence, it can be seen as a useful companion diagnostic in oncology and as pre-screening/pre-selection tool. Both biology-driven and biology-agnostic algorithms have been pursued in the implementation of AI in the CRC pathology field (Table 1).

The main challenges for AI-supported digital pathology are currently to demonstrate that can diffusely be applied and significantly help in the clinical decision-making especially as predictor of efficacy of specific therapeutic options. Such a demonstration can only come with an enhancement of the AI application itself to different cancer patient settings and different clinical scenarios and problem-solving tasks. Future directions rely on the prospective validation of AI-based tools in randomized phase III trials, which delineates the so-called "IA level" of evidence.

Table 1 Summary of main applications and findings of artificial intelligence in colorectal cancer digital pathology

Target	Description	Ref.
Cancer cell shape and organization to predict N+	Digital assessment of cancer cells using Feret's diameters allows to predict lymph node metastasis in pT1 colon cancer	[11]
Assessment of anti-cancer immune response	Simultaneous assessment of all immune cell subpopulations and demonstration that eosinophils, other than T cells, may play a role in CRC immune response	[12,14,15,17]
Identification of Microsatellite instable tumors	Rapid and large size screening of histopathologic features in conventional HE-stained slides increasing the probability of being a MSI-H tumor, without the need of specific immunohistochemical or molecular testing	[18]
Quantification of stroma within the tumor	Algorithms for tissue –specific recognition, even when sparse within the tumor mass have been development. These algorithms have allowed the validation of "deep stroma score" which is significantly associated with survival in CRC	[20]
Biology-agnostic prediction of survival	Development of tissue "digital" profiles without specific underlying biologic background or significance that are predictive of distinct survivals, bad vs good outcome	[21]

CRC: Colorectal cancer; MSI-H: Microsatellite instability high.

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AIMS AND SCOPE

The primary aim of *Artificial Intelligence in Gastroenterology* (*AIG*, *Artif Intell Gastroenterol*) is to provide scholars and readers from various fields of artificial intelligence in gastroenterology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

AIG mainly publishes articles reporting research results obtained in the field of artificial intelligence in gastroenterology and covering a wide range of topics, including artificial intelligence in gastrointestinal cancer, liver cancer, pancreatic cancer, hepatitis B, hepatitis C, nonalcoholic fatty liver disease, inflammatory bowel disease, irritable bowel syndrome, and *Helicobacter pylori* infection.

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MINIREVIEWS

Artificial intelligence: A new budding star in gastric cancer

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Abstract

The pursuit of health has always been the driving force for the advancement of human society, and social development will be profoundly affected by every breakthrough in the medical industry. With the arrival of the information technology revolution era, artificial intelligence (AI) technology has been rapidly developed. AI has been combined with medicine but it has been less studied with gastric cancer (GC). AI is a new budding star in GC, and its contribution to GC is mainly focused on diagnosis and treatment. For early GC, AI's impact is not only reflected in its high accuracy but also its ability to quickly train primary doctors, improve the diagnosis rate of early GC, and reduce missed cases. At the same time, it will also reduce the possibility of missed diagnosis of advanced GC in cardia. Furthermore, it is used to assist imaging doctors to determine the location of lymph nodes and, more importantly, it can more effectively judge the lymph node metastasis of GC, which is conducive to the prognosis of patients. In surgical treatment of GC, it also has great potential. Robotic surgery is the latest technology in GC surgery. It is a bright star for minimally invasive treatment of GC, and together with laparoscopic surgery, it has become a common treatment for GC. Through machine learning, robotic systems can reduce operator errors and trauma of patients, and can predict the prognosis of GC patients. Throughout the centuries of development of surgery, the history gradually changes from traumatic to minimally invasive. In the future, AI will help GC patients reduce surgical trauma and further improve the efficiency of minimally invasive treatment of GC.

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Core Tip: Artificial intelligence (AI) is an important part of the information technology revolution. AI can be used in the following three aspects: (1) Gastroscopy for gastric cancer (GC) can improve the diagnostic accuracy of early GC and reduce the missed diagnosis of atypical parts of advanced GC; (2) Imaging doctor determination of the location of the lymph nodes. More importantly, it can more effectively determine lymph node metastasis of GC; and (3) Improving robotic surgical systems and further reducing patient injuries, by advancing from minimally invasive to nearly non-invasive surgery.

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INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer and the third leading cause of cancer death worldwide. The incidence of GC in East Asia has increased significantly in recent years[1], ranking second in incidence in China, representing the most common cause of cancer death[2]. In recent years, with the transformation of information technology, AI (AI) technology is gradually becoming an alternative to traditional technology or an integral part of an integrated system. AI has been used to solve complex practical problems in various fields and is becoming more and more popular today[3]. AI can learn from examples, has certain fault tolerance, can deal with noisy data and incomplete data, can deal with nonlinear problems, and can be predicted and summarized at high speed once it has been trained. AI-based systems are being widely developed and deployed worldwide, mainly because of their symbolic reasoning, flexibility, and interpretation capabilities. Thanks to the rapid development of large amounts of labeled data and computers, AI, especially deep learning, has begun to penetrate the medical field. AI is of great significance to medicine and has been partially applied in clinic. Topol[4] enumerates and analyzes the main aspects and functions of AI in clinical application at present (refer to Figure 1 for details). AI can make accurate judgments on diseases through large-scale learning, and can assist clinicians in the diagnosis and treatment of GC. As such, AI-assisted diagnosis has become an important direction for the diagnosis of GC.

APPLICATION OF AI IN GASTROSCOPE

Gastrointestinal endoscopy is the most important and potential direction for AI-assisted diagnosis. In previous studies, much of the initial work of endoscopic AI technology has focused on the detection and optical diagnosis of colonic polyps[5]. Esophagogastric duodenoscope (EGD) is widely regarded as one of the standard methods for diagnosing gastric diseases. However, a study[6] has shown that the missed rate of endoscopy in the 3 years before diagnosis of gastrointestinal tumors is 11.3%. Two other studies[7,8] showed that the proportion of missed GCs was 9.4% and 25.8%. AI-based detection's potential usefulness in GC was first reported by Hirasawa *et al*[9]. For gastroenterology, AI is another important direction for the diagnosis of GC.

Application of AI in the diagnosis of early GC by endoscopy

Topol[4] thinks that AI can be help make clinical diagnosis fast and accurate, optimizing processes in the health-care system to reduce diagnostic errors and malpractice. More than this, it can benefit the patient's daily life, helping in observing

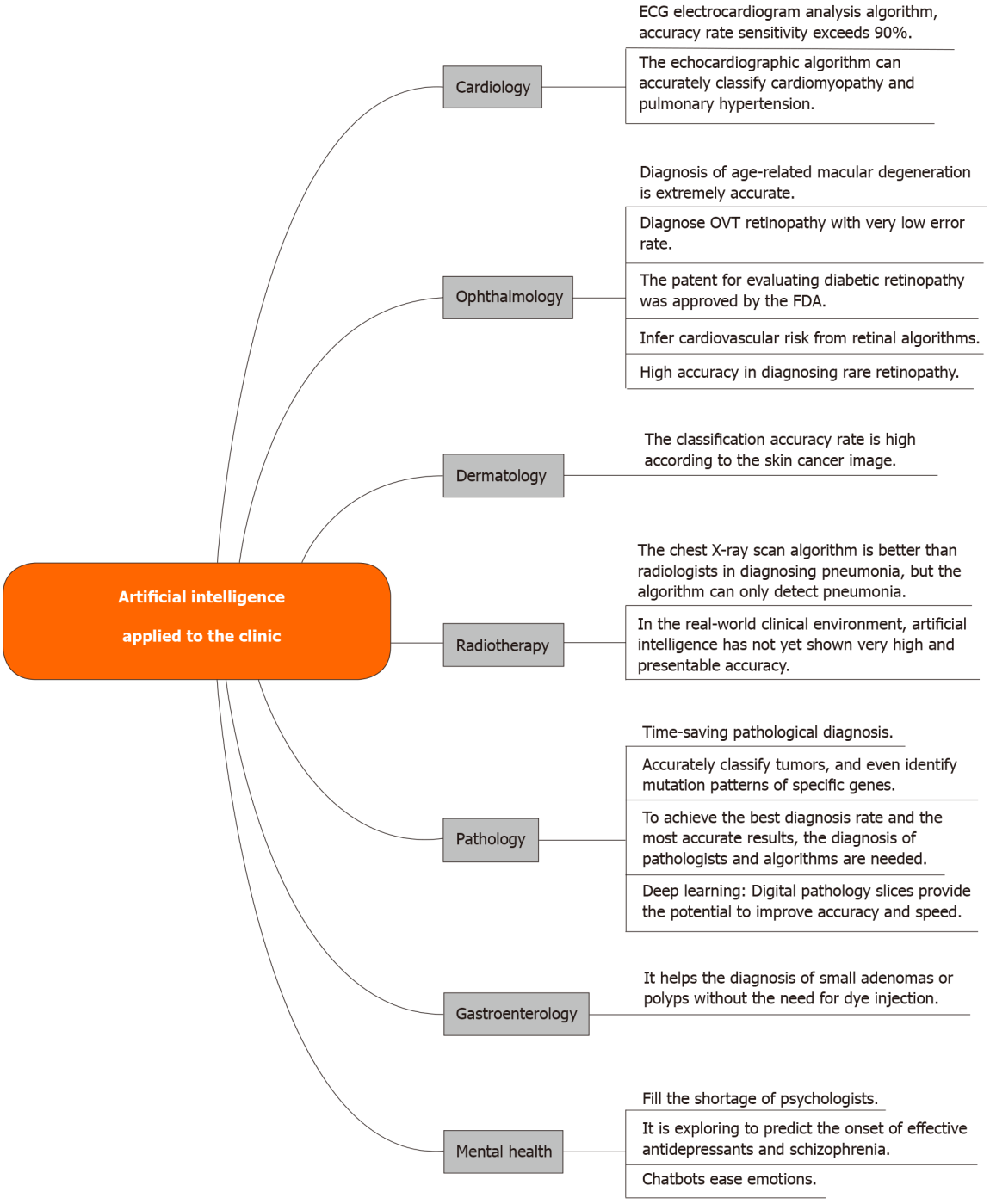

Figure 1 Artificial intelligence applied to the clinic.

and analyzing their health data to accelerate rehabilitation. Gastrointestinal endoscopy is an important and rapidly developing research field in the application of AI in gastrointestinal surgery, specifically in the diagnosis and treatment of early cancer. Endoscopic submucosal dissection (referred to as ESD) and endoscopic mucosal resection (referred to as EMR) are considered to be the most beneficial procedures for patients with early GC (EGC), and surgical treatment is considered when endoscopic treatment is not possible. The risk of lymph node metastasis in the mucosal layer (referred to here as "M")/shallow submucosal layer (referred to here as "SM1"; < 500 mm from the muscularis mucosa) is very low but the potential of metastasis in the deep submucosal layer (referred to here as "SM2"; > 500 mm invasion) is quite high. As usual, for patients with EGC and an infiltration depth greater than 500 mm, surgery is considered the first choice. However, for patients with EGC whose depth of

invasion is limited to the M or superficial submucosa (~ 500 mm from the muscularis mucosa), ESD/EMR should be provided.

The accuracy of endoscopists in using endoscopy, endoscopic ultrasonography, or both to predict the depth of invasion was only 69% to 85% in previous studies[10]. Therefore, it is an important clinical problem to accurately predict the invasion depth of EGC. Research has shown that machine vision can interpret specific medical images more accurately and faster than humans using high magnification[11]. In a separate study that is more accurate, Zhu *et al*[12] report significant progress in the use of endoscopy in EGC. They developed and validated an AI system model that uses deep learning algorithms to determine the depth of invasion of EGC. The model is called a convolutional neural network computer-aided detection (CNN-CAD) system, which can determine whether the intrusion depth is "M/SM1" and "SM2" or deeper. In the research results of Zhu *et al*[12], the AI machine learned a total of 790 GC images and tested 203 GC images, which are different and independent of the learning images. The result is that when the threshold of CNN-CAD system is 0.5, the sensitivity is 76.47%, the specificity is 95.56%, and the accuracy is 89.16%. The positive and negative predictive values were 89.66% and 88.97%, respectively. The sensitivity of the endoscopist was 87.80%, the specificity was 63.31%, the accuracy was 71.49%, and the positive and negative predictive values were 55.86% and 91.01%, respectively.

For experienced endoscopists, the CNN-CAD system has once again achieved higher accuracy and specificity. High specificity of 96% will help to enhance the accurate diagnosis of the depth of invasion, distinguishing EGC from deeply invasive submucosal layer cancer. However, there are still some limitations in the research of Zhu *et al*[12]. First there are relatively few materials for deep learning. Second, in AI learning algorithms, only high resolution and clear images are selected as learning and testing materials. These two points lead to a serious defect whereby AI models may show excellent performance in clean and clear images of GC, but the diagnostic accuracy may be greatly affected when faced with poor quality images which endoscopists often encounter in clinical practice. This disadvantage can be overcome by enabling AI to learn a large number of images which are common among clinical gastroscopic pictures, such as mucus on the surface of the lesion, the lesion not being concentrated, or the location being too narrow to be seen clearly.

On colonoscopy, it is considered very difficult to find small adenoma or pedicleless polyps. In a first prospective clinical trial of AI, in a real-time routine colonoscopy, a total of 466 images of 466 tiny polyps were analyzed, with an accuracy of 94% and a negative predictive value of 96%. The speed of AI optical diagnosis is 35 s, which is faster than that of clinical endoscopists[11]. The algorithm is equally effective for novices and gastroenterologists and does not require dye injection. This study and Zhu *et al*[12] reached similar conclusions and revealed the application potential of AI in gastrointestinal endoscopy.

With AI, it's like opening a third eye to an endoscopist. AI for the diagnosis of disease, especially for EGC, is not only reflected in high accuracy but also it the quick training of junior doctors, improved diagnosis rate of EGC, and reduced missed cases.

Application of AI in endoscopic diagnosis of advanced GC

Gastroscopy easily detects advanced GC but there is also a certain risk of missed diagnosis. Korean scholars[13] prospectively collected undiagnosed cases of advanced GC with recent endoscopies, from 1997 to 2008, and reviewed the medical records of advanced GC diagnosed before 1991 to 1996. In total, 2310 cases of GC were analyzed. In that study, more than one-third of patients with advanced GC were not found in the previous endoscopy and they were located around the cardia.

Wu *et al*[14] has developed a new deep (D)CNN for endoscopic vision. This DCNN system is used to screen for EGC without blind spots during gastroenteroscopy (*i.e.* EGD). As a result, DCNN identified EGC from non-malignant tumors with an accuracy of 92.5%, sensitivity of 94.0%, specificity of 91.0%, positive predictive value of 91.3%, negative predictive value of 93.8%; these results were better than any achieved by an endoscopist. The accuracy of EGC detection by endoscopists is surpassed by the DCNN system of Wu *et al*[14], and that can better identify the location of the stomach. The advantage of the system is that it can detect EGC actively and track suspicious cancer lesions during EGD. Although the above study was aimed at EGC, we can see that an AI system has great potential for accurate diagnosis of advanced GC. The accuracy of GC diagnosis will be improved because of the intervention of an AI system. The high rate of missed diagnosis of advanced GC in the cardia will also be overcome by an AI system.

The prevalence and incidence rates of advanced stage GC are high, and the diagnosis rate is about 2/3. This has prompted doctors and researchers from all over

the world not only to improve the detection rate of EGC but also to optimize the clinical management of advanced GC[15].

Perspectives

Ishioka *et al*[16] believe that the application of a CNN system in video should be expanded, and the image is expected to improve the standard of early detection of GC. Luo *et al*[17] developed a gastrointestinal-AI diagnostic system. Seven validation sets were used in their multicenter study, with accuracy ranging from 91.5% to 97.7%. The diagnostic sensitivity of "griaids" was higher than that of endoscopists (85.8%) and interns (72.2%). Kanesaka *et al*[18] collected and randomly selected 66 EGC magnifying narrow-band imaging (m-Nbi) images and 60 non cancer m-Nbi images as training sets, and 61 EGC m-Nbi images and 20 non cancer m-Nbi images as test sets. The test shows that the cadx system has great potential in the real-time diagnosis and sketching of EGCS in m-Nbi images. The study by Horiuchi *et al*[19] also supports this conclusion.

Whether it is EGC or advanced GC, the invasion depth of the tumor is related to the prognosis of the patients. Accurate determination of the invasion depth is beneficial to the patients. The overall accuracy rate of using "WLis" to evaluate the invasion depth of Zhu *et al*[12] was 89.16%, which was significantly higher than that of endoscopists

Many research studies on AI and the stomach have been focused on Japan, China and South Korea. At present, the combination of GC and AI mainly focuses on the detection and diagnosis of GC. In addition, AI systems may have potential applications in other areas. There are also many research studies on the application of AI technology in the detection and diagnosis of GC.

AI has great potential in the field of digestive diseases. Using AI for accurate diagnosis can make more accurate optical biopsy and reduce unnecessary biopsy or endoscopic resection, which is beneficial to patients. This can reduce the risk of bleeding, the incidence of complications, and the economic expenditure caused by the disease.

APPLICATION OF AI IN LYMPH NODE METASTASIS OF GC

Just as AI is gradually changing gastroenterology and endoscopy, it has also changed imaging doctors greatly. Preoperative localization diagnosis of lymph nodes is an ongoing and substantial challenge for radiologists. At present, the detection of lymph nodes is mainly achieved by imaging methods, which extracts a variety of diagnostic features. Some feature extraction methods are used to extract the effective diagnosis features, and then to realize the diagnosis of lymph node metastasis. Lymph node metastasis is an important independent factor affecting the prognosis of GC. Before medical and surgical treatment, lymph nodes must be understood as accurately as possible to determine treatment options and evaluate prognosis. Lymph node metastasis is an important independent factor affecting the prognosis of GC. Some studies have shown that the diagnosis of lymph node metastasis is of great significance[20-22]. AI and the diagnosis of GC lymph nodes can be divided into two aspects. The former is the application of AI in the diagnosis of lymph nodes, and the latter is the application of AI in the diagnosis of lymph node metastases. Because artificial detection is time-consuming and laborious, AI detection of abdominal lymph nodes is considered to be one of the development trends.

Barbu *et al*[23] propose an automatic detection method based on learning, which can detect and segment axillary and pelvic lymph nodes at the same time. First, the learning-based method is used to detect the suspected lymph nodes; then, the segmentation model is used to extract the boundary of each suspected lymph node. Finally, some features of the lymph nodes are used to score all the suspected lymph nodes; ultimately, the portion with the highest score is the lymph nodes. Although there has been some work to achieve automatic or semi-automatic detection of lymph nodes, so far few have detected gastric lymph nodes in the treatment of GC. Due to the different structure of different parts of the gastric system, it is difficult to detect gastric lymph nodes, so it is necessary to use AI technology to detect gastric lymph nodes.

Application of AI in lymph node detection

Lymph nodes are mainly detected by the observation of radiologists. Although this method has high clinical value, it takes a lot of time to detect every lymph node, so it is difficult to detect every lymph node in clinical application. In addition, radiologists need continuous training to detect lymph nodes accurately. In order to improve the efficiency of imaging doctors, it is a potential direction to detect lymph nodes with the

help of computer.

In the treatment of GC, it is necessary to resect the metastasis and the lesion at the same time. The abdominal lymph node is one of the main metastasis routes of GC. It is very important for the prognosis of patients to accurately determine the resection area.

AI can learn to distinguish lymph nodes better and greatly reduce the work burden of imaging doctors. There are few reports about the use of AI technology to locate lymph nodes in GC. However, lung cancer, breast cancer, prostate cancer[24-28] and other reports are more common.

Application of AI in detection of lymph node metastasis

The medical decision-making method mainly depends on the clinical practice experience of doctors, their own medical knowledge, and various kinds of doctors. The therapeutic instrument diagnoses the patient's examination results. On the one hand, this traditional decision-making method depends on the professional level and subjective factors of doctors, which will lead to misdiagnosis, missed diagnosis, and other wrong decisions. On the other hand, modern diseases usually have the characteristics of multi-attribute, instability, complexity and time-varying, which require the information in medical diagnosis to have the characteristics of timeliness, accuracy, acceptability and traceability. With the development of computer technology and the production of a large amount of medical data, it is imperative to use computers to realize auxiliary decision-making, which has a positive role in improving the accuracy of medical diagnosis, reducing missed diagnosis and improving work efficiency.

The most common path of GC metastasis is lymph node metastasis, which is due to the abundance of lymphatic vessels and lymph nodes around the stomach[29]. In most studies, lymph node metastasis has been judged by size alone[30,31]. However, large lymph nodes may be caused by inflammation, and small lymph nodes may also have metastases. In addition, some studies have shown that lymph node metastasis is related to multiple characteristics[32-34]. However, it is difficult for doctors to make final diagnosis with multiple features at the same time, so it is necessary to introduce a clinical decision support system[35].

According to National Comprehensive Cancer Network (commonly known as NCCN) guidelines[36], preoperative evaluation of metastatic lymph nodes is considered to be an indication of neoadjuvant chemotherapy. In our opinion, surgery is still the most effective way to treat GC. Radical resection of metastatic lymph nodes is recommended by NCCN guidelines and Japanese GC guidelines as the key to the success of radical gastrectomy[36,37]. In this regard, accurate standard dissection and dissection of metastatic lymph nodes can greatly improve the 5-year survival rate of patients[38]. Until now, enhanced computer tomography (CT) has been used to judge gastric lymph node metastasis and tumor stage, which is the most reliable and commonly used method for evaluating lymph nodes in GC[39]. However, for the CT diagnosis of GC lymph nodes, the false negative and false positive of perigastric metastatic lymph nodes are inevitable technical problems[40]. Gao *et al*[41] found that, through in-depth study, faster region-based CNNs have higher judgment efficiency and recognition accuracy for CT diagnosis of perigastric metastatic lymph nodes.

Perspectives

The number of gastric lymph node dissections has been shown to be an independent predictor of the prognosis of GC by most studies. Many guidelines and studies have recognized that the minimum standard is to clear more than 15 lymph nodes during operation[42-44]. An AI system is helpful to reduce the imbalance of image source distribution, to the diagnosis and treatment of GC, and to determining the location of lymph nodes and lymph node metastasis.

AI AND ROBOTIC SURGERY

During the operation of the robotic surgery system, the doctor controls the bedside robotic arm system through the console. There are a total of three robotic arms through which the surgery is completed; the imaging system follows the robotic arm to enter the body for imaging, providing a field of vision for the doctor's surgery. Compared with traditional surgical operations, the surgical trauma performed by surgical robots is less invasive and basically minimally invasive. In recent years, with the rise of rapid rehabilitation surgery and the popularization and application of the Leonardo da Vinci robotic surgery operating system in China, many medical institutions have carried out

robotic surgery. For example, minimally invasive robotic surgery is used increasingly in interventional therapy of urinary tumors[45,46]. In the field of gastrointestinal surgery, robotic radical gastrectomy has also become one of the minimally invasive radical methods commonly used in central hospitals specializing in GC[47]. The implementation of robotic surgery emphasizes the concept of "precise surgery"[48]. Robotic surgery uses a technologically advanced platform, with the chief knife doctor sitting at the console and operating in the operating room or by remotely controlling the robot. With the increasing complexity of mechanical surgery technology, the accuracy and proficiency of robotic surgery will be increased only by developing advanced training modes[49,50].

AI in Da Vinci robotic GC surgery

Traditional laparotomy, laparoscopic surgery and robotic surgery are considered as three surgical treatments for GC. Laparoscopic surgery was first performed in 1991[51] because it caused less trauma to patients than traditional surgery, gradually replacing the former. Robotic surgery has the advantages of using wristed instruments, tremor filtering, and high-resolution 3D images over laparoscopic surgery[52], which were also reported in another article first[53].

Robot-assisted applications in minimally invasive surgery were first described in 1985, and this technology has evolved to its current state in the form of a Da Vinci surgical system (Intuitive Surgery, Sunnyvale, CA, United States)[54]. Studies have shown that prediction by deep learning systems combined with diagnosis by human pathologists has reduced the error rate by about 85%. It was demonstrated that medical professionals and machine deep learning significantly improved decision-making[55].

Machine learning (ML) is widely used in many fields, such as communication and engineering manufacturing, but rarely be used in medicine, especially in surgery[56]. The efficiency of doctors can be improved by ML. With the continuous development of medicine, efficiency is also increasingly valued by the public[57]. Before the birth of the laparoscopic technique, the surgeon's operation often brought great trauma to the patient, and it is a long process for a young doctor to accumulate experience and learn through laparotomy. Especially in some operations with high accuracy requirements, although the surgeons have undergone long professional training and repeated operations, there is also a risk of errors and the efficiency of doctors' diagnosis and treatment is a little low. However, after the birth of endoscopic technology, traditional laparotomy was gradually replaced because of its high trauma, and after learning the endoscopic surgical technology, the surgeon's clinical treatment efficiency has been greatly improved. The robotic surgery technology born after the endoscopic technology is even more so. Robotic surgery technology can greatly enhance the surgical efficiency of doctors who are lacking surgical experience and further reduce the trauma suffered by patients.

In addition to the above points, the robot can also be combined with AI in the following aspects. First of all, the level of operator can be distinguished by AI combined with robot. Fard *et al*[57] extracted eight global motion features for surgeons at novice and expert levels. The ability of AI to automatically classify experts and novice surgeons has been proved by research. Dai *et al*[58] developed and validated an integrated system to alert operators before suture breaks. The results show that this system can improve the results related to knotting tasks in robotic surgery and can reduce suture failure without reducing the quality of the resulting knots. Iranian scholars[59] used the Cox proportional hazard model and artificial neural network model to predict the survival rate of Iranian GC patients, and found that the prediction accuracy of the neural network was 83.1%, and that of the Cox regression model was 75.0%. Compared with the Cox proportional hazard regression model, the neural network model was deemed a more powerful statistical tool to predict the survival rate of GC patients.

Perspectives

Robotic surgery provides a good platform for the application of AI in surgical systems (gastrointestinal surgery). It is possible for a large number of clinical data to be evaluated and interpreted by ML methods. The rapid acquisition of surgical technology by junior doctors, the efficiency of a surgeons' operation, and the small trauma to patients are the results of the combination of ML method and robotic operation for the prognosis judgment and prediction of GC patients. However, there is a big flaw in this, which is the standardization of data.

AI affects and narrows the training growth cycle of robotic GC surgeons, reduces patient injury, changes the surgical results, and may even make GC surgery a robotic

automated surgery in the future. To be honest, it is still difficult to do this, but we firmly believe that when surgeons, GC patients, robotic engineers and AI programmers cooperate in multiple disciplines, advanced robotic AI surgery for GC will be realized.

CONCLUSION

The problem of population aging has been increasing in East Asian countries in recent years, especially in China, where the incidence of cancer has increased year by year. As a new and comprehensive subject, AI will become an important means to promote the development of the medical industry. The application of AI in GC is mainly focused on digestive endoscopy, lymph node image positioning diagnosis, and working in combination with a robotic surgery system. In terms of gastrointestinal endoscopy, AI can detect EGC earlier and faster, with higher accuracy than clinical endoscopists. For advanced GC, AI can increase the detection rate of cancers in areas where gastroscopy is performed, such as pump-door cancer, which reduces the missed diagnosis rate. In the face of GC lymph nodes, the intervention of AI not only reduces the burden of radiologists, but also increases the accuracy of lymph node localization. Just as for the location of lymph nodes, it is also of great significance for detection of lymph node metastasis with higher accuracy. It also has important potential for robotic surgery of GC. AI has further revolutionized GC surgery by training young doctors to perform robotic GC surgery, improving surgical trauma of patients and predicting patient prognosis in timely and accurate manners - precision surgery was gradually promoted by AI to improve the relevant outcomes of GC disease and surgery without affecting patient survival and safety.

In addition to gastroscopic detection of GC or precise localization of lymph nodes, as well as use of Da Vinci robotic surgery to improve the patient's intraoperative experience and prognosis, the aim is to minimize trauma suffered by patients. The development of technology is constantly being updated, and the invention of laparotomy has saved the lives of many patients with GC but also brought great trauma to these patients. After the advent of endoscopic techniques, the concept of minimally invasive surgery began to gain popularity, and laparoscopic surgery gradually replaced open surgery because of its smaller damage. However, in the development of technology and times, the limitations of its operation are also increasingly exposed.

With the arrival of the big data era, AI technology has gradually matured, and its combination with robotic surgical systems has become a research hotspot. Robotic surgery, boasting accuracy that laparoscopic surgery does not have, is an emerging surgical system for the future. Through the deep integration of this system with AI, the trauma of the patient's operation is further reduced. In the future, there may even be a fully automated robotic surgical system controlled by AI, in which case the trauma of GC surgery will be very small and can be considered noninvasive. In other words, the change that AI will bring to GC is that the surgical treatment of GC will change from greater trauma to minimally invasive, and from minimally invasive to nearly noninvasive.

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MINIREVIEWS

Artificial intelligence in gastrointestinal cancer: Recent advances and future perspectives

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Abstract

Artificial intelligence (AI) using machine or deep learning algorithms is attracting increasing attention because of its more accurate image recognition ability and prediction performance than human-aid analyses. The application of AI models to gastrointestinal (GI) clinical oncology has been investigated for the past decade. AI has the capacity to automatically detect and diagnose GI tumors with similar diagnostic accuracy to expert clinicians. AI may also predict malignant potential, such as tumor histology, metastasis, patient survival, resistance to cancer treatments and the molecular biology of tumors, through image analyses of radiological or pathological imaging data using complex deep learning models beyond human cognition. The introduction of AI-assisted diagnostic systems into clinical settings is expected in the near future. However, limitations associated with the evaluation of GI tumors by AI models have yet to be resolved. Recent studies on AI-assisted diagnostic models of gastric and colorectal cancers in the endoscopic, pathological, and radiological fields were herein reviewed. The limitations and future perspectives for the application of AI systems in clinical settings have also been discussed. With the establishment of a multidisciplinary team containing AI experts in each medical institution and prospective studies, AI-assisted medical systems will become a promising tool for GI cancer.

Key Words: Artificial intelligence; Gastric cancer; Colorectal cancer; Endoscopy; Pathology; Radiology

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Core Tip: Artificial intelligence (AI) is attracting increasing attention because of its more accurate image recognition ability and prediction performance than human-aid analyses. The application of AI models to gastrointestinal clinical oncology has been investigated, and the findings obtained indicate its capacity for automatic diagnoses with similar accuracy to expert clinicians and the prediction of malignant potential. However, limitations in the evaluation of gastrointestinal tumors by current AI models have yet to be resolved. The limitations of and future perspectives for the application of AI-assisted systems to clinical settings have been discussed herein.

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INTRODUCTION

Recent advances in diagnostic technology and treatment strategies for gastrointestinal cancer have improved clinical outcomes. Even with the development of novel imaging modalities with high accuracy and resolution, image reading, and novel biomarkers, such as the genetic screening of tumors, circulating tumor DNA, and micro RNA, the diversity and quantity of data on tumor malignant potential is beyond the limits of human interpretation[1-8]. Therefore, the establishment of more accurate diagnostic methods with high objectivity using computer-aided diagnosis systems (CAD), such as technologies involving artificial intelligence (AI), is needed in clinical settings[9-11].

AI is defined by the intelligence of machines in contrast to the natural intelligence of humans. It is generally applied when a machine mimics the cognitive functions of humans, such as learning and problem solving[12]. The concept of AI was initially advocated in 1956 by McCarthy *et al*[13], and the development of machines with the ability to think like humans with intelligence was anticipated. However, machines or computer programs that function as classifiers or detectors, such as image classification and recognition and the prediction of characteristics in populations, are currently regarded as AI.

Recent AI technologies were developed due to technical advances in machine learning and deep neural network algorithms[14-17]. Convolutional neural networks (CNN) are one of the deep neural networks that are useful for image analyses. Algorithms using CNN models have been applied to many research fields in gastrointestinal cancer, such as the automatic endoscopic detection of tumors, the automatic diagnosis of cancer in pathological specimens, and image analyses of radiological modalities[10,18]. In endoscopic research, CNN are trained using thousands of endoscopic images to detect tumors, differentiate between benign and malignant tumors, and predict tumor invasion depth[9,19-22]. In recent years, a real-time CAD endoscopic system was developed using trained CNN. In the area of pathology, deep learning has been performed using non-cancerous and cancer images to automatically identify and segment the cytoplasm, nucleus, and stromal cells. CNN and machine learning models with image analyses, such as a texture analysis, were subsequently built to identify cancerous regions or diagnose cancer[23]. In the field of radiology, a CAD system of image modalities, such as X-ray, computed tomography (CT), and magnetic resonance images (MRI), was developed using a deep learning model constructed using cancer and non-cancer images to recognize anatomy and detect and segment tumors[24]. The malignant potential of tumors has been analyzed using a radiomics approach, which aims to quantitatively assess tumor heterogeneity by an analysis of medical images through the deep or machine learning of histograms, textures, and shapes[25-27]. AI models of gastrointestinal cancer are summarized in Figure 1.

AI with strong analytical power has attracted the attention of many researchers; therefore, the number of studies on diagnostic AI systems in gastrointestinal cancer has rapidly increased in the past decade. We herein investigate recent advances and future perspectives through a review of the literature.

In this minireview, the bibliographic search was performed using the database MEDLINE (through PubMed) for identifying studies published on AI technology in

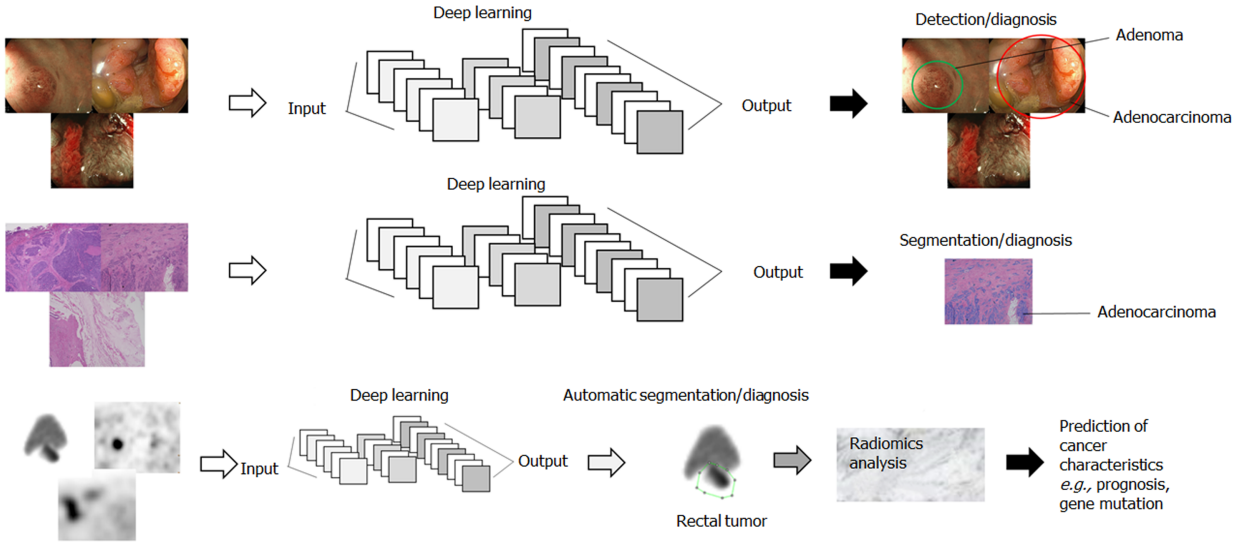

Figure 1 Clinical research using artificial intelligence in gastrointestinal cancer. Deep learning based on convolutional neural networks showing the input layer with raw data of the image, such as endoscopic, pathological, and radiological images, the hidden layer with a series of convolutions computed for each layer and the classification of the image, the prediction of malignant potentials, and the segmentation of tumor in the output layer.

the endoscopy, pathology, and radiology of gastric and colorectal cancer between 2016 and 2020. We summarized the application of AI in each area according to the extracted 49 Literatures; subsequently, the consideration about current issues and future perspectives of AI in gastrointestinal cancer was stated with some literature review.

APPLICATION OF AI TO ENDOSCOPY IN GASTROINTESTINAL CANCER

Previous studies on the endoscopic diagnosis of gastric cancer (GC) and colorectal cancer (CRC) using AI between 2016 and 2020 were summarized in Tables 1 and 2.

Gastric cancer

The purposes of the studies reviewed on AI for GC were (1) tumor detection; (2) the diagnosis of malignancy; (3) real-time detection; and (4) the prediction of tumor invasion depth. The basic method of these studies was as follows: Endoscopic images of GC, gastritis, and non-cancerous mucosae, which were diagnosed pathologically or by an expert endoscopist, were captured and CNN was subsequently trained using these images. Diagnostic and detection accuracy were then assessed using the constructed CNN models.

Yoon *et al*[28] attempted to develop CNN models with the ability to detect early GC and predict invasion depth. The areas under the curves of receiver operating characteristic curves (AUC) for early GC detection and depth prediction were 0.981 and 0.851, respectively. Moreover, the diagnostic accuracy of invasion depth was lower for undifferentiated GC than for differentiated GC[28]. Zhu *et al*[29] also trained a CNN model to predict the invasion depth of GC. The AUC, positive predictive value (PPV), and negative predictive value (NPV) of their model were 0.94, 89.6%, and 88.9%, respectively. The CNN-CAD system achieved significantly higher accuracy and specificity than a human endoscopist. Li *et al*[30] also developed CNN models for the detection of GC with high diagnostic accuracy (sensitivity: 91.1%, specificity: 90.6%, and PPV: 90.9%). Hirasawa *et al*[31] reported that CNN models exhibited difficulties distinguishing between differentiated-type intramucosal cancers with a diameter of 6 mm or less and gastritis. Ishioka *et al*[32] examined the detection accuracy of a real-time endoscopic diagnosis of GC using CNN models that they had constructed; the detection rate of GC using these models was 94.1%. CNN identified the region of GC that had been difficult to distinguish from background gastritis, even by experienced endoscopists. Luo *et al*[33] developed a gastrointestinal AI diagnostic system (GRAIDs) and compared its diagnostic accuracy with that of expert and trainee endoscopists. PPV was 0.814 for GRAIDs, 0.932 for the expert endoscopist, and 0.824 for the trainee endoscopist, while NPV was 0.978 for GRAIDs, 0.980 for the expert endoscopist, and

Table 1 Previous studies on upper endoscopy of gastric cancer using artificial intelligence

Ref.	Targets	Sample sizes	Inputs	Tasks	Analysis method	Diagnostic performance
Yoon *et al*[28]	GC (ESD/surgery)	800 cases	GC/non-GC images in close-up and distant views	Detection and invasion depth prediction	CNN	AUC: detection, 0.981; depth, 0.851
Zhu *et al*[29]	GC	993 images	GC images	Diagnosis of invasion depth	CNN	Sensitivity: 76.4%, PPV: 89.6%
Li *et al*[30]	GC and healthy	386 GC and 1702 NC images	NBI images	Diagnosis of GC	CNN	Sensitivity: 91.1%, PPV: 90.6%
Hirasawa *et al*[31]	GC	13584 training and 2296 test images	GC images	Diagnosis of GC	CNN	Sensitivity: 92.2%, PPV: 30.6%
Ishioka *et al*[32]	EGC	62 cases	Real-time images	Detection	CNN	Detection rate: 94.1%
Luo *et al*[33]	GC	1036496 images	GC images	Detection	CNN	PPV: 0.814, NPV:0.978
Horiuchi *et al*[34]	GC and gastritis	1492 GC and 1078 gastritis images	NBI images	Detection	CNN	Sensitivity: 95.4%, PPV: 82.3%

GC: Gastric cancer; CNN: Convolutional neural network; AUC: Area under the curve; PPV: Positive predictive value; NC: Non-cancer; NBI: Narrow-band image; EGC: Early gastric cancer.

Table 2 Previous studies on colonoscopy using artificial intelligence

Ref.	Targets	Sample sizes	Inputs	Tasks	Analysis method	Diagnostic performance
Akbari *et al*[35]	Screening endoscopy	300 polyp images	Polyp images	Auto segmentation of polyps	CNN	Accuracy: 0.977, Sensitivity: 74.8%
Jin *et al*[36]	Screening endoscopy	Training: 2150 polyps, test: 300 polyps	NBI images	Differentiation of adenoma and hyperplastic polyps	CNN	The model reduced the time of endoscopy and increased accuracy by novice endoscopists
Urban *et al*[37]	Screening endoscopy	8641 polyp images and 20 colonoscopy videos	Polyp images	Detection of polyps	CNN	AUC: 0.991, Accuracy: 96.4%
Yamada *et al*[38]	Screening endoscopy	4840 images, 77 colonoscopy videos	Real-time images	Differentiation of the early signs of CRC	CNN	Sensitivity: 97.3%, Specificity: 99.0%

CNN: Convolutional neural network; NBI: Narrow-band image; AUC: Area under the curve.

0.904 for the trainee endoscopist. These findings demonstrated that the diagnostic accuracy of GRAIDs for the detection of GC was similar to that of the expert endoscopist and superior to that of the trainee endoscopist. CNN models of narrow-band imaging (NBI) for GC have been reported, with sensitivity and PPV of 91.1-95.4% and 82.3-90.6%, respectively[34].

Colorectal cancer

The purposes of the studies reviewed on AI for CRC were (1) the segmentation and detection of polyps; and (2) the diagnosis of polyp pathology. In the development of efficient automatic diagnostic models, models need to automatically segment polyps and extract their features. Akbari *et al*[35] attempted to construct CNN models of colonoscopy for automatic segmentation and feature extraction. The accuracy, specificity, and sensitivity of the model for automatic segmentation were 0.977, 0.993, and 0.758, respectively. An ideal CAD system of colonoscopy needs to have the ability to predict the pathological diagnosis of an automatically detected tumor and subsequently recommend appropriate treatment strategies for lesions. Jin *et al*[36] reported a CNN model for predicting the pathological diagnosis of small lesions (≤ 5 mm) using NBI data from colonoscopy. The accuracy, sensitivity, specificity, PPV, and NPV of their model for predicting the pathological diagnosis of polyps, adenoma *vs* hyperplasia were 86.7%, 83.3%, 91.7%, 93.8%, and 78.6%, respectively. On the other hand, the accuracies of polyp diagnoses by novices, experts, and NBI-trained expert endoscopists were 73.8%, 83.8%, and 87.6%, respectively. Using CNN-processed

results, overall accuracy by novice endoscopists significantly increased to 85.6%. A real-time diagnostic system in colonoscopy was developed using CNN models. Urban *et al*[37] constructed CNN models to identify polyps, which were subsequently adapted to colonoscopy videos, and these models exhibited the ability to detect either type of polyp equally well and identify polyps with an ROC value of 0.991 and accuracy of 96.4%. Yamada *et al*[38] applied their CNN model, which was developed to detect early signs of CRC, to colonoscopic videos. The sensitivity and specificity of their AI system for detecting the regions of CRC were 97.3% and 99.0%, respectively, while the sensitivity and specificity of endoscopists were 87.4% and 96.4%; respectively. Therefore, the AI system may be used to alert endoscopists in real-time to overlooked abnormalities, such as non-polypoid polyps, during colonoscopy, thereby increasing the early detection of this disease.

APPLICATIONS OF AI TO THE PATHOLOGICAL DIAGNOSIS OF GASTROINTESTINAL CANCER

Previous studies on the pathological diagnosis of GC and CRC using AI between 2016 and 2020 are summarized in Tables 3 and 4. An automatic pathological diagnosis of gastrointestinal cancer generally involves the following processes: (1) Automatic segmentation: Distinguishing various structures, such as the cytoplasm, nuclei, and stoma, and the recognition of atypia; (2) The diagnosis and grading of carcinoma; (3) The diagnosis of malignant potential, such as invasion depth and lymphovascular invasion; and (4) The prediction of survival. Therefore, previous studies aimed to develop a CAD system with the ability to perform these processes.

Gastric cancer

Qu *at al*[39] attempted to develop CNN models for (1) and (2), proposed a novel stepwise fine-tuning-based deep learning scheme for gastric pathology image classification, and established a novel protocol to further boost the performance of state-of-the-art deep neural networks and overcome the insufficiency of well-annotated data. In their proposed two-stage method, CNN was initially trained using tissue-wise data on the background, epithelium, and stoma as well as cell-wise data on nuclei and the cytoplasm, and was then tuned using well-annotated data from benign or malignant data sets. The diagnostic accuracy of their constructed two-stage CNN models was higher than that of one-stage models. Yoshida *et al*[40] attempted to develop CNN models for (1) and (2) with the ability to automatically segment malignant regions in full-slide images of biopsy samples and subsequently diagnose histological classifications through a nuclear analysis at high magnification. In negative biopsy specimens, the concordance rate between their AI system and expert pathologists was 90.6%; however, the concordance rate for positive biopsy specimens was less than 50%. Mori *et al*[41] trained CNN models for (3) to discriminate the tumor invasion depth of gastric signet-ring cell carcinoma. Their models exhibited the ability to diagnose intramucosal or advanced histological characteristics with an accuracy of 85%, sensitivity of 90%, specificity of 81%, and AUC of 0.91. The prediction of survival in GC patients using the deep learning method has also been examined. Jiang *et al*[42] investigated the efficacy of deep learning models for (4) using a support vector machine (SVM). They classified GC patients into two groups using SVM based on patient characteristics and immunohistochemistry (IHC) data on the following immunomarkers: CD3, CD8, CD45RO, CD45RA, CD57, CD68, CD66b, and CD34. The findings obtained revealed that the classifier of SVM was a stronger prognostic factor than the TNM stage or CA19-9.

Colorectal cancer

Numerous studies on the pathology of CRC using AI were reported compared to GC, are classified as follows.

Studies on AI models for automatic segmentation: Van Eycke *et al*[43] and Graham *et al*[44] developed CNN models to segment the glandular epithelium. The F1 values of these models ranged between 0.9 and 0.912. Abdelsamea *et al*[45] developed tumor parcellation and quantification (TuPaQ), which is a tool for refining biomarker analyses through the rapid and automated segmentation of the tumor epithelium. Tissue microarray (TMA) cores from CRC were manually annotated and analyzed to provide the ground truth, epithelial or non-epithelial tissue. CNN (TuPaQ) was trained using these data. The accuracy, sensitivity, and specificity of TuPaQ were

Table 3 Previous studies on the pathology of gastric cancer using artificial intelligence

Ref.	Targets	Sample size	Input	Task	Analysis method	Diagnostic performance
Qu *et al*[39]	GC	15000 images	Pathological images	Evaluation of stepwise methods	CNN	AUC: 0828-0.920
Yoshida *et al*[40]	GC	3062 biopsy samples	Pathological images stained by H&E	Automatic segmentation, diagnosis of carcinoma	CNN	Sensitivity: 89.5%, specificity: 50.7%
Mori *et al*[41]	GC (surgery)	516 images from 10 GC cases	Pathological images stained by H&E	Diagnosis of invasion depth in signet cell carcinoma	CNN	Sensitivity: 90%, Specificity: 81%
Jiang *et al*[42]	GC (surgery)	786 cases	IHC (CD3, CD8, CD45RO, CD45RA, CD57, CD68, CD66b, and CD34)	Prediction of survival	SVM	The immunomarker SVM was useful for predicting survival

GC: Gastric cancer; AUC: Area under the curve; H&E: Hematoxylin eosin staining; CNN: Convolutional neural network; IHC: Immunohistochemistry; SVM: Support vector machine.

0.939, 0.779, and 0.946, respectively. Yan *et al*[46] examined the diagnostic accuracy of their AI models for the classification, segmentation, and visualization of large-scale tissue histopathology images. The accuracies of their models ranged between 81.3 and 93.2%. Haj-Hassan *et al*[47] attempted to develop CNN models for the automatic segmentation of benign hyperplasia, intra-epithelial neoplasms, and carcinoma, and the findings obtained showed that the models segmented tumors with a high accuracy of 99.1%.

Diagnosis and grading of carcinoma: Rathore *et al*[48] reported deep learning models for cancer detection and grading. The features of CRC biopsy samples were extracted based on pink-colored connecting tissues, purple-colored nuclei, and white-colored epithelial cells and lumina. The extracted features, particularly white-colored epithelial cells and lumina, were classified using SVM and classification performance was subsequently assessed. The accuracies of cancer detection and grading by their model were 95.4 and 93.4%, respectively. Yang *et al*[49] proposed a combination of SVM and color histograms to classify pathological images. The AUC of the model for diagnosing carcinoma was 0.891. Chaddad *et al*[50] reported that the classification of images using a texture analysis effectively diagnosed carcinoma (accuracy: 98.9%). Yoshida *et al*[51] showed that a CAD system using a previously described CNN model for GC was useful for diagnosing adenoma and carcinoma (undetected rate of carcinoma and adenoma: 0-9.3% and 0-9.9%, respectively).

Diagnosis of malignant potential: Takamatsu *et al*[52] reported the prediction of lymph node metastasis using a machine learning analysis of morphological parameters (such as shape and roundness) in cytokeratin-stained T1 CRC images. The AUC of the model was 0.94. The automatic evaluation of tumor budding in IHC with CNN and machine learning was previously performed[53]. Models were constructed to assess tumor budding using TMA on pan-cytokeratin-stained tumors, and the R^2 value of the correlation of the models with manual counting for the diagnosis of tumor budding was 0.86.

Prediction of survival: Bychkov *et al*[54] proposed AI models for the automatic prediction of survival in CRC patients using the TMA of CRC pathological images. The automatic detection of tumors was initially achieved using CNN; CNN cases were subsequently classified by a recurrent neural network. Predicted survival by their model correlated with actual clinical outcomes. Kather *et al*[55] reported automatic models for discriminating structures in tissue samples and then predicting survival. Their models predicted the survival of CRC more accurately than the TNM stage or manual evaluations of cancer-associated fibroblasts. Moreover, survival prediction SVM models using immunomarkers evaluated by IHC, such as CD3 and CD8, have been developed[56], and the classifier correlated with patient survival.

Table 4 Previous studies on the pathology of colorectal cancer using artificial intelligence

Ref.	Targets	Sample size	Input	Task	Analysis method	Diagnostic performance
Van Eycke *et al*[43]	CRC		H&E staining, IHC image	Segmentation of the glandular epithelium	TMA, CNN	F1 value: 0,912
Graham *et al*[44]	CRC		H&E staining	Differentiation of intratumor glands	CNN	F1 values: 0.90
Abdelsamea *et al*[45]	CRC	333 samples	H&E staining, IHC (CD3)	Differentiation of the tumor epithelium	TMA, CNN	Accuracy: 0.93-0.94
Yan *et al*[46]	CRC		H&E staining	Tumor classification,segmentation of tumors,	CNN	Accuracy: Classification, 97.8%; segmentation, 84%
Haj-Hassan *et al*[47]	CRC		Multispectral images	Segmentation of carcinoma	CNN	Accuracy: 99.1%
Rathore *et al*[48]	CRC	Biopsy samples	H&E staining	Detection and grading of tumors	Texture and morphology patterns, SVM	Recognition rate: Detection, 95.4%; grading; 93.4%
Yang *et al*[49]	CRC	180 samples	H&E staining	Diagnosis of benign tumors, neoplasms, and carcinoma	SVM, histogram, texture	AUC: 0.852
Chaddad *et al*[50]	CRC	30 cases	H&E staining	Diagnosis of carcinoma, adenoma, and benign tumors	Automatic segmentation, texture	Accuracy: 98.9%
Yoshida *et al*[51]	CRC	1328 samples	H&E staining	Diagnosis of benign tumors, neoplasms, and carcinoma	CNN, automatic analysis of structure	Undetected rate of carcinoma and adenoma: 0-9.3% and 0-9.9%, respectively
Takamatsu *et al*[52]	CRC surgery	397 samples	H&E staining	Prediction of lymph node metastasis	LR, shape analysis	AUC: 0.94
Weis *et al*[53]	CRC	596 cases	IHC (AE1/AE3)	Automatic evaluation of tumor budding	TMA, CNN	Correlation; R2 value: 0.86
Bychkov *et al*[54]	CRC surgery	420 cases	H&E staining	Prediction of survival	TMA, CNN	Good biomarker for predicting survival
Kather *et al*[55]	CRC	973 slides	H&E staining	Prediction of survival	Stromal pattern, CNN	Good biomarker for predicting survival
Reichling *et al*[56]	CRC surgery	1018 cases	HE, IHC (CD3, CD8)	Prediction of survival	RF, monogram	Good biomarker for predicting survival

CRC: Colorectal cancer; H&E: Hematoxylin eosin staining; IHC: Immunohistochemistry; TMA: Tissue microarray; CNN: Convolutional neural network; SVM: Support vector machine; AUC: Area under the curve; LR: Linear regression.

APPLICATIONS OF AI TO A RADIOLOGICAL DIAGNOSIS OF GASTROINTESTINAL CANCER

Previous studies on the radiological diagnosis of GC and CRC using AI between 2016 and 2020 were summarized in Tables 5 and 6.

Gastric cancer

Regarding GC, many researchers have attempted to develop AI models using (1) a radiomics approach; or (2) CNN models predicted malignant potential, such as survival, lymph node metastasis, and post-operative recurrence, through analyses of the radiological image features of GC.

Radiomics approach: Li *et al*[57] developed a survival prediction model involving a general radiomics analysis of CT. The region of interest was manually drawn along the margin of the tumor on CT images, and radiological features were extracted. After manual image segmentation, the heterogeneity of the extracted feature was quantified using an image analysis, such as texture and histogram analyses. Analyzed cases were then classified based on the risk score (R-signature) evaluated using the least absolute shrinkage and selection operator method. The performance of a radiomics nomogram, including factors correlating with survival, was then evaluated. The findings obtained showed that the R-signature correlated with the survival of GC patients. Furthermore, the prediction of survival by the radiomics monogram including the R-signature was

Table 5 Previous studies on the radiological diagnosis of gastric cancer using radiomics or artificial intelligence

Ref.	Targets	Sample size	Input	Task	Analysis method	Diagnostic performance
Li *et al*[57]	GC, radical surgery	181 cases	Primary tumor, preoperative CT	Prediction of survival	Manual segmentation, radiomics, Nomograms	The TNM stage and radiomics signature were good biomarkers
Zhang *et al*[58]	GC, radical surgery	669 cases	Primary tumor, preoperative CT	Predication of early recurrence	Manual segmentation, radiomics, Nomograms	AUC: 0.806-0.831
Li *et al*[59]	GC, radical surgery	204 cases	Primary tumor, pre-operative dual-energy CT	Pre-operative diagnosis of LNM	Manual segmentation, radiomics, Nomogram	AUC; 0.82--.84
Li *et al*[60]	GC, radical surgery	554 cases	Primary tumor, preoperative CT	Prediction of a pathological status, survival	Semi-automatic segmentation, radiomics	AUC for prediction of the pathological status: 0.77, the TNM stage and radiomics signature were good biomarkers
Wang *et al*[61]	GC, radical surgery	187 cases	Primary tumor, preoperative dynamic CT	Pre-operative prediction of intestinal-type GC	Manual segmentation, radiomics, Nomograms	AUC: 0.904
Jiang *et al*[62]	GC, surgery	214 cases	Primary tumor, preoperative PET-CT	Prediction of survival	Manual segmentation, radiomics, Nomograms	C-index: DFS, 0.800; OS, 0.786
Chen *et al*[63]	GC, surgery	146 cases	Primary tumor, preoperative MRI	Pre-operative diagnosis of lymph node metastasis	Manual segmentation, radiomics analysis	AUC: 0.878
Gao *et al*[64]	GC, surgery	627 cases, 17340 images	Lymph nodes, preoperative CT	Pre-operative diagnosis of lymph node metastasis	Manual segmentation, deep learning	AUC: 0.9541.
Huang *et al*[65]	GC, surgery		Primary tumor, preoperative CT	Pre-operative diagnosis of peritoneal metastasis	Manual segmentation, CNN	Ongoing, retrospective cross-sectional study

GC: Gastric cancer; CT: Computed tomography; AUC: Area under the curve; LNM: Lymph node metastasis; DFS: Disease-free survival; MRI: Magnetic resonance imaging; CNN: Convolutional neural network.

more accurate than that by normal nomograms (T and N stages and differentiation). Previous studies investigated the prediction of malignant potential using a radiomics approach. Zhang *et al*[58] evaluated the diagnostic accuracy of CT radiomics models for predicting post-operative recurrence in GC patients, and the AUC of the models were 0.806-0.831. Li *et al*[59] reported CT radiomics models for predicting lymph node metastasis, with an AUC of 0.82-0.84. Li *et al*[60] also developed CT radiomic models with the ability to predict the pathological status and survival with high accuracy. Wang *et al*[61] analyzed primary tumors on CT images of the arterial phase, portal phase, and delay phase for the discrimination of intestinal-type GC by a radiomics approach. The AUC of their model was 0.904. Jiang *et al*[62] described a radiomics model of PET-CT for predicting survival. The C-indexes of this model for overall survival and disease-free survival were 0.786 and 0.800, respectively. A radiomics analysis of MRI for GC has also been conducted. Chen *et al*[63] examined the heterogeneity of primary tumors on MRI using a radiomics approach, and showed that the model was useful for predicting the N stage.

CNN model: Gao *et al*[64] developed a CNN model of CT for predicting lymph node metastasis. Radiologists initially labeled upper abdominal-enhanced CT images of metastatic lymph nodes. CNN models were then constructed using the labeled image data, and the AUC of the model was 0.954. Huang *et al*[65] described a protocol for predicting peritoneal metastasis using CNN models, and this research is ongoing.

Colorectal cancer

Treatment strategies for lower rectal cancer (LRC) have recently been attracting increasing attention because of the difficulties associated with achieving curative treatment. Therefore, many researchers have targeted LRC patients for the development of AI models for radiological diagnoses. The aims of a recent AI study on CRC were (1) the automatic detection or segmentation of primary tumors; (2) the

Table 6 Previous studies on the radiological diagnosis of colorectal cancer using radiomics or artificial intelligence

Ref.	Targets	Sample size	Input	Task	Analysis method	Diagnostic performance
Trebeschi *et al*[66]	LRC	140 cases	Primary tumor, MRI	Automatic detection, segmentation	CNN	DSC: 0.68-0.70, AUC: 0.99
Wang *et al*[67]	LRC	568 cases	Primary tumor, MRI	Automatic segmentation	CNN	DSC: 0.82
Wang *et al*[68]	LRC	93 cases	Primary tumor, MRI	Automatic segmentation	Deep learning	DSC: 0.74
Men *et al*[69]	LRC	278 cases	Primary tumor, CT	Automatic segmentation	CNN	DSC: 0.87
Shayesteh *et al*[70]	LRC, NCRT followed by surgery	98 cases	Primary tumor, pre-treatment MRI	Prediction of CRT responses	Manual segmentation, radiomics, machine learning	AUC: 0.90
Shi *et al*[71]	LRC, NCRT followed by surgery	45 cases	Primary tumor, pre-treatment MRI, mid-radiation MRI	Prediction of CRT responses	Manual segmentation, CNN	AUC: CR, 0.83; good response, 0.93
Ferrari *et al*[72]	LRC, NCRT followed by surgery	55 cases	Primary tumor, MRI before, during and after CRT	Prediction of CRT responses	Manual segmentation, radiomics, RF	AUC: CR: 0.86, non-response: 0.83
Bibault *et al*[73]	LRC, NCRT followed by surgery	95 cases	Primary tumor, pre-operative CT	Prediction of CRT responses	Manual segmentation, radiomics, CNN	80% accuracy
Dercle *et al*[74]	CRC, FOLFILI with/without cetuximab	667 cases	Metastatic tumor, CT	Prediction of tumor sensitivity to chemotherapy	Manual segmentation, radiomics, machine learning	AUC: 0.72-0.80
Ding *et al*[75]	LRC, radical surgery	414 cases	Lymph nodes, pre-operative MRI	Pre-operative diagnosis of lymph node metastasis	Manual segmentation, CNN	AI system > radiologist
Taguchi *et al*[76]	CRC	40 cases	Primary tumor, CT	Prediction of the KRAS status	Manual segmentation, radiomics	AUC: 0.82

LRC: Lower rectal cancer; MRI: Magnetic resonance imaging; CNN: Convolutional neural network; DSC: Dice similarity coefficient; AUC: Area under the curve; NCRT: Neoadjuvant chemoradiotherapy; CR: Complete response; RF: Random forest; CT: Computed tomography; CRC: Colorectal cancer.

prediction of treatment responses; and (3) the prediction of malignant potential.

Automatic detection or segmentation of primary tumors: Trebeschi *et al*[66] reported a CNN model for the automatic segmentation of primary tumors on MRI. CNN models were trained using T2-weighted images (T2WI) and diffusion-weighted images with primary tumor labeling by expert radiologists. The CNN model showed high segmentation accuracy, with a dice similarity coefficient (DSC) of 0.68-0.70. The AUC of the resulting probability maps was 0.99. Two CNN models were also developed for the automatic segmentation of primary tumors on T2WIs, with DSC of 0.82 and 0.74, respectively[67,68]. Men *et al*[69] attempted to develop CNN models for automatic segmentation on CT images with an application to the delineation of the clinical target volume (CTV) and surrounding organs for radiotherapy. The mean DSC values of the models were 87.7% for the CTV, 93.4% for the bladder, 92.1% for the left femoral head, 92.3% for the right femoral head, 65.3% for the intestines, and 61.8% for the colon.

Prediction of treatment responses: Shayesteh *et al*[70] reported radiomics models predicting treatment responses to neo-adjuvant chemoradiotherapy. Primary tumors on MRI T2WI were manually segmented and an image analysis of the data, shape, texture as well as a histogram analysis were performed. The relationship between the pathological features and treatment responses to CRT was assessed by a machine learning approach, which revealed that the AUC and accuracy of the model were 95 and 90%, respectively. Shi *et al*[71] and Ferrari *et al*[72] also described the efficacy of radiomics models for predicting CRT responses using pre-treatment, mid-radiation, post-treatment MRI (AUC for predicting a complete response (CR): 0.83 and 0.86, respectively). Bibault *et al*[73] compared the diagnostic accuracy of several models, Cox's regression, CNN, and SVM for predicting CR in pre-operative CRT using CT data. CNN exhibited the ability to predict CR with the highest accuracy (80%). A radiomics model for predicting chemotherapeutic responses has also been reported. Dercle *et al*[74] demonstrated that their radiomic model using CT images successfully predicted sensitivity to anti-EGFR therapy (AUC: 0.80).

Prediction of malignant potential: Ding *et al*[75] developed AI models to predict lymphatic node metastasis using pre-operative MRI. CNN models were constructed using MRI lymph node images manually labeled by radiologists. They compared the diagnostic accuracy of CNN and a radiologist for predicting lymph node metastasis. As a result, CNN was more accurate than radiologists in identifying pelvic metastatic lymph nodes. A model for predicting gene profiles was also reported. These research methods are generally called radiogenomics. Taguchi *et al*[76] showed that a machine learning model using a texture analysis of CT images and SUV values of PET-CT predicted KRAS mutations with high accuracy (AUC: 0.82).

CURRENT ISSUES AND FUTURE PERSPECTIVES

AI research for endoscopy

The majority of studies previously reported that a CAD system using AI for endoscopy had the ability to diagnose gastrointestinal tumors with high accuracy; however, there were many limitations. Researchers were more likely to use high-quality endoscopic images to construct AI models, which cannot always be acquired in clinical settings[9]. Furthermore, outcome indicators for clinical applications have not yet been defined. Therefore, parameters to assess the functional performance of AI models need to be established[19]. In addition, the majority of studies have been retrospective in nature using still images from non-clinical settings. These conditions do not mimic real-time clinical settings, in which endoscopists often encounter difficult-to-analyze images in daily practice. Moreover, it currently remains unclear whether AI models will enhance medical performance, reduce medical costs, and increase the satisfaction of patients and medical staff in clinical settings. Another limitation is that many clinicians and clinical researchers do not have sufficient knowledge to understand AI systems; therefore, non-AI experts as well as medical journal reviewers may encounter difficulties when assessing research on AI and its applications. Furthermore, the number of medical staff with the skill to educate physicians on AI is very limited[19].

Nevertheless, once these limitations are resolved, CAD systems using AI will markedly improve diagnostic quality in endoscopic examinations. CAD systems for endoscopy are expected to serve as a second observer during real-time endoscopy, facilitating the detection of more neoplasms by endoscopists. Some CAD systems may also provide "optical biopsies" to differentiate the types of colon polyps[9]. Therefore, CAD systems have a promising future in the effective training of junior endoscopists as assistant observers.

AI research for pathology

Previous studies reported that AI models distinguish structures in tissues and detect cancerous regions with high accuracy. Furthermore, survival may be predicted using image analyses by AI. However, there are also a number of limitations in research. AI models are educated using pathological images of cancer tissue labeled by pathologists. However, interobserver disagreement in pathological diagnoses commonly occurs between pathologists[77,78]. Therefore, the quality of teaching data varied in each study. Furthermore, the majority of AI models were constructed using a small cohort. It might be possibility non-reproducible laboratory-specific machine learning methods. In addition, the clinical use of AI models requires a digital slide scanner, image storage, maintenance contracts, image analysis software, and IT support systems, which may be expensive in clinical settings. Moreover, many pathologists and technicians do not have sufficient knowledge to understand AI systems. Therefore, the recruitment of AI experts to introduce AI systems into clinical settings is needed for education and the adjustment of systems to different clinical settings.

Despite these limitations, whole-slide scanning using AI models, such as the TMA method, is advantageous for pathologists and clinicians. This method may be a second observer in the prevention of false diagnoses by pathologists and the teaching of trainees. Furthermore, the heterogeneities of cancer tissue cannot be precisely evaluated by the human eyes of pathologists. Therefore, the assessment of cancer tissue using AI models is a novel research method beyond human cognition that is expected to predict proteomics, genomics, and the molecular signaling pathways of tumors as precision medicine by cancer genome sequencing.

AI research for radiology

Previous studies reported the efficacy of automatic segmentation or diagnosis in solid malignant tumors[77-79]. However, difficulties are associated with automatic segmentation by AI models in the field of gastrointestinal cancer because of large individual differences in imaging features of the gastrointestinal tract, except for the rectum. The radiomics approach represents an attractive method for detecting malignant potential and imaging biomarkers for precision medicine through image analyses of intratumor heterogeneity. However, a number of limitations need to be considered. The manual or semi-automatic segmentation of tumors is generally needed in the radiomics approach. Interobserver variability in manual segmentation often occurs in this process, resulting in the poor reproducibility of data by the radiomics model. Furthermore, previous studies demonstrated that radiomic features may be affected by a number of parameters, such as the scanning equipment[80], image pre-processing[81], acquisition protocols[82,83], image reconstruction algorithms[84,85], and delineation. In addition, although researchers of radiology or AI experts are knowledgeable about radiomics and AI models, they often cannot target the clinical task that needs to be improved for clinicians or patients in clinical settings. However, clinicians are not sufficiently aware of AI, and few reviewers of scientific literature on clinical medicine often are developing AI models or are able to judge research involving AI. Therefore, a multidisciplinary team needs to be introduced into research and medical teams to promote AI-supported medicine.

Despite these limitations, radiomic models for the image diagnosis or prediction of malignancy have the potential to support clinical teams for more accurate and rapid diagnoses. These models may increase patient satisfaction levels for homogenized diagnostic accuracy. Moreover, radiogenomics may have a major impact on precision medicine. Non-invasive assessments of the entire tumor tissue may be possible, without having to rely on a single biopsy to represent all cancer lesions within a patient. As further information becomes available on these imaging markers, the characteristics of cancers will be elucidated in more detail. Therefore, the radiomics approach will enhance the treatment effects of molecular biological approaches for oncological precision medicine.

DISCUSSION

AI will be an important component of diagnostic methods to diagnosis patient disease, determine most appropriate treatments, and predict prognosis and drug resistance. A lot of research methods have been developed with the aims and found to have varying levels of performance. For clinical use of disease diagnosis, AI seems valuable for use in endoscopy, where it could increase detection of benign polyp and malignant tumor. Meanwhile, AI may be useful to analysis intratumor heterogeneity of radiological and pathological images in order to predict malignant potentials, such as the prognosis of patients and therapeutic effects. Our minireview covered only articles listed in MEDLINE, and might have missed some literatures in medical image analysis journals and computer science. Despite of the limitation, AI has become an important part of clinical cancer research in recent years.

There is no turning back for the development of AI in gastrointestinal cancer, and future implications are large. However, some limitations that require caution should be recognized. Most studies were performed using low-quality datasets from pre-clinical studies. Furthermore, AL algorithms are often considered to be black-box models. The difficulty in understanding the process of AI decision may prevent physicians from finding the potential confounding factors. Ethical challenge is one of the problems to be considered. In the present AI system, AI is not aware of the human preferences or legal liabilities. Therefore, medical staff will have to make decisions for patients according to their preferences, environment, and ethics. AI will not completely replace doctors, and computer technology and medical staff will always have to work together. However, the diagnostic accuracy of AI systems has markedly increased and may detect novel biomarkers that cannot be identified by the human eye or in human-aid analyses. AI systems will be introduced into general hospitals in the near future under the management of multidisciplinary teams consisting of medical staff and AI experts.

CONCLUSION

We reviewed the recent published literatures on AI in gastrointestinal cancer, suggesting that AI may be used to accurately diagnose clinical images, identify new therapeutic targets, and process clinical data from large patient datasets. Although the physicians must recognize the limitations of AI diagnostic system, AI-assisted medical systems will become a promising tool for gastrointestinal cancer.

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