Review

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# Artificial intelligence in theranostics of gastric cancer, a review

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**Abstract:** Gastric cancer (GC) is one of the commonest cancers with high morbidity and mortality in the world. How to realize precise diagnosis and therapy of GC owns great clinical requirement. In recent years, artificial intelligence (AI) has been actively explored to apply to early diagnosis and treatment and prognosis of gastric carcinoma. Herein, we review recent advance of AI in early screening, diagnosis, therapy and prognosis of stomach carcinoma. Especially AI combined with breath screening early GC system improved 97.4 % of early GC diagnosis ratio, AI model on stomach cancer diagnosis system of saliva biomarkers obtained an overall accuracy of 97.18 %, specificity of 97.44 %, and sensitivity of 96.88 %. We also discuss concept, issues, approaches and challenges of AI applied in stomach cancer. This review provides a comprehensive view and roadmap for readers working in this field, with the aim of pushing application of AI in theranostics of stomach cancer to increase the early discovery ratio and curative ratio of GC patients.

**Keywords:** artificial intelligence; diagnosis; gastric cancer; prognosis; screening; therapy.

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## Introduction

Up to date, Gastric cancer (GC) is the fourth commonest carcinoma and the third primary cause of cancer associated deaths in the world [1]. As the rapid expansion of precise medicine, the mortality of stomach carcinoma has begun to decrease in some countries. However, so far China is still one of the top five countries with high morbidity and mortality of GC [2]. GC is closely associated with those factors such as lifestyle, heredity and environment [3]. GC is divided into two stages: (1) EGC: Early Gastric Cancer; (2) AGC: Advanced Gastric Cancer. In hospital, endoscopy and pathological biopsy are general means for diagnosis of EGC and AGC [4]. Up to date, discovery rate of EGC in China is still less than 15 % due to vague symptoms of EGC [5]. The patients with AGC have 24 % five-year survival rate, whereas the patients with EGC have more than 90 % [6]. To screen out EGC patients owns huge clinical requirement.

In order to solve problem of detection of EGC, prewarning and early diagnosis system of GC has been being developed since 1999 [7]. Gene expression profile chip was used to screen out differently expressed genes associated with EGC, AGC and normal gastric tissues respectively, and GC prewarning gene chips with primary diagnosis standard was developed, GC pre-warning database and information analysis platform was established [8].

GC prewarning and early theranostics system based on biomarkes was also studied [9]. Some GC biomarkers associated with prewarning, diagnosis and staging of GC were screened and identified [10–14]. For example, two novel plasma microRNA biomarkers such as miR-16-5p and miR-19b-3p were identified to be capable of distinguishing GC patients with different tumor node metastasis (TNM) stages and differentiation grades [10]. Four key GC circulating exosomal microRNAs such as hsa-miR-130b-3p, hsa-miR-151a-3p, hsa-miR-15b-3p and hsa-miR-1246 were identified [11], a suspension array with aggregation-induced emission luminogen barcodes microspheres was developed, and was successfully used for multiplex detection of GC microRNAs [12, 13].

Fourteen of volatile organic compound (VOC) breath biomarkers were screened out to distinguish EGC and AGC patients from healthy persons, a graphene oxide-gold

nanoparticles-based sensor was prepared to detect these VOC biomarkers. This method was successfully used to detect 200 breath samples from clinical patients with a sensitivity of 83 % and a specificity of 92 % [14].

Ten kinds of amino acids in human saliva were screened out as metabolic biomarkers to differentiate EGC and AGC patients from healthy people [15]. Then, the ultrasensitive sensors based on graphene oxide nanoscrolls wrapped with gold nanoparticles were fabricated to measure amino acid biomarkers in saliva, which successfully distinguished EGC and AGC patients from healthy population by using 220 clinical saliva samples with excellent performance (specificity>87.7 % and sensitivity>80 %) [15, 16]. The salivary detection method based on the surface enhanced raman scattering (SERS) sensors will revolutionize the technique of screening EGC and AGC patients from population.

As rapid development of molecular imaging, multi-functional nanoprobes used for theranostics of GC were developed, realizing simultaneous imaging and treatment of GC [17–25]. Magnetic nanoparticles-labeled lateral flow test chips and quantitative devices were developed [26–28], and a series of biosensors and microfluidic chip were developed for fast ultrasensitive detection of GC biomarkers [26, 29–34], including carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), *Helicobacter pylori* CagA protein (H.P.), P53 oncoprotein (P53), pepsinogen I and II (PG I, PG-II), HAI-178, GC circulation cancer cells (CTC) [35, 36].

Up to date, GC therapeutic methods mainly include surgery, radiation and chemotherapies, which are generally very effective for early and *in situ* GC, but advanced and metastatic cases do not produce effective respond to chemotherapy or radiation therapy [37]. Resistance to chemotherapy-induced apoptosis is one main factor for the failure of conventional therapies. The current prognosis of GC patients is very poor with 5-year survivals of less than 24 % [38]. Therefore, how to recognize, track or kill EGC cells is still a great challenge.

GC is not very sensitive to traditional treatment such as chemotherapy, and radiation therapy, which may be closely associated with many intrinsic or acquired properties of gastric cancer stem cells (CSCs) [39, 40]. GC stem cells can result in GC and are main cause for invasion, metastasis, and resistance to conventional therapies [41]. Therefore, GCSC-based targeted therapy is one innovative effective therapeutic direction, multifunctional nanoprobes for targeted imaging and therapy of GCSCs were developed [42].

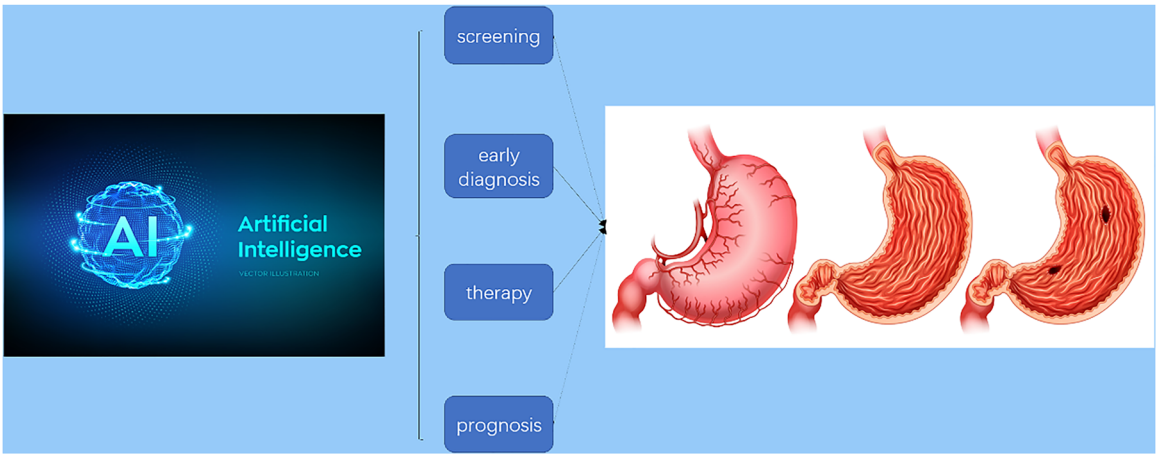
The factors for recurrence and metastasis of GC are summarized as follows [43]: (I) The intrinsic antigenicity weakness of tumor cells, immunological surveillance of the host cannot identify and eliminate the malignant cells that are distributed out of the resection field and the peripheral lymphoid organs. (II) Immunological surveillance defect or dysfunction of the host. (III) Most tumor therapeutic drugs own serious toxicities, may cause extreme weak immunity of the patients. Therefore, it is very necessary to develop new therapeutic strategies that could enhance the host immunosurveilliance and/or improve immunogenicity of the tumor cells. We also developed GC antigens fused vaccine and achieve better therapeutic efficacy [44].

Artificial intelligence (AI) means the ability of a machine to learn and display intelligence [45]. Machine learning (ML) is an implementation method of AI, is also the core of AI, and is the study of learning algorithms. Common ML algorithms include supervised learning, unsupervised learning, semi-supervised learning, reinforcement learning, deep learning (DL), transfer learning, etc. [46]. For example, DL, which is an innovative method of ML, is capable of keeping machines to analyze various training images and use backpropagation algorithms to extract specific image features [47]. This approach is inspired by the biological neural network of the human brain, and uses a layered structure of algorithms called multi-layered artificial neural networks. In addition, just like our brains, DL models can use logic to analyze data, recognize patterns, draw conclusions, and make decisions [48].

In the past decade, AI has been widely explored to apply for medical engineering [48, 49], which is displayed as the increasing number of medical devices with embedded AI algorithms on the market, and the increasing number of AI papers published in journals.

AI has three obvious technology advantages. Firstly, AI is easy to optimize and can perform cost-effective and flexible nonlinear modeling of large data sets. Secondly, these models can make knowledge dissemination easier by providing explanations. For example, using rule extraction or sensitivity analysis [49]. Thirdly, unlike machines, the performance of the human brain may be affected by fatigue, stress, or limited experience. AI technology will make up for the limited capabilities of humans, prevent human error, give machines some reliable autonomy, and improve work productivity and efficiency.

There are different types of AI computer systems to achieve different functions in cancer management. The two main categories of AI systems are computer-aided detection (CADe) for lesion detection and computer-aided diagnosis (CADx) for optical biopsy and lesion characterization. Other AI systems provide treatment assistance, such as personalized therapy training and surgical skills training and assessment [50]. In addition, there are other AI systems that provide technical support for disease prediction based on patient data. Some examples of applying AI in cancer management include image interpretation [51], surgical interventions [52], drug discovery [52], hospital-wide data analysis [53], and personalized treatment [54].




**Scheme 1:** Application of AI in GC. AI, artificial intelligence; GC, gastric cancer.

Herein, we review the recent advances of AI-assisted GC diagnosis, especially in the early screening and diagnosis of GC, and GC treatment and prognosis (Scheme 1). We also discuss the concept, issue and approaches and challenges, with the aim of attracting a lot of scientists to use AI to solve precise theranostics of GC to increase the early discovery ratio and curative ratio of GC patients in near future.

## Advance of AI in GC

The 5-year survival rate for advanced GC is 5 %–25 %, while it can be 90 % for EGC [55]. Early detection and curative treatment are the best strategies to improve the survival rate of patients. For example, Japan's nationwide large-scale GC screening program has reduced related mortality [56]. However, so far morbidity and mortality of GC in the world is still very high, how to realize precise theranostics of GC has great clinical requirement. In recent years, AI are actively applied for clinical GC research, great advances of AI application for GC have been achieved, and deeply improve precise theranostics of GC. Up to date, AI can offer invaluable assistance in the management of EGC from following seven different levels:

(1) Screening: Deep staked sparse autoencoder neural network (DSSAENN) for EGC screening based on VOC biomarkers.
(2) Screening: Support vector machine (SVM) for EGC screening via Saliva biomarkers.
(3) Diagnosis: CADx for EGC detection in esophagogastroduodenoscopy (EGD).
(4) Diagnosis: CADx for invasion depth estimation and cancer staging.
(5) Diagnosis: AI systems for prediction of *H. pylori* infection.
(6) Treatment: AI systems for GC treatment.
(7) Prognosis: AI Systems for lymph node metastasis (LNM) prediction and survival prediction.

Herein, we review the main advances of AI in GC from above-mentioned seven levels.

### AI in screening EGC via VOC biomarkers

Muhammad et al. constructed a CADe system which used a softmax classifier and a DSSAENN (DSSAENN is a network model that automates the process of encoding and decoding operations) to classify GC based on VOC breath biomarkers to distinguish EGC, advanced GC and healthy persons [14]. All the breath samples were collected from the Shanghai Tongren Hospital, Shanghai, China [57]. They got an overall accuracy of 89.7 % for AGC and 97.3 % for EGC detection [57].

As shown in Figure 1, the second model was developed with [100 40] size of autoencoder, 100 and 40 are the number of neurons in the 1st and 2nd hidden layers respectively. This model produces an overall accuracy of 96.3 %, this model misclassified only four samples of early-stage gastric cancer.

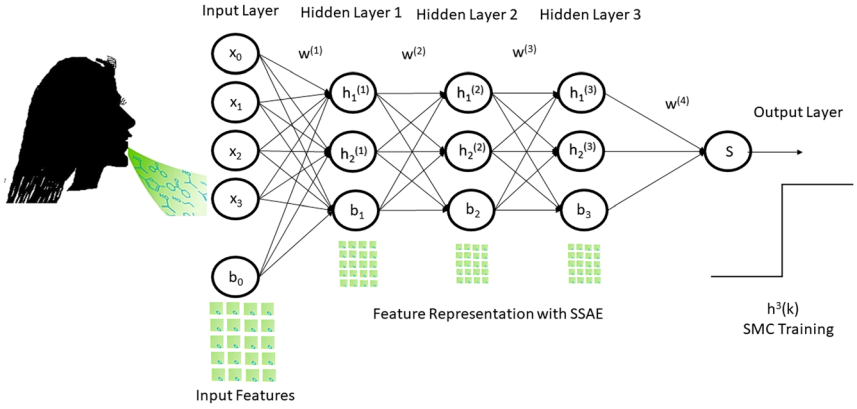



**Figure 1:** Breath analysis based EGC classification from DSSAENN (Image source: Reproduced from Aslan et al. [57], 2021 with permission of Springer Nature). DSSAENN, deep staked sparse autoencoder neural network; EGC, early gastric cancer.

Moreover, this model produces very good accuracy for predicting healthy person and advanced GC as well. This model yields an accuracy of 97.4 %, 98.0 % and 93.3 % for EGC, Healthy and AGC patients respectively [57]. Up to date, this model is being tested and optimized in multi-clinical centers, own clinical translation prospects.

## SVM based classification system for GC via saliva

Based on our previous report [15], 220 saliva samples were collected and analyzed, 10 kinds of amino acid biomarkers were identified to distinguish the patients with GC from persons without GC in the saliva samples with dominant peaks. As shown in Figure 2, the SVM was used for binary classification. The learning algorithm of SVM is the optimization algorithm for solving convex quadratic programming. The processed Raman dataset was used to train and test the established model. SVM based neural networks were developed using different kernels. Accuracy, specificity, sensitivity, and receiver operating characteristics (ROC) were applied to evaluate the classification model, along with mean average error (MAE), mean square Error (MSE), sum average error (SAE), and sum square error (SSE). Finally, we obtained an overall accuracy of 97.18 %, specificity of 97.44 %, and sensitivity of 96.88 % for the proposed model [58, 59].

Our proposed method for the classification of GC is non-invasive, cheap, and faster. With the combination of SERS sensors, our proposed model has provided us an entirely new diagnostic way of GC. The proposed model is capable of playing an important role in clinics. This established method owns the prospect of clinical translation.

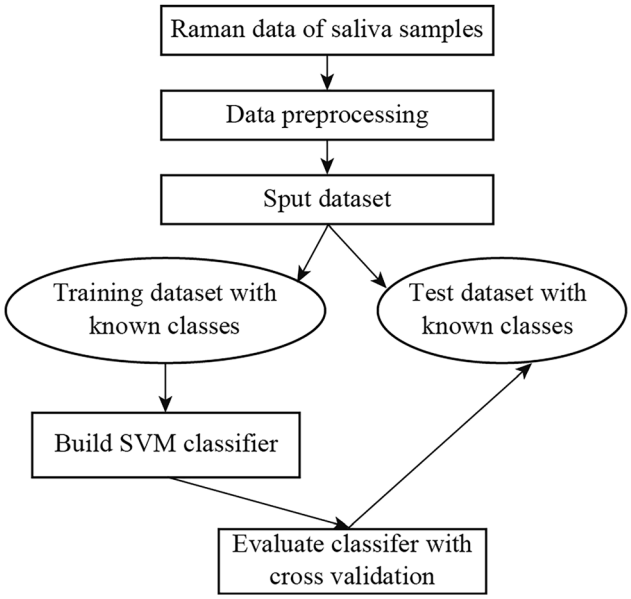



**Figure 2:** Methodology of GC diagnosis model using SVM (Image source: Aslam et al. [58]). GC, gastric cancer; SVM, support vector machine. (Reproduced from Aslan et al. [58], 2015 with permission of NBE).

## CADx for EGC detection in EGD

EGD and biopsy are two methods that are mostly used for the diagnosis of EGC. Although EGD is the standard procedure for diagnosing GC, the false negative rate of EGD for GC is 4.6 %–25.8 % [60–65]. According to recent studies [66, 67], the missed diagnosis rate of gastroscopy doctors with less than 10 years of work experience is about 25 %. In addition, even experienced Chinese gastroscopists, due to the heavy burden of medical image analysis, that is, each gastroscopist has about 50 patients per day, so it is almost inevitable that they will encounter missed or misdiagnosed.

The application of CADx technology in EGD has many advantages. It can reduce the variability between

operators, improve the accuracy of diagnosis, and help make treatment decisions quickly and accurately on site. In addition, CADx will reduce the time, cost and burden of endoscopic surgery [68].

Hirasawa et al. constructed a convolutional neural network (CNN)-based diagnostic system for detecting GC using stored images of EGD [69]. CNN is to convert a picture into a feature vector, through multiple layers of convolution, pooling, full connection, reduce the dimension of the picture, and finally transform it into a one-dimensional vector, this vector contains the characteristics of the picture. The CNN required 47 s to analyze 2296 test images obtained from two hospitals (Cancer Institute Hospital Ariake, Tokyo, Japan, and TokatsuTsujinaka Hospital, Chiba, Japan) and two clinics (Tada Tomohiro Institute of Gastroenterology and Proctology, Saitama, Japan, and Lalaport Yokohama Clinic, Kanagawa, Japan) and it correctly diagnosed 71 of 77 GC lesions with an overall sensitivity of 92.2 %, and 161 non-cancerous lesions were detected as GC, resulting in a positive predictive value of 30.6 %. Seventy of the 71 lesions (98.6 %) with a diameter of 6 mm or more as well as all invasive cancers were correctly detected. As shown in Figure 3, Li et al. developed a new system based on CNN to analyze gastric mucosal lesions observed by magnifying endoscopy with narrow-band imaging (M-NBI). They concluded that there is no significant difference in diagnostic specificity and accuracy between CNN and experts, but the diagnostic sensitivity of CNN is significantly higher than that of experts. However, this study excluded type 0-I and type 0-III lesions, and the scope of application of the CNN system was limited [51].

Shibata et al. developed a method to detect and segment EGC regions from gastrointestinal endoscopic images using Mask-CNN [71]. Ikenoyama et al. evaluated whether CNN is better than endoscopists in detecting EGC [72].To sum up, AI based on deep learning through CNN has made significant progress in the field of gastroenterology.

In addition to CNN can be used for the diagnosis of GC, SVM is also often used in GC. Miyaki et al. designed an SVM-based analysis system to be used with an endoscope system [73]. It can quantitatively identify GC through blue laser imaging (BLI) magnified images obtained by endoscopy. The SVM output value for cancerous lesions being significantly greater than that for reddened lesions or surrounding tissue [73]. Cheng et al. developed a fourier transform infrared (FTIR) feature extraction method. It used continuous wavelet transform (CWT) analysis and SVM for classification to improve the accuracy of the EGC diagnosis rate by FTIR [70]. Kanesaka et al. trained two SVM to develop a CADx system and to help endoscopists identify and describe EGC. But their study focused on the small depression type EGC. Other EGCs may require different algorithms [74].

Podder et al. considered random forest (RF), decision tree (DT), k-nearest neighbor (KNN), and adaptive boost (AdaBoost) classifiers for the diagnosis of GC. The results show that when the test sample is 20 , 30, and 40 % of the data sample, RF is superior to DT, AdaBoost, and KNN in terms of accuracy, precision, and recall. For example, when testing a data set of 30 %, the accuracy values obtained by RF, DT, AdaBoost, and KNN were 86.67 , 83.33, 86.57, and 83.33 %, respectively [75].

## CADx for invasion depth estimation and cancer staging

Invasion depth was classified into M, SM1, or SM2 (cancer with submucosal invasion ≥ 500 μm), MP (cancer invading the muscularis propria), SS (cancer invading the subserosa), SE (cancer invasion contiguous to the serosa or penetrating the serosa, and exposed to the peritoneal cavity), or SI (cancer invading adjacent structures) [76].

Endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR) can often be used for intramucosal carcinoma (M) and cancers with submucosal invasion <500 μm (SM1), while GC with deeper invasion requires surgical resection [77]. Therefore, accurate prediction of invasion depth is crucial for screening patients for endoscopic resection.

However, there is currently no reliable method to determine the invasion depth. In current clinical practice, experienced endoscopists usually use conventional endoscopes or use endoscopic ultrasound (EUS) to evaluate macroscopic features to diagnose the depth of EGC infiltration. According to reports, the accuracy of these two methods is limited, and no significant differences have been found in the diagnostic accuracy and macroscopic characteristics of EUS [78, 79]. The overall accuracy of conventional endoscopy is 69–79 % [78, 80], depending on the doctor's experience in identifying endoscopic features. Therefore, a more accurate and objective method is needed to diagnose the invasive depth of GC.

CNN as a deep learning algorithm is often used to detect the depth of cancer invasion [81]. As shown in Figure 4, Zhu et al. constructed a CNN-CAD system, which uses ResNet50 to determine the depth of invasion and screen patients for endoscopic resection. The result is that the area under the receiver operating characteristic curve of the CNN-CAD system is 0.94 (95 % confidence interval [CI], 0.90–0.97). At a threshold of 0.5, the sensitivity is 76.47 % and the specificity is 95.56 %. The overall accuracy rate is 89.16 %. The positive

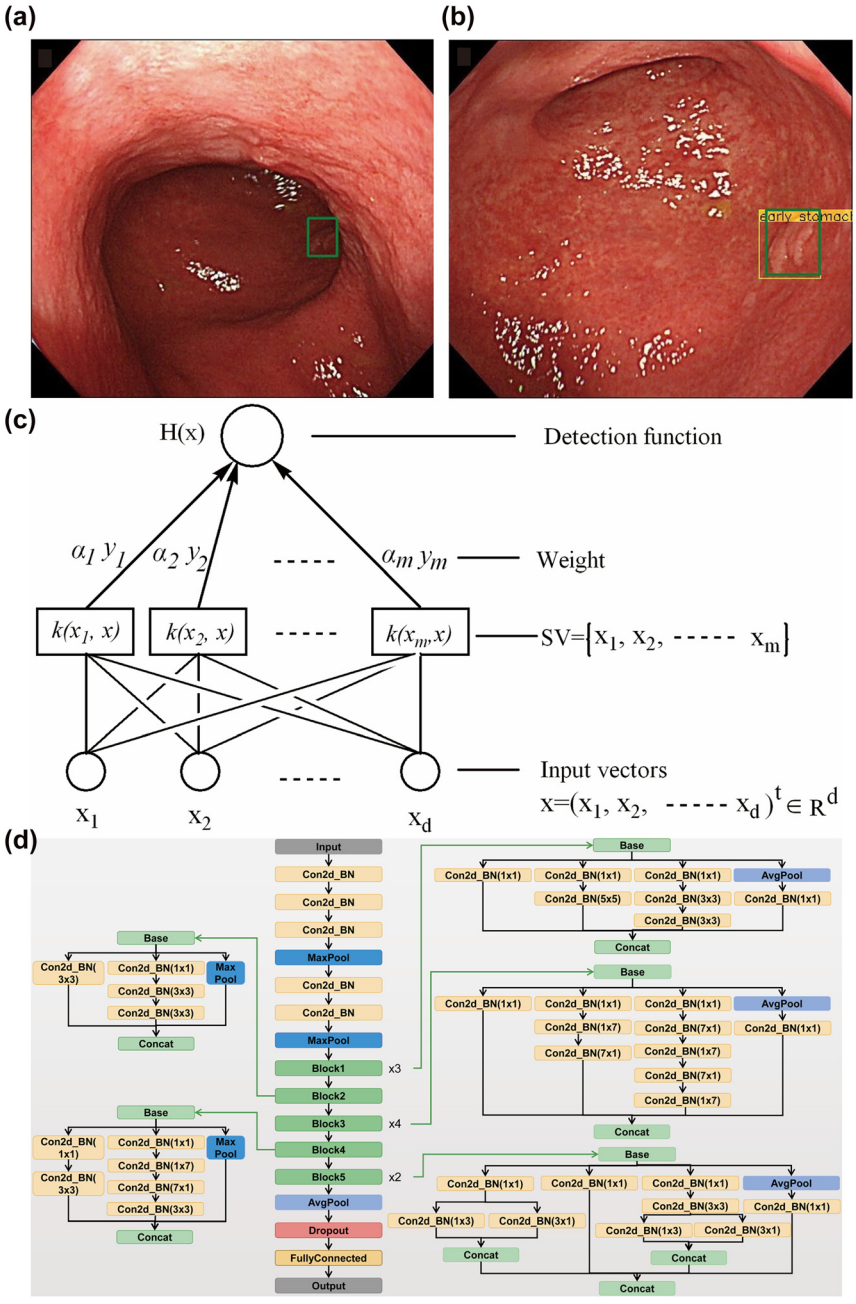



**Figure 3:** The endoscopist uses the green rectangle to manually mark the location of the cancer in each image. The yellow rectangle is generated by CNN to identify suspected lesions and indicate the degree of GC. Although CNN did not identify GC in the distant view (a) it correctly located the GC in the near view (b) (Image source: Reproduced from Hirasawa et al. [69], 2018 with permission of Springer). (c) The Structure of SVM that Cheng et al. developed (Image source: Reproduced from Cheng et al. [70], 2007 with permission of IEEE). (d) Inception v3 model architecture that Li et al. develop (Image source: Reproduced from Li et al. [51], 2019 with permission of Springer).

and negative predictive values were 89.66 and 88.97 %, respectively. The CNN-CAD system achieves higher accuracy (17.25 %; 95 % CI, 11.63–22.59) and specificity (32.21 %; 95 % CI, 26.78–37.44) than human endoscopists [82].

Yoon et al. developed a visual Geometry Group (VGG)-16 model to classify endoscopic images as EGC (T1a or T1b) or non-EGC [83]. Nagao et al. devised three AI systems that use ResNet50 to predict the invasion depth of GC using white-light imaging (WLI), non-magnifying narrow-band imaging, and indigo-carmine dye contrast imaging respectively [76]. Kubota et al. developed a CNN system that uses the back-propagation (BP) algorithm to calculate the accuracy of diagnosing the T1, T2, T3, and T4 stagings of GC. As shown in Figure 5, the discrimination accuracy of T1–T4

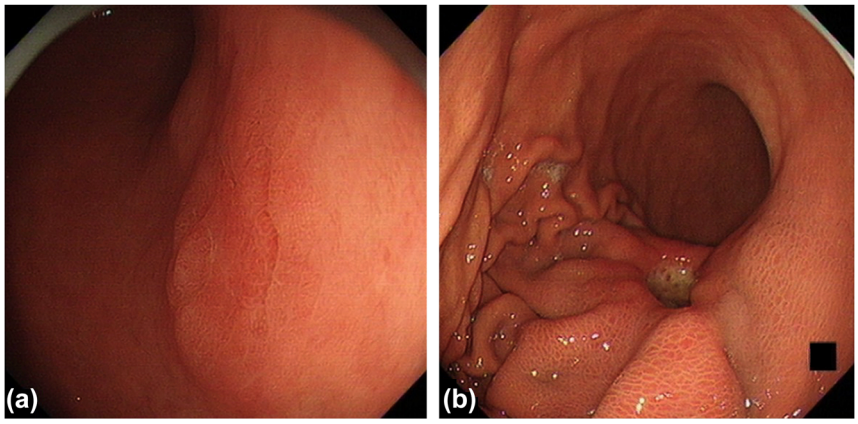



**Figure 4:** Endoscopic images: (a) A tumor invasion depth restricted to the M or SM1. (b) A tumor invasion depth deeper than the SM1 (Image source: Reproduced from Zhu et al. [82], 2015 with permission of Elsevier). M, mucosa; SM1, submucosa.

stages is 77.2 %, 49.1 %, 51.0 %, and 55.3 % (the accuracy of distinguishing T1a [restricted mucosa] and T1b [submucosal invasion] is 68.9 %). The accuracy of their system can be improved by modifying the program [84]. Cho et al. established a DL algorithm for accurately predicting submucosal infiltration in endoscopic images of gastric tumors. In internal testing, the average area under the curve for the DenseNet-161 network was 0.887 (95 % CI: 0.849–0.924). In external tests, the average area under the curve reached 0.887 (0.863–0.910) [85].

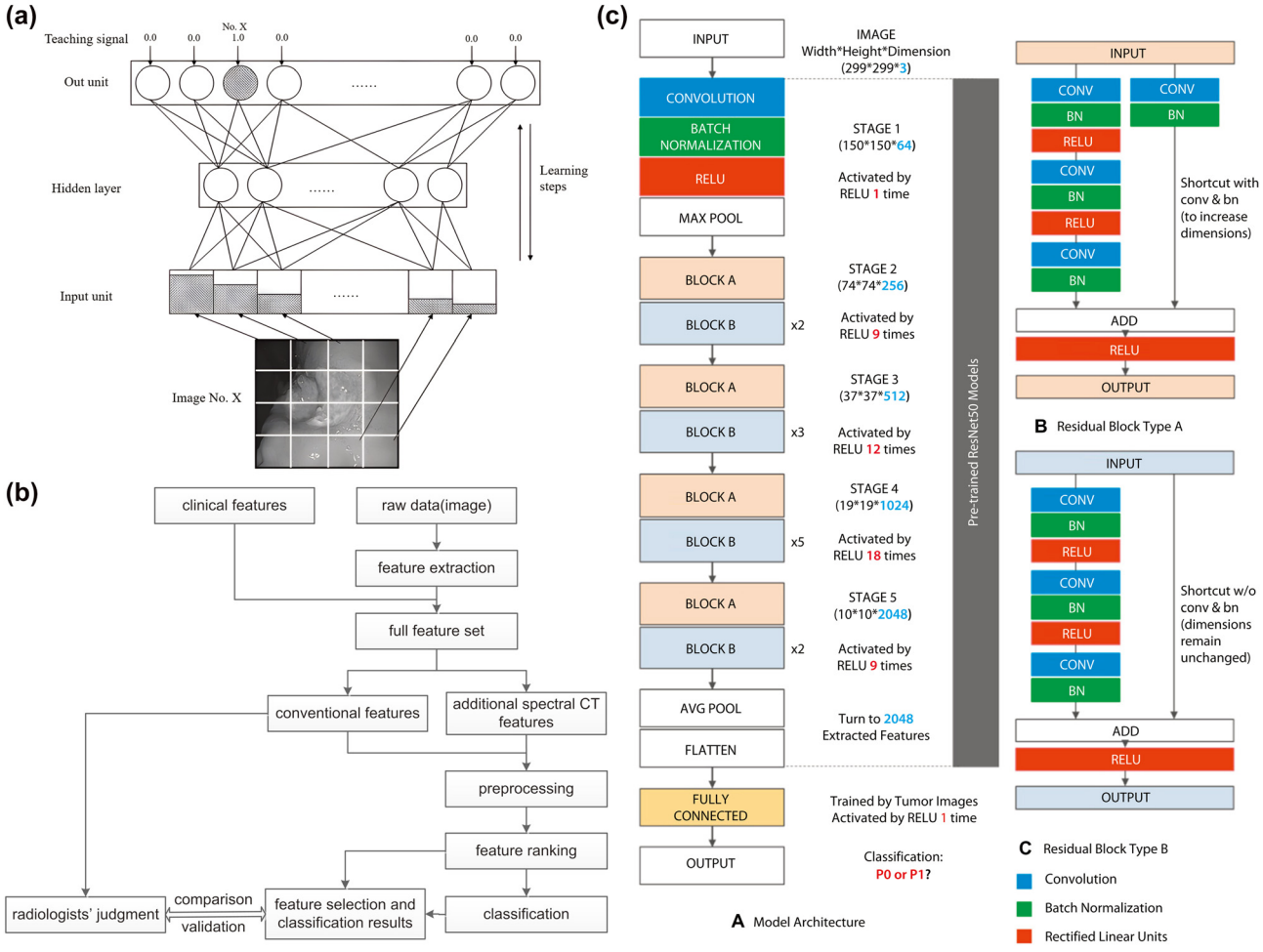



**Figure 5:** Deep learning algorithm. (a) A scheme of the computer learning program with the BP algorithm that Kubota et al. proposed (Image source: Reproduced from Kubota et al. [84], 2012 with permission of Springer). (b) Schematic diagram of computer-aided diagnosis system that Li et al. proposed to diagnose the invasion depth of GC (Image source: Reproduced from Li et al. [86], 2015 with permission of Elsevier). (c) Convolutional neural network computer-aided detection system architecture (Image source: Reproduced from Zhu et al. [82], 2019 with permission of Elsevier).

SVM is also often used to diagnose the depth of GC invasion. Jiang et al. developed an SVM-based GC prognostic classifier (GC-SVM) based on a variety of clinicopathological features and immune markers to predict overall survival (OS) and disease-free survival (DFS), and explore whether the GC-SVM classifier can identify patients with stage II and stage III of GC [87]. Li et al. evaluated the accuracy of dual-energy spectrum computed tomography (DESCT) imaging with the aid of a CADx system, which uses the SVM classification method to assess the serosal infiltration of GC patients. The total classification accuracy rate reaches 90 % [86].

KNN is also a good way to diagnose the depth of GC invasion. Li et al. used the KNN classifier to distinguish between lymph node metastasis and non-lymph node metastasis, and the overall accuracy rate was 96.33 %. Compared with traditional diagnostic methods such as spiral CT (sensitivity 75.2 %, specificity 41.8 %) and multislice spiral CT (82.09 %), the diagnostic accuracy of lymph node metastasis (LNM) is higher [88]. As shown in Figure 6, Li et al. proposed an improved Citation-KNN method to identify the depth of tumor invasion of GC through dual-energy CT imaging. The total accuracy is 0.7692 [89].

## AI systems for prediction of *H. pylori* infection

As shown in Figure 7, *H. pylori* infection can induce atrophic gastritis and intestinal metaplasia, and eventually develop into GC [90–93]. According to reports, patients with *H. pylori* infection have an increased risk of GC, and the incidence of *H. pylori* infection has decreased after *H. pylori* eradication. This fact has led the International Agency for Cancer Research to classify *H. pylori* as a clear carcinogen [94–98], which in turn has led to an increase in the prevalence of eradication therapy [99–101].

Endoscopy can help diagnose *H. pylori* infection. Accurate endoscopic diagnosis of *H. pylori* positive should be confirmed by various tests, such as blood or urine anti-*H. pylori* IgG and fecal antigen, urease breath, or rapid urease tests, followed by eradication therapy. In addition, patients who have been eradicated from *H. pylori* have a moderate risk of developing GC. Even if the eradication is successful, GC may still occur [98, 102, 103], which is why post-eradication status should be distinguished from *H. pylori*-negativity.

Shichijo et al. constructed a CNN and evaluated its ability to diagnose *H. pylori* infection. Compared with the

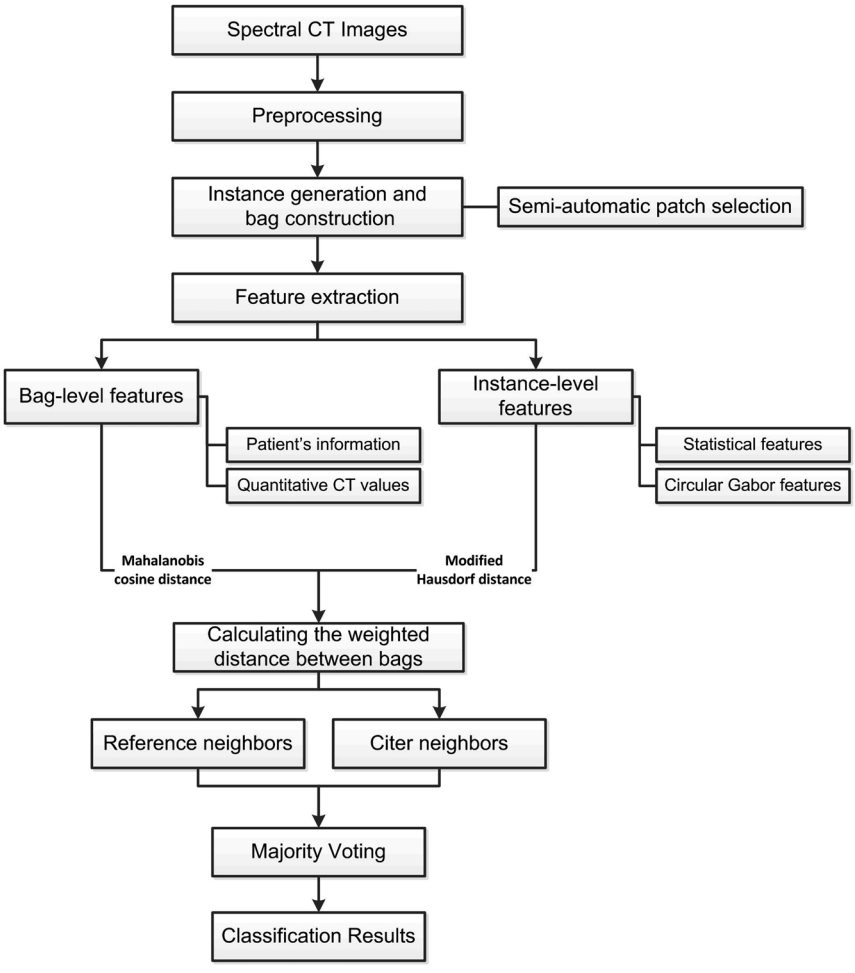



**Figure 6:** The flowchart of the multiple instance learning based CADx system that Li et al. proposed (Image source: Reproduced from Li et al. [89], 2015 with permission of Elsevier).

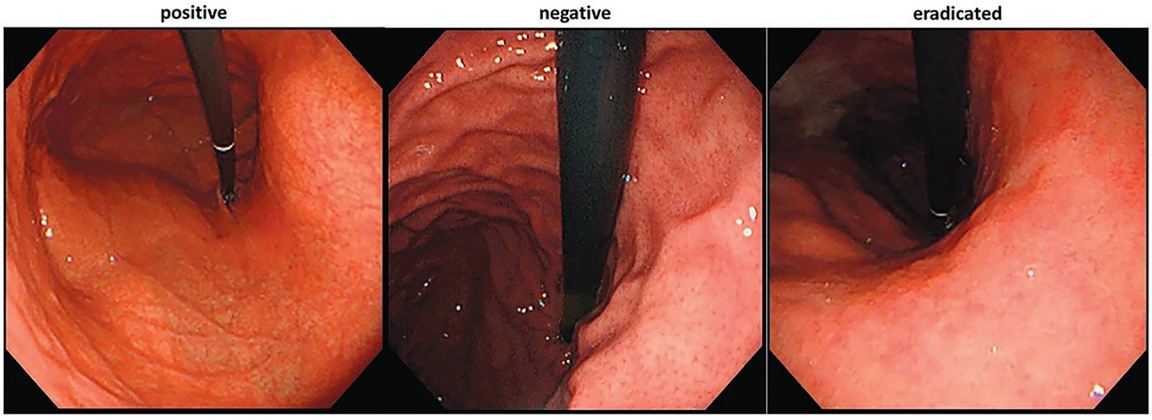



**Figure 7:** Representative endoscopic images of H. pylori positive, negative and eradicated stomach. Atrophy and diffuse redness can be seen during infection. The regular arrangement of collecting venules (RAC) can be seen in the uninfected stomach. A map-like red appears in the stomach where H. pylori has been eradicated (Image source: Reproduced from de Vrles et al. [102], 2009 with permission of WWW).

manual diagnosis of endoscopists, CNN has higher accuracy and shorter time [104]. However, the study only included *H. pylori* positive and negative patients, and excluded patients after *H. pylori* eradication. So Shichijo et al. constructed a CNN and evaluated its ability to determine the status of all *H. pylori* infections [105]. Mohan et al. evaluated the comprehensive performance of CNN-based AI in diagnosing *H. pylori* infection. Compared to physicians, CNN seemed to perform equivalently [106]. Zheng et al. used CNN to achieve high diagnostic accuracy for evaluating *H. pylori* infection. The area under the curve of the poly gastric image of each patient is 0.97, and the sensitivity, specificity, and accuracy are 91.6 %, 98.6 % and 93.8 %. Their system achieved a high degree of accuracy [107]. Itoh et al. developed a CNN to detect *H. pylori* infection and it turned out that CNN-assisted *H. pylori* infection diagnosis is feasible [108].

SVM is also commonly used to diagnose *H. pylori* infection. Ishihara et al. proposed a method for detecting *H. pylori* infection based on the combination of SVM and multiple kernel learning (MKL), and the experimental results obtained by applying this method to real X-ray images proved its effectiveness [109]. Huang et al. proposed a computer-aided diagnosis system that uses sequential forward floating selection (SFFS) and SVM to diagnose *H. pylori* gastric histology from endoscopic images [110]. Ishihara et al. constructed an SVM to automatically detect *H. pylori* infection in multi-gastric X-ray images [111].

There are other algorithms that can detect *H. pylori* infection. Ishihara et al. used MKL to build a system that can automatically detect *H. pylori* infection [112]. The MKL algorithm essentially defines M base kernel functions and uses a weighted linear combination of the base functions as the kernel function of the SVM.

## Treatment: AI systems for GC treatment

Despite advances in computer systems and simulation methods, surgical training is still based on the direct observation of expert surgeons [113]. Due to the subjectivity of human observation, these methods lack consistency, reliability and efficiency [114]. In addition, the widespread implementation of robotic surgery has led to an increasing need for appropriate structured training models and objective evaluation tools for clinical capabilities. The ability of ML methods to find hidden patterns in large data sets (such as sports and video data) provides the possibility to better understand and simulate surgical data to evaluate surgeons' skills and personalized training.

Fard et al. introduced a framework for objective skill assessment and prediction based on motion trajectory data. Their goal is to establish a classification framework to automatically assess the performance of surgeons with different levels of expertise. They used three classification methods: KNN, logistics regression and SVM and they proved that this system can classify the expertise of surgeons as novices or experts [50]. Wang et al. proposed an analytical deep learning framework for surgical training skills assessment. Implement a deep CNN to map multivariate time series data of kinematics to a single skill level. The results are that in-depth architecture has great potential for efficient online skill assessment in modern surgical training [115].

As shown in Figure 8, Ershad et al. proposed a sparse coding framework. Compared with the use of principal component analysis (PCA) features or raw data, the proposed dictionary learning method can use the user's joint

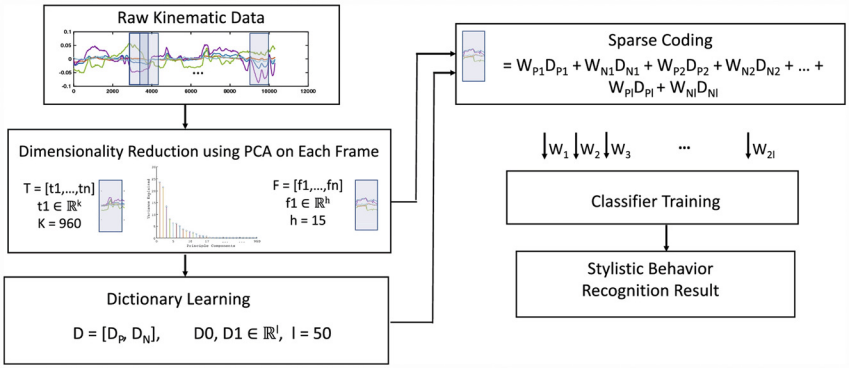



**Figure 8:** Feature reduction and basis vector transformation process of Ershad's model (Image source: Reproduced from Ershad et al. [116], 2015 with permission of Springer).

position data to evaluate the performance of stylistic behavior in near real-time, and has higher accuracy [116].

## Prognosis: AI systems for LNM prediction and survival prediction

Predicting LNM is important for clinical decisions including endoscopic mucosal resection, neoadjuvant chemotherapy, or radical surgery. In many cases, the preoperative staging of N status is not satisfactory [117]. Recently, artificial neural network (ANN) has been used to predict LNM and have significantly improved accuracy. Gao et al. used a deep neural network (DNN) to calculate a CT of the proximal metastatic lymph node (PGMLN) to simulate the radiologist's recognition of the lymph node and obtain more accurate recognition results [118]. Matsumoto et al. used DNN analysis to test the accuracy, effectiveness and practicality of deep-UV-laser-induced fluorescence imaging in detecting LNM in patients with GC [119]. Hensler et al. used the QUEEN system to predict the LNM of GC [120]. Su et al. developed a DL system to achieve early diagnosis of peritoneal metastasis (PM). The detection network based on fast Region-CNN uses pre-trained Resnet18 to achieve cell detection with an average accuracy of 0.8316. The classification network based on Resnet50 achieved an area under curve (AUC) of 0.8851, an accuracy of 96.80 %, and an FNR of 4.73 % in cell classification [121]. As shown in Figure 9, Li et al. established a deep learning radiology nomogram based on dual-energy CT (DECT) for the prediction of LNM in GC [122].

Most GC patients have metastatic disease when they relapse, and the overall prognosis is still poor. The expected survival period after recurrence is less than 1 year. The high tumor recurrence rate in patients with advanced GC highlights the importance of considering adjuvant therapy. Based on the survival prediction of GC patients, as shown in Figure 10, Li et al. developed a new DL prediction algorithm (survival recurrence network [SRN]). Their SRN predicted a high survival rate, reaching 92 % in the 5th year after surgery [54]. Biglarian et al. used the Cox proportional hazard and ANN model to predict the survival rate of GC patients. Compared with the Cox proportional hazard regression model, the neural network model is a more powerful tool for predicting the survival rate of GC patients [123]. Li et al. used an SVM-based method to generate radiological signature (RS), which can predict disease-free survival (DFS) and chemotherapy response in stage II/III GC [124].

### Technique challenges and prospects

AI has achieved big success in screening, diagnosis, therapy and prognosis of GC. AI can handle successfully complex nonlinear relationships, fault tolerance, parallel distributed processing and learning [125]. In view of its advantages in the simultaneous processing of adaptive, quantitative and qualitative knowledge, as well as the verification results of multiple clinical studies in multiple fields [126], AI has multiple uses in the field of clinical medicine [127]. It not only makes full use of all aspects of clinical diversity [128, 129], but also helps to solve the problem of lack of objectivity and universality in the current expert system [130]. DL techniques, in particular, are transforming our ability to interpret imaging data [131, 132].

AI technology faces some great challenges, which must be solved to ensure its application in cancer screening, diagnosis, therapy and prognosis [133]. First, medical imaging data cannot be used as input data directly. To solve this problem, it is necessary to improve the perception of the machine so that it can get real images and process them. Second, they also have the risk of overfitting the training

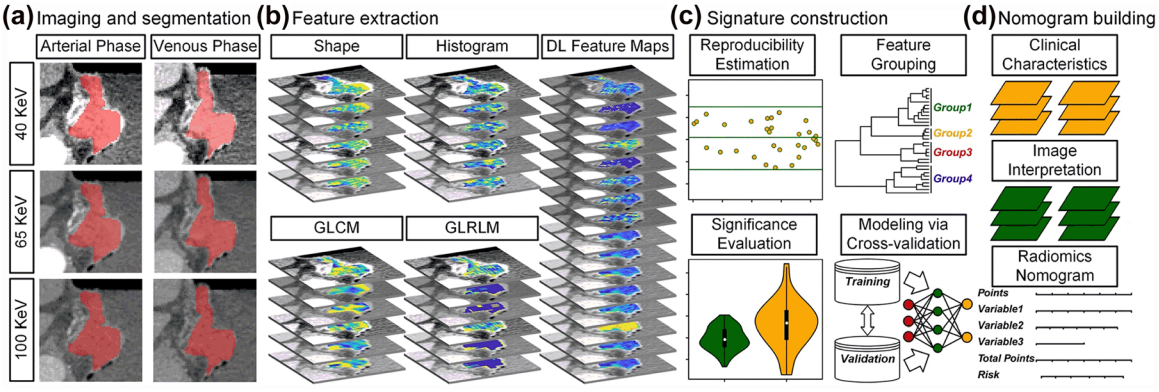



**Figure 9:** Workflow of the dual-energy CT–based radiomics nomogram (Image source: Reproduced from Li et al. [122], 2020 with permission of Springer).

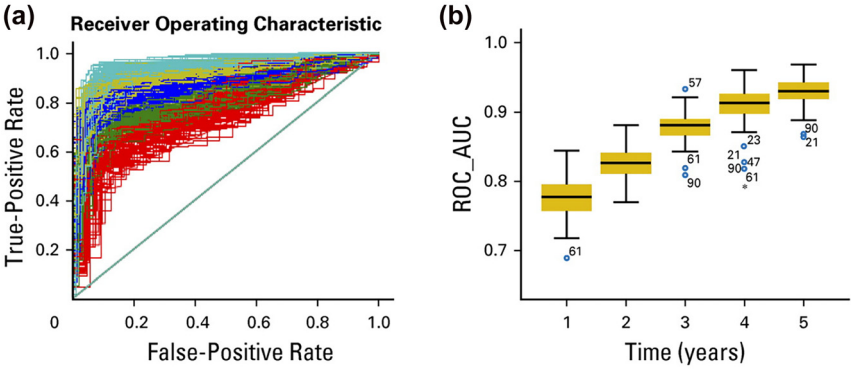



**Figure 10:** DL prediction algorithm. (a) Use the corresponding test patients to perform iterative tests on 100 well-trained SRNs, and generate ROC curves to evaluate the average predictive power at each time point. (b) The AUC of the test data set (Image source: Reproduced from Lee et al. [54], 2018 with permission of ASCO).

data, resulting in a sharp drop in performance under certain settings [134]. Continuous algorithm optimization can solve this challenge. Third, Cabitza et al. [135] puts forward a more pessimistic view, which mentions the inherent uncertainty in medicine and the "black box" of neural network/ML applications that may reduce the skills of doctors and may soon change certain aspects of healthcare. Deep learning, a seemingly practical and economical method that will bring unexpected negative consequences. It is necessary to focus on a wider range of AI application scenarios, and pay attention to various issues such as data algorithm security, technology adaptation, organizational reengineering, social risk and governance that may arise from technology application before AI has a large-scale irreversible impact on human society, so as to form a systematic understanding and forward-looking prediction of the social impact characteristics and dynamics of AI and other technologies as early as possible and provide timely feedback on the optimization of the technology development path. Fourth, there are some ethical and safety issues, such as using AI after obtaining patient consent and determining who is responsible for misdiagnosis or wrong treatment [55]. In addition, AI cannot determine causality, and predictions generated by AI must be critically evaluated and interpreted by doctors in a clinically meaningful way [55]. To solve the safety and ethical issues, the design must be continuously optimized and improved, and the ethical design can be introduced to make the AI have the ability to judge the behavior similar to human through ethical design. Fifth, reflection makes people improve, and so should the progress of machine. But AI cannot reflect on experience and learn from them. Using language to guide computers to think is a good way to solve this problem. This process is similar to humans learning to think by receiving language instruction.

In the era of precision medicine, the predictability of AI in GC management is promising in the future. But we believe that AI cannot completely replace doctors, and the way to achieve the best performance is through human–machine collaboration. In the era of precision medicine, combining omics data with clinical information is necessary for future clinical practice. To this end, AI must be combined with multiple disciplines. In addition, larger and higher-quality random events need to be used to test the AI model.

In the near future, we can further study the application of AI in the whole process of GC management. In particular, some possible areas include early detection, stage recognition and prognosis. For GC detection, it has now entered an accuracy platform. To transfer CNN from the research environment to clinical practice, this accuracy platform must be established. For GC treatment, future research will focus on applying the proposed method to data from other parts of the robot, and be able to provide relevant feedback for trainees to improve performance in the case of poor detection performance. Regarding the prognosis of GC, in the future, it is necessary to study a system that can predict not only one type of cancer, but also predict other types of cancer.

## Conclusions

In summary, AI has been actively explored in prewarning, early screening, diagnosis, therapy and prognosis of clinical GC, and has achieved great advances. However, how to use AI to realize precise theranostics of GC still face some big challenges, further works will focus on innovative algorithm, optimized models and validating models with big data to suit for requirement of clinical GC theranostics in near future.

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