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Review Article

Application of artificial intelligence to the diagnosis and therapy of colorectal cancer

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Abstract: Artificial intelligence (AI) is a relatively new branch of computer science involving many disciplines and technologies, including robotics, speech recognition, natural language and image recognition or processing, and machine learning. Recently, AI has been widely applied in the medical field. The effective combination of AI and big data can provide convenient and efficient medical services for patients. Colorectal cancer (CRC) is a common type of gastrointestinal cancer. The early diagnosis and treatment of CRC are key factors affecting its prognosis. This review summarizes the research progress and clinical application value of AI in the investigation, early diagnosis, treatment, and prognosis of CRC, to provide a comprehensive theoretical basis for AI as a promising diagnostic and treatment tool for CRC.

Keywords: Artificial intelligence, colorectal cancer, colonoscopy, pathological biopsy, diagnosis, therapy

Introduction

Colorectal cancer (CRC) is the most common type of malignant tumor in the digestive system and ranks as the fourth leading cause of cancer death worldwide [1, 2]. According to epidemiology investigations, in 2012, there were approximately 1.36 million new cases of CRC, which was the third highest incidence of malignant tumors in the world, ranking third for men and second for women. There were approximately 690,000 deaths, which is ranked as the fourth highest death toll caused by malignant tumors [3, 4]. It was estimated that in 2015, there will be 777,987 new cases and 352,589 deaths caused by CRC in developed countries [5, 6]. However, the five-year survival time varies by country, ranging from 4.3% to 5.3% for men and from 2.7% to 4.9% for women. Although significant progress has been made in terms of understanding and treating CRC, high morbidity and mortality rates based on recurrence and metastasis in therapy are inevitable [7-9]. Currently, endoscopic screening is the most commonly used method for clinical screening of CRC, particularly colonoscopy [10-14]. However, there are several problems with this approach, including poor patient compliance, a lack of family history [15, 16], inconvenience of real-time monitoring, expenses, and risk of complications [17, 18]. Therefore, there is significant research interest in identifying effective strategies for early diagnosis, detection of recurrence, and monitoring the progression of CRC [19].

Artificial intelligence (AI), which is also called machine intelligence, refers to a type of intelligence exhibited by machines. In computer science, AI research involves any device that can perceive its environment and act autonomously to achieve its goals [20]. Researchers have continuously studied and developed AI technology since its inception. AI technology has been widely used in medicine, the economy, and daily life. In medicine, AI is mainly used for the diagnosis, treatment, and prognosis prediction of diseases. AI has two main branches in the medical field: a virtual branch and physical branch [21]. The virtual branch includes medical imaging, clinical assistant diagnosis and treatment, and drug research and development. The physical branch includes surgical and nursing robots. Based on the

continuous development and widespread application of AI in the medical field, AI has diverse application prospects for the diagnosis and treatment of tumors. Recent studies have shown that AI can play an important role in the diagnosis and treatment of CRC patients, which not only improves early screening efficiency, but also significantly improves the five-year survival rate of CRC patients following treatment. This review intends to provide an in-depth discussion of the research progress and clinical application value of AI in the investigation, early diagnosis, treatment, and prognosis of CRC by summarizing findings relevant to AI and CRC, which should provide a comprehensive theoretical basis for AI as a promising diagnostic and treatment tool for CRC.

Development of artificial intelligence in medical research

AI is one of the most popular topics in modern research. It is an emerging discipline that focuses on studying and developing theories, methods, technologies, and application systems for simulating, extending, and expanding human intelligence. At its core, AI is a branch of computer science. Researchers attempt to understand the essence of intelligence and design novel intelligent machines that can respond in a manner similar to human intelligence. Research in this area includes robotics, language recognition, image recognition, and natural language processing. The progress of science and development of engineering technology will be applied to medicine to promote the development of medical technology. AI technology has played a key role in the medical field in terms of constructing fast and accurate intelligent medical systems.

Based on the rapid development of computer technology, imaging levels and the quality of medical imaging equipment have steadily improved in recent years [22]. The four main directions of future medical development are "personalization, precision, minimally invasive, and remote". With assistance from computer technology, these directions have become increasingly clear [23]. Introducing AI technology into the field of medical image recognition is a goal with tremendous potential benefits for both patients and doctors. Leveraging AI to analyze medical images can significantly reduce costs and improve efficiency. However, for the practical application of medical image processing, systems must be sufficiently flexible to adapt to the actual characteristics of processed images [24]. The development of AI has recently entered a new era. AI has begun developing rapidly in professional applications. Although many applications are far from practical, they are very likely to be realized in the next 10 to 15 years [25].

Laboratory medicine is an important sector of modern medicine. Approximately 70% of the information required for clinical decisions comes from laboratory testing. The main goals of such testing are sample detection and interpretation. However, image recognition and decision-making systems incorporating AI technology can play a major role in this field and can even subvert existing technology. AI applications in the pre-analysis stage mainly focus on sample collection and transfer, as well as the identification of unqualified samples. Such applications include blood drawing robots, sample transfer robots, automatic sample delivery, and the automatic identification of unqualified samples [26]. In the analysis stage, image recognition is the most prominent technology because it can help solve morphological interpretation problems in test items, including bone marrow slices, blood smears, urinary sediment, fluorescent slices, and bacterial colonies. Through deep learning, computers can classify red blood cells based on their cell morphology. In the post-analysis phase, AI plays a more important role. Machine learning techniques can perform intelligent report reviewing and reexamination, generate critical value reports, and even find test tube labeling errors by analyzing historical data for multiple test items. Furthermore, AI technology can contribute to the transition from test reports to diagnostic reports. Using AI technology, through multi-parameter data mining, key indicators related to atrial fibrillation in peripheral blood can be identified to predict the risk of acute myocardial infarction, which cannot be achieved using a traditional single test item [27, 28].

Through deep learning, AI can be applied to diagnosing and treating clinical reproductive diseases. For example, one can use multi-layer neural networks to predict the pregnancy outcomes of infertility patients and extract texture features to identify embryos with more de-

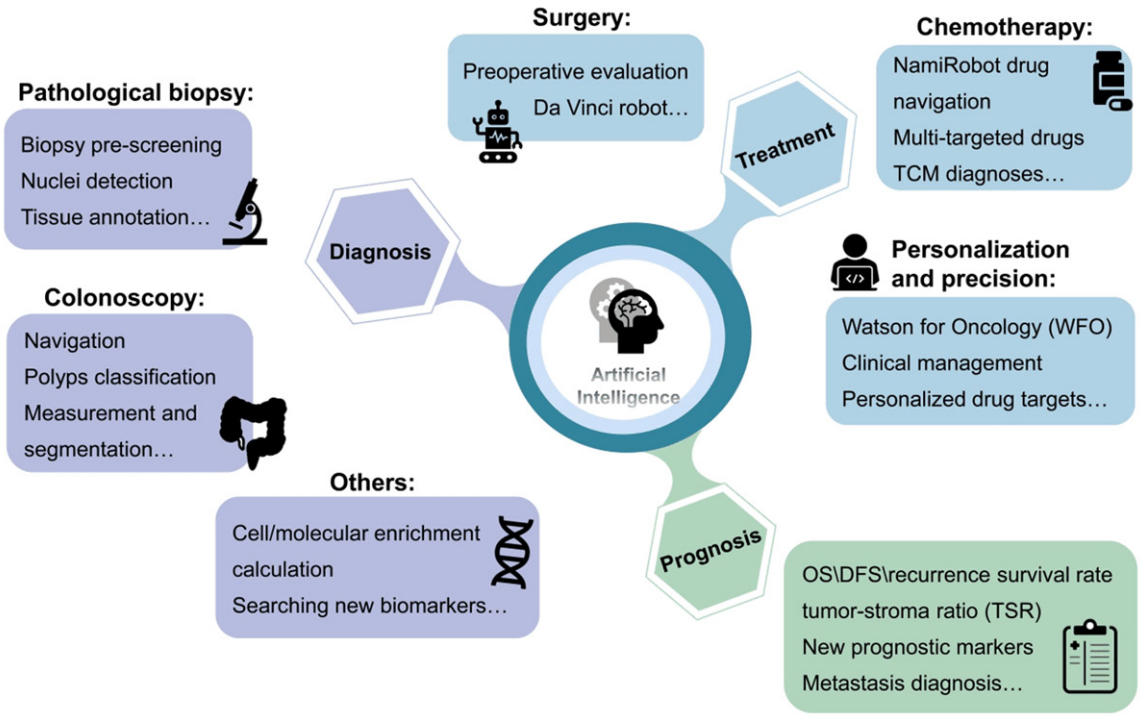

Figure 1. The application of AI in CRC diagnosis and treatment.

velopmental potential among a series of embryo images. AI makes medical workers more accurate in their diagnosis and more personalized in their treatment of reproductive diseases, and allows patients to predict their fertility more accurately. The directions of AI technology research in the assisted reproduction field are largely focused on how to use AI to predict the fertility of patients more accurately, allowing doctors to develop individual optimal solutions to solve fertility problem; how to use intelligent embryo images to recognize and select embryos with the highest development potential; and how to create AI platforms with multi-omics intelligent analysis, diagnosis, and treatment. Currently, AI is mainly applied to the prediction of abnormal sperm morphology and intra-cytoplasmic sperm injection (ICSI) [29], as well as evaluating ovum quality [30, 31], and embryonic development potential [32-35] and predicting in vitro fertilization or ICSI pregnancy outcomes [36].

AI can also be widely used for the rapid diagnosis [37], prediction [38], and treatment of tumors [39]. Additionally, AI can be used for medical journal editing and publishing [40], as well as in other medicine-related fields. The rapid development of AI is accompanied by numerous opportunities and challenges. We should take full advantage of these opportunities and prepare for the future and make use of AI technology to promote the development of medicine and realize faster diagnosis and more accurate treatment of diseases.

Applications of AI to CRC

Since 2010, the research and application of AI in medically assisted gastrointestinal disease diagnosis and treatment have grown significantly [41]. In terms of the lower gastrointestinal tract, AI has assisted in the examination of colorectal diseases and has been applied to colon polyps, adenomas, colon cancer, ulcerative colitis, and intestinal motor diseases. Although the application of AI to the diagnosis and treatment of CRC still lacks systematic research, the continuous development of AI applications in the medical field is an indication that AI will be used for the diagnosis and therapy of CRC eventually (**Figure 1**).

AI and CRC monitoring and diagnosis

Diagnosis is one of the core principles of medicine and relies on the integration of multi-

source data analysis and clinician experience. Based on the wide variety of tumor symptoms, the rapidity of tumor progression, individual differences, and drug susceptibility, it is difficult to perform accurate tumor diagnosis. AI can aid doctors in the qualitative diagnosis and staging diagnosis of colon cancer, which currently rely heavily on colonoscopy and pathological biopsy [42].

AI application during colonoscopy

Colonoscopy can be used to directly observe lesions in the intestinal wall and colonoscopy doctors can determine whether lesions are related to CRC through the analysis and screening of lesion images. As early as 2006, Lefere introduced the concept of virtual colonoscopy [43]. The advent of virtual colonoscopy was based on computed tomography colonography [44], which originated in 1994 and transformed local axial computed tomography images into three-dimensional cavity images. These images simulated optical colonoscopy and used various types of films or virtual crosses to detect CRC and their adenomatoid polypoid precursors, as well as other neoplastic lesions. In recent years, the rapid development of AI technology has made colonoscopy a convenient and accurate examination for screening CRC. To detect polyps, Fernandez-Esparrach et al. [45] designed an automatic colonic polyp detection method based on energy maps. They inputted 31 types of polyp information into a computer learning system and achieved a sensitivity of 70.4% and specificity of 72.4%. This approach was subsequently refined through the development of deep learning technology [46, 47]. In 2017, Zhang et al. [48] developed a novel algorithm that automatically classifies polyps as hyperplasia and adenomatosis. Takemura et al. [49] distinguished neoplasia polyps from non-neoplasia polyps using narrow-band imaging (NBI) and support vector machine (SVM) technology, achieving a detection accuracy of 97.8%. Gregor et al. [47] designed and trained a convolutional neural network (CNN) system to improve the adenoma detection rate (ADR) for colonoscopy. They collected 8,641 representative marked images from more than 2,000 colonoscopy results for machine learning and tested their system's predictive capabilities on 20 sets of colonoscopy results. Their assistant system achieved a cross-validation accuracy of 96.4% and an area under the receiver operating characteristic curve (AUC) of 0.991. Kominami et al. [50] demonstrated the practicability of real-time computer-aided diagnosis (CAD) for detecting small adenomatous polyps. Mori et al. [51] combined NBI with staining image technology to perform real-time image recognition to screen small neoplastic polyps and conducted prospective verification of auxiliary diagnoses. They achieved a final pathologic prediction rate of 98.1%. Wang et al. [52] demonstrated that real-time image recognition systems can significantly increase the ADR of colonoscopy. Akbari et al. [53] applied a polyp segmentation method to screen tumors in colonoscopy polyps using a CNN. During the training phase, they improved the image patching method. In the testing phase, they conducted effective post-processing of a probability graph generated by their CNN. Their method achieved a specificity of 74.8%, sensitivity of 99.3%, and accuracy of 97.7%. Renner et al. [54] used AI to construct a computer-assisted optical biopsy system. When a colorectal intestinal tract was examined using endoscopy, 602 collected images were uploaded to their system for deep learning. Their system processed the image information and distinguished neoplastic polyps. The diagnostic accuracy and sensitivity of their system were 78.0% and 92.3%, respectively. EndoBRAIN is an AI-assisted endoscopic diagnosis system that analyzes cell nuclei, crypt structures, and microvessels in endoscopic images, to identify colon neoplasms. Kudo et al. [55] performed a retrospective comparative analysis of the diagnostic performance of EndoBRAIN with those of 30 endoscopists. While analyzing staining in endoscopic images, EndoBRAIN distinguished neoplastic lesions from non-neoplastic lesions with 96.9% sensitivity, 94.3% specificity, 96.0% accuracy, a 96.9% positive predictive value, and 94.3% negative predictive value. These values were significantly higher than those of the endoscopists. Blanes-Vidal et al. [56] extended AI technology to capsule endoscopy. They developed a CNN for the autonomous detection and localization of colon polyps in colon capsule endoscopy. Compared to previous methods, their algorithm achieved unprecedented levels of accuracy (96.4%), sensitivity (97.1%), and specificity (93.3%).

In the case of nonpolyposis colon cancer, the mucosa of malignant colon tumors under colo-

noscopy are characterized by irregular, discontinuous crypt structures, which can be diagnosed using CAD. Infocus-Breakpoint, which was designed in 2015, can measure the length and area of a neoplasia in a 2D colonoscopic image directly, yielding accuracy at the millimeter level [57]. Stefanescu et al. [58] used CAD to process images from confocal laser endomicroscopy and trained their model using a two-layer feed forward neural network to diagnose malignant samples automatically based on seven tested parameters. Their diagnostic error was 15.5%. Takeda et al. [59] studied endocytoscopy CAD for the diagnosis of invasive CRC. They trained their system on 5843 endocytoscopy images of 375 lesions and tested it on 200 images. It achieved a sensitivity of 89.4%, specificity of 98.9%, and accuracy of 94.1%. Magnifying narrow-band imaging (M-NBI) can be used to make detailed observations of microvascular structures. Tamai et al. [60] used CAD based on M-NBI to classify mucosal lesions in the colon, including hyperplastic polyps, adenoma/adenocarcinoma (intramucosal to submucosal-superficial) lesions, and submucosal-deep lesions with accuracies of 83.9%, 82.6%, 53.1%, 95.6%, and 82.8%, respectively.

AI application in pathological biopsy

Pathological biopsy is necessary for the diagnosis and grading of colon cancer. However, results are typically subjective assessments based on the past experience and knowledge of pathologists. Therefore, significant differences between different observers are inevitable. The application of AI technology can automatically classify and diagnose biopsy samples, significantly improving the accuracy of diagnosis while reducing time and costs [61]. Rathore et al. [62] developed a novel colorectal cancer detection (CCD) system based on the SVM radial basis function algorithm, which classifies normal colon biopsy images and malignant images, and then automatically determines malignant grades. Compared to previous techniques, this CCD system has superior cancer detection (accuracy 95.40%) and grading (accuracy 93.47%) capabilities. Subsequently, based on this system, the same team proposed a hybrid feature-space-based colon classification (HFS-CC) technique [63] that classifies biopsy sample images using multiple features, including geometric features, morphology, and texture. An SVM was used as a classification tool to classify 176 subjects, and the HFS-CC technique achieved a test accuracy of 98.07%. Yang et al. [64] combined a subpatch weight color histogram and least squares SVM to design a novel application of AI to CRC pathology. This method not only displays the color and spatial information of tumor images, but also reveals heterogeneous information and achieves excellent accuracy for tumor classification (96.78%). Korsuk et al. [65] used AI for the classification of nuclei in colon cancer biopsies. Nuclei detection and classification in histopathology images of cancerous tissues stained with standard hematoxylin and eosin (HE) stains are challenging tasks, based on cellular heterogeneity. Therefore, they designed a spatially constrained CNN (SC-CNN) to test nuclei and performed classification with the aid of a neighboring ensemble predictor (NEP). Korsuk examined 100 HE-stained colon cancer specimens and demonstrated that joint detection and classification using the SC-CNN and NEP yielded a high average F1 score (0.802) and enhanced accuracy (78.1%).

Regarding immunohistochemistry (IHC), Abdelsamea et al. [66] developed an algorithm called TuPaQ to segment CRC tumor epitheliums, providing a basis for automated biomarker quantification. TuPaQ can perform image preprocessing, extract regions of interest, and quantify tumor epithelial cells. The sensitivity and specificity were 84% and 95%, respectively, and the mean tumor area obtained was extremely close to the area quantified via manual annotation ($r = 0.956$, $P < 0.001$). AI can also be used to design pure image processing tools. Eycke et al. [67] proposed a method for automatically annotating slide images from colorectal tissue samples. This method is equipped with a deep learning function and convolutional network system, and can segment glandular epitheliums in histological images in both HE staining and IHC sections.

AI application in blood tests and other tests

Blood testing is a noninvasive, accurate, and cost-effective diagnostic method. Therefore, improving the accuracy of blood tests can promote early tumor detection in CRC screening. Soares et al. [68] designed a classification me-

thod based on blood fluorescence spectroscopy. By training an SVM to identify CRC samples and normal samples, their method achieved a sensitivity and specificity for CRC of 87% and 95%, respectively. For nonmalignant findings, these values were 60% and 79%, respectively. ColonFlag is a machine learning algorithm that uses basic patient information and complete blood cell counts to identify individuals at elevated risk of CRC for intensified screening. A large colon cancer screening center in Calgary, Alberta studied the performance of ColonFlag for CRC screening [69]. ColonFlag generated scores based on the ages, sexes, red blood cell parameters, inflammatory cells, and platelets of 17,676 subjects and allowed them to undergo colonoscopy. For advanced precancerous subjects, the odds ratio for a positive ColonFlag result was 2.0 compared to those with normal colonoscopy results with a specificity of 95%. This demonstrated that ColonFlag can use routine blood test results to help identify high-risk groups for precancerous polyps and CRC. The CellMax (CMx®) platform is a system for the enrichment calculation of epithelial circulating tumor cells in the blood [70]. For a cohort of 47 subjects, including 32 donors who underwent colonoscopy and were determined to have CRC, adenomas, or negative results, CMx achieved 100% experimental specificity and 80% clinical sensitivity, and its clinical feasibility was confirmed. In addition to blood cells, a recent study revealed that AI can also be used to analyze the content of serum protein biomarkers to achieve the noninvasive diagnosis of CRC [71].

AI has also been found to play an important role in genetic testing for CRC. Hu et al. [72] designed an experiment to compare the accuracies of three different neural networks (S-Kohonen, BP, and an SVM) for cancer classification based on gene expressions. They clas sified 53 colon cancer patients with UICC II into a relapse group and no-relapse group. They found that the classification accuracy obtained by the S-Kohonen neural network reached 91%, which was much higher than that of the BP (66%) and SVM (70%). In 2017, Xu et al. [73] used an SVM system to identify differentially expressed genes (DEGs) to distinguish patients with high risk and predict prognoses. Through a series of screening and validation studies, 15 genetic markers were identified as predictors of recurrence risk and prognosis for colon cancer patients. Kel et al. [74] developed a method called the “walking pathway” to search for methylated DNA biomarkers for CRC and used AI to analyze cancer-specific enhancers. Zhang et al. [75] developed a counterpropagation artificial neural network (CP-ANN) to obtain higher sensitivity and lower cost for the detection of the BRAF gene mutation, which involves a substitution of valine for glutamic acid at codon 600 (V600E), in CRC using near-infrared testing. When testing for the BRAF V600E mutation in CRC, the CP-ANN achieved a diagnostic sensitivity of 100%, specificity of 87.5%, and accuracy of 93.8%. Furthermore, this method can distinguish the BRAF V600E mutation from the wild type.

AI application in clinicopathological feature analysis

The incidence of CRC is a multi-step process. Most CRC cases are sporadic and span several years, transforming from adenoma to carcinoma [76]. Therefore, screening individuals with early precancerous lesions may lead to a significant decrease in the incidence of CRC [77]. Ito et al. [78] developed an AI endoscopy system for the diagnosis of colon cancer based on a CNN using machine learning images, including 14 cTis cases with endoscopic resection, and 14 cT1a and 13 cT1b cases with surgical resection. Their method analyzed protruding, flat, and recessed lesions, and assisted in detecting colon cancer. The cT1b sensitivity, specificity, and accuracy were 67.5%, 89.0%, and 81.2%, respectively. However, based on its high cost, low efficiency, and poor patient compliance, colonoscopy screening of CRC has encountered many obstacles. As a result, CAD systems have been developed to screen potential CRC patients in high-risk groups prior to colonoscopy. Researchers have developed AI systems to analyze patient information comprehensively to predict the occurrence CRC. Selected information includes gender, age, and complete blood count data. Researchers hope that such systems can encourage patients with positive prediction results to accept endoscopic checkups over time [38]. Similarly, to solve the issue of patient compliance, a team led by Professor Xu designed a method for the early screening of CRC based on copy-number variation (CNV) in plasma

[79]. They determined the arm level of CNV by sequencing whole genomes and then trained an SVM to perform diagnosis. The results demonstrated that the method had higher specificity (88.9%) and sensitivity (91.7%) for early CRC diagnosis compared with the conventional z-score method. Regarding biopsy, Haj-Hassan et al. [80] used a CNN to predict three tissue types in CRC progression, namely benign hyperplasia, intraepithelial neoplasia, and carcinoma, with an accuracy of 99.17%. Song et al. [81] combined machine learning with Fourier transform infrared technology to classify CRC patients into different periods. They adopted the random forest algorithm and the overall prediction accuracy of their method reached above 90%. The manual segmentation of gland specimens is typically time intensive and heavily reliant on subjective judgment. To facilitate CRC grading diagnosis, the Rathore [82] team developed a gland segmentation method based on a deep learning neural network. Two different CNNs were used to classify benign and malignant CRC images with pixel-wise HE staining and their accuracy rates were 98% and 95%, respectively. Subsequently, this team constructed an end-to-end computational pathology pipeline to eliminate subjective differences. They also designed a novel segmentation method. Based on previous studies, Graham et al. [83] improved a CNN and proposed a fully convolutional network called MILD-Net, which compensated for the loss of information caused by max-pooling by reintroducing original images at multiple points within their network to reduce the uncertainty of diagnosis. In 2015, a team of researchers designed an artificial neural network (ANN) to explore the association between CRC-related genes and environmental factors [84]. Since then, methylated DNA has been widely used in AI diagnosis as a biomarker for early CRC. Kel et al. [74] developed an analytical method called the walking pathway to diagnose early CRC by extracting human methylated CpG from blood and feces. Cell-free DNA (cfDNA) has also been used to detect advanced CRC [85]. The proportion of tumor-sourced cfDNA in plasma is small; therefore, Wan et al. [86] designed an AI program to improve the sensitivity of plasma cfDNA extraction for CRC patients. For a CRC cohort heavily weighted toward the early stages of cancer (80% stage I/II), they achieved a mean AUC of 0.92 with a mean sensitivity of 85%. Based on the Cancer Genome Atlas database, Wang et al. [87] designed several ANN models to assist in CRC pathological feature analysis. By using a back propagation and learning vector quantization neural network, they established four diagnostic models for qualitative diagnosis, M0/M1, carcinoembryonic antigen testing, and clinical staging, respectively. Shahbazy et al. [88] introduced optimal factors into their classification algorithm and improved the early diagnosis of CRC by visualizing the relationship between different spectral patterns in a case-control study. Based on an updated random forest model, the F-measure score for TNM staging was 0.89, and the accuracy for five-year disease-free survival (DFS) rates was 84% (AUC of 0.82).

Gupta et al. [89] selected 4021 CRC patients and applied machine learning algorithms to tumor stage prediction by considering tumor aggression scores as a prognostic factor. They found that tumor budding is an auxiliary prognostic factor in the TNM staging system. Therefore, it was set up as an additional prognostic parameter in their CRC diagnosis guide [90]. However, based on the diversity of evaluation systems, the artificial evaluation of tumor budding is inefficient and difficult to popularize. To overcome this issue, Weis et al. [91] established and validated an automatic image processing method to quantify tumor budding in IHC sections of CRC. They combined morphological operations and machine learning techniques, such as k-means and hierarchical clustering, and reliably detected tumor buds in CRC samples.

AI application combined with non-coding RNAs (ncRNAs) in CRC diagnosis

Although the human genome project has been completed, many physiological mechanisms remain unexplained based on present gene sequence information, particularly questions related to tumorigenesis. Therefore, the potential of ncRNAs for tumor diagnosis and treatment has been explored gradually. However, the mechanisms of ncRNAs in tumorigenesis involve a large amount of information and computations, which implies that their analysis requires advanced detection methods and accurate processing instruments. Therefore, AI technology is considered as a bridge to connect ncRNAs with tumor researchers [92]. In

2011, Chang et al. [93] measured different expression profiles of micro RNAs (miRNAs) in 20 pairs of stage II CRC tissues and corresponding normal tissues, designed an ANN algorithm, and then tested its accuracy on 102 samples. They identified three miRNAs (miR-139-5p, miR-31, and miR-17-92) that can predict the tumor status of stage II CRC. However, this approach assumes a general interaction relationship between miRNAs and tumors, which may lead to poor predictive accuracy. To optimize this method, Amirkhah [94] proposed a miRNA-associated tumor prediction method based on naive Bayes classification, called CRCmiRTar. Their model not only predicts miRNAs, but also reveals the interactions between miRNAs and target messenger RNAs, facilitating the construction of a miRNA-tumor interaction network from a new perspective. There, although CRCmiRTar has only been demonstrated for CRC patients, it can be widely used for the detection of other disease-specific genes. ShrinkBayes is an improvement of the traditional prediction model from another perspective [95]. Its designers considered that extrapolation based on the Bayes model could yield excessive degrees of freedom when sample sizes are insufficient; therefore, they introduced ShrinkBayes and demonstrated its predictive accuracy through studies with small sample sizes or complex designs. Xuan et al. [96] proposed a dual-CNN-based prediction method for disease-related miRNA called CNNDMP. CNNDMP explores the deep features of miRNA similarities and disease similarities. It also analyzes the deep features of miRNA-disease associations. Case studies on breast cancer, CRC, and lung cancer have demonstrated the powerful capabilities of CNNDMP for detecting potential disease-associated miRNAs. Afshar et al. [97] screened four CRC-specific miRNAs from a database and accurately classified the sample data as cancerous and non-cancerous data using an ANN. This classification method has also been demonstrated in clinical trials. Classification testing on 297 patients from eight medical centers in Spain revealed that the sensitivity of an SVM classification model was 85%, while its specificity was 90% [98]. In general, AI has been explored in ncRNA-related fields to design new methods for screening CRC molecular markers, which has significantly accelerated the study of ncRNA mechanisms in tumor processes.

In summary, in the field of CRC diagnosis, AI has played an auxiliary role through image processing, tissue segmentation, molecular marker detection, gene prediction, etc. Although some applications have not been completely realized, the potential for AI to make CRC diagnosis more convenient and efficient is beyond question.

AI and CRC therapy

Traditional treatment methods for CRC consist of surgery, chemotherapy, radiotherapy, and immunotherapy. The application of AI technology to CRC treatment can help patients choose treatment methods that are appropriate for them and improve the curative effects of treatment protocols by designing regimens that are more individualized and precise.

AI application in CRC surgery

CRC therapy is primarily surgical. However, some patients may have contraindications and cannot undergo surgeries. Additionally, complications following surgical therapy, such as obstruction or perforation, are problematic for most CRC patients [99]. Therefore, if an accurate preoperative evaluation can be performed, it will aid CRC patients in selecting individualized treatments to improve their prognoses. Ding et al. [100] randomly selected 414 patients with rectal cancer and performed "faster R-CNN" evaluation on magnetic resonance imaging (MRI) plain scan images of pelvic lymph nodes. They designed controlled trials and postoperative follow-up evaluations of rectal cancer to obtain recurrence data. The results demonstrated that compared to conventional MRI evaluation, N staging evaluated based on the faster R-CNN was closer to the pathological criteria, indicating that applying a faster R-CNN has greater clinical value for preoperative staging and prognosis assessment for rectal cancer. Additionally, a faster R-CNN can also evaluate extramural vascular invasion (EMVI) in CRC patients. EMVI refers to tumor metastasis in the vascular lumen, where original tumor cells invade the area outside the muscularis propria of the intestine, which is associated with poor outcomes for CRC [101]. AI can conduct a complete clinical evaluation of rectal cancer EMVI prior to surgery, which implies that patients with positive EMVI can receive neoadjuvant chemoradiotherapy prior to surgical therapy, which can significantly re-

duce local recurrence and improve prognosis. Ichimasa et al. [102] designed an AI for the preoperative prediction of lymph node metastasis (LNM), to aid in predicting the need for additional surgery following endoscopic resection of T1 CRC. They selected T1 CRC patients who had undergone endoscopic resection from 2001 to 2016 to perform machine learning. Their AI model analyzed 45 clinicopathological factors, where surgical specimens were used as the gold standard for the existence of LNM. For all models, sensitivity was 100%, specificity was 66%, and accuracy was 69%. Overall, the number of unnecessary surgeries identified by the AI model was more compared to the guidelines in America, Japan, and Europe. The emergence of the Da Vinci robot was a major milestone in tumor surgical therapy. This robot is constantly updated based on continual technological progress and evolving social requirements [103]. We will witness the growing popularity of robot-assisted surgery in the CRC surgical therapy field. A retrospective study of 71 patients who underwent rectal low anterior resection revealed that robot-assisted surgery had a lower conversion rate and lower complication rate compared to traditional surgery [104]. Another study with 61 patients found that robot-assisted surgery resulted in a less pronounced inflammatory response compared to open surgery [105]. Yang et al. [106] explored the security of robots combined with laparoscopic surgery. In addition to the existing benefits of laparoscopic surgery, robot-assisted surgery has the potential advantage of protecting the pelvic autonomic nerve. Some researchers have analyzed the learning curve of robot-assisted colorectal surgery and pointed out that robots have a faster learning curve, which implies that fewer training cases will be required for robot-assisted colorectal surgery in the future [107]. Overall, robot-assisted colorectal surgery has better performance in terms of both short- and long-term outcomes [108].

AI application in CRC chemotherapy

While exploring the improvement of CRC drugs, a team led by Professor Sylvain Martel developed a system called NamiRobot that can deliver drugs to cancer cells in a targeted manner. This robot can target cancer tumors more precisely by sensing the reduced oxygen levels caused by the proliferation of cancer cells and can also deliver drugs to hypoxic regions [109]. They went on to develop a computer-assisted magnetotactic displacement method to drive the drug-loaded magnetotactic bacteria MC-1, further enhancing the ability to target hypoxic regions [110]. AI technology can also promote research on new drugs. In combination with natural products, Cruz et al. [111] used machine learning with molecular and nuclear magnetic resonance to detect the half-maximal inhibitory concentration (IC50) of a new drug that targeted the colon cancer cell line HCT116. The overall prediction accuracy was over 63%. The improvement of molecular-docking-based virtual screening has facilitated the emergence of drug polypharmacology. A DNN-based filter was designed to develop tumor chemotherapeutic drugs that inhibit both PI3K and tankyrase. This technique has provided technical support for designing multi-targeted drugs [112]. AI technology has also been applied in traditional Chinese medicine (TCM). Lin et al. [113] examined 261 cases of CRC treated by herbalists. They designed a model called DeepMedic to provide standardized terminologies for symptoms and prescriptions in TCM and trained their system to deliver accurate TCM diagnoses and suggest prescriptions for the treatment of CRC. Ferrari et al. [114] developed an AI model based on MRI texture analysis to assess whether patients went into a pathology complete response (pCR) or non-response (NR) following neoadjuvant chemotherapy (CRT). They used the random forest algorithm to construct two AI models and achieved AUC values of 0.86 and 0.83 for pCR patients and NR patients, respectively. The most significant effect of this AI model is that it can identify patients who will exhibit low acceptance at the early stages of chemotherapy and help doctors adjust treatment regimens as soon as possible. Shi et al. [115] processed data from pretreatment MRI and mid-radiation follow-up MRI images captured three to four weeks after the start of CRT. They implemented a CNN and analyzed a multi-parametric MRI protocol, including T2. Multi-period analysis effectively reduces errors and increases the accuracy of predictions. Oyaga-Iriarte et al. [116] constructed an SVM-based AI model to predict the rate of toxicity (resulting in leukopenia, neutropenia, and diarrhea) of irinotecan in metastatic CRC. They collected basic information from 20 CRC patients, collected their serums at different periods of treatment, and constructed an AI model based on the

contents of irinotecan and its metabolites. They predicted high degrees of leukopenia, neutropenia, and diarrhea with accuracies of 76%, 75%, and 91%, respectively.

AI application in the personalization and precision of CRC

The personalization and precision of cancer treatments have become major themes in oncology research. The International Business Machines Corporation, in conjunction with the Memorial Sloan Kettering Cancer Center, developed a system called "Watson for Oncology" (WFO). WFO is an AI system that can assist in the precision medicine treatment of tumors. It can automatically extract medical characters from doctor records and translate them into a practical language for learning. According to Dr. Anderson, approximately 90% of Watson's current recommendations during clinical trials are in line with those of its human counterparts [117]. In South Korea, the concordance rate between chemotherapy regimens for CRC determined by a multidisciplinary team (MDT) and WFO recommendations was also analyzed [118]: In 61 CRC samples, the concordance rate between WFO and the MDT was 46.4%, which increased to 88.4% after including the "for consideration" category. This experiment proved that the functionality of WFO can be enhanced through continuous adjustments. Tokyo University Hospital has also used WFO for the gene sequencing of cancer patients and received results within four to five days, significantly reducing wait time [119]. The WFO human caring model provides more individualized and considerate nursing services, which can effectively alleviate the discomfort of patients during the process of chemotherapy [120]. Personalized medicine has predominantly focused on genetically altered cancer genes that stratify drug responses. An AI model designed by Keshava et al. [121] can identify subpopulations that react differently to inhibitors of the same or different targets and can help doctors understand the mechanisms of resistance and pathway cross-talk. As the corresponding database continues to be enriched, this model can be used to identify new cancer subpopulations, analyze their genetic biomarkers, and find effective drug combinations. AI has also shown impressive performance for targeted drugs. Ding et al. [122] trained an AI system to screen effective molecular markers by integrating transcriptomics and proteomics data at the system biology level. Candidate molecular markers were integrated to predict biomarkers and develop targeted drugs, which provide assistance for the clinical treatment of CRC. S100A9 is a potential protein target for the targeted therapy of CRC, but the scarcity of atom-level data makes it difficult to develop drugs for S100A9. Lee et al. [123] designed an AI model to predict the protein-protein interactions of S100A9 with various drugs and tested the specificity of the drugs on 2D molecular descriptors, providing technical support for the design of new targeted drugs. AI can also be combined with metabolomics to identify drugs that target cancer-specific metabolism [124]. Nowak et al. [125] focused on drug repurposing to use existing cancer drugs to treat new indicators. They combined specific phenotypic studies with mechanistic studies, chemical genetics, and omics assays to create AI models that successfully predicted disease-drug pairs. Additionally, the application of AI in clinical management cannot be ignored. Horta et al. [126] collected information from CRC surgical patients at a private hospital in Lisbon over a 10-month period, to train an AI model to support decisions regarding the selection of patients who should be offered co-management services.

In summary, with the advent of the big data era, treatment for CRC will become personalized and diversified. The development of AI cannot only reduce the burden on clinicians effectively, but also help provide more accurate and humanistic medical services for each patient.

Artificial intelligence and predicted colorectal cancer prognosis

The prognoses of patients with CRC are some of the most important indicators for therapy evaluation. A poor prognosis often refers to tumor metastasis and lymphocyte infiltration. In recent years, although medical technology has developed continuously, the prognoses of CRC patients have not improved significantly. The emergence of AI has allowed clinicians to predict the prognoses of CRC patients more quickly and accurately.

Grundner et al. [127] used the genetic markers of CRC patients to train a model based on

different algorithms. Their model can be used to predict overall survival (OS), DFS, recurrence survival rates, and other clinical prognostic results. Peng et al. [128] developed a prognostic ANN scoring system for CRC in stage IIA, which can predict the 10 y OSs and DFSs of IIA CRC patients based on clinical data. Mezheyeuski et al. [129] proposed a computer-aided analysis method for tissue sections based on multifractal analyses of cytokeratin-stained tumor sections. Their method quantitatively evaluates the morphological complexity of tumor-stroma interfaces and proves that it is possible to obtain prognosis information from graph data with the assistance of AI. A study by Kather et al. [130] demonstrated that AI can assess the independent prognostic factors of CRC (such as OS, CRC-specific OS, and recurrence-free OS) based on pathological images with an accuracy of 94%. Geesink et al. [131] used a semi-automatic method based on deep learning to classify the tumor-stroma ratios (TSRs) of CRC pathological specimens. The TSR is an independent prognostic factor and patient assignment that can effectively assist in prognosis prediction. Tumors are assigned "stroma-high" or "stroma-low" based on TSRs. Skrede et al. [132] constructed 10 CNNs to search for CRC prognostic biomarkers. They collected more than 12 million image tiles with distinct outcomes to train the 10 models and integrated the results of using cancer-specific survival as the primary metric for selecting novel prognostic biomarkers. Based on potential prognostic biomarkers, such as mesothine, researchers can also use AI techniques to assess correlation coefficients [133].

The metastasis of CRC is typically a marker of a malignant prognosis. As early as 2015, researchers constructed deep learning models based on protein-protein interaction networks to diagnose CRC metastases and improved these models by selecting more effective molecular markers and algorithm parameters [134]. Subsequently, Saghapour et al. [135] combined the logistic regression model (LRM) with an ANN system to create a mixed prediction model in which the LRM performed parameter selection for the ANN, which was used for analysis. This model was determined to provide high accuracy for predicting the metastasis of late-stage CRC. Zhi et al. [136] found that SVM models can be used to screen the DEGs of metastatic CRC. Through the integration of five databases, their SVM system identified 40 characteristic genes, as well as protein processing in the endoplasmic reticulum, AMP-activated protein kinase signaling pathways, and ubiquitin-mediated proteolysis pathways. Their model can help precisely distinguish metastatic CRC samples from non-metastatic samples. Regarding CRC LNM, Takamatsu et al. [137] extracted information from cytokeratin immunohistochemical images and trained an AI model for the prediction of LNM. They obtained a sensitivity of 80.0%, specificity of 94.5%, and AUC of 0.938. These values are higher than those of traditional prediction methods. The DNN model designed by Zhou et al. [138] can assist in the automatic identification of metastatic lymph nodes in the pelvic cavities of CRC patients. Lu et al. [139] assessed the accuracy of a faster R-CNN system for LNM diagnosis. Nearly 80000 training epochs were used to construct an automatic testing platform that realized an MRI diagnosis time of 20 s, which is 30 times faster than the average time taken by radiologists. The corresponding AUC was 0.912, indicating good clinical feasibility. The infiltration of immune cells is also a key factor in CRC metastasis [140]. Eyraud et al. [141] performed computer-aided analysis of whole-slide digital images derived from tissue microarrays to assess the cell infiltration of CRC and explored the relationship between tumor microenvironments and CRC metastasis. Ge et al. [142] used CIBERSORT to analyze the infiltration of 22 immune cells in tumor microenvironments and screened 404 immune-related genes in CRC, as well as 40 immune-related genes in adjacent non-tumor tissues. Reichling et al. [143] used digital tumor parameters to quantify lymphocyte density and the surface area of infiltration in the tissues surrounding tumors automatically and analyzed the prognoses of CRC patients in stage III.

In the near future, AI technology will help doctors perform diagnosis and treatment, and also provide CRC patients with personalized and accurate prognosis evaluations. AI makes it possible to predict outcomes based on various factors before accepting a treatment, thereby helping clinicians make sound medical decisions.

Conclusions and prospects

The development of AI for CRC diagnosis and treatment has progressed through the following stages: 1) understanding cancer at the molecular level through deep learning, 2) assisting in the diagnosis and prognosis of CRC based on images and pathological specimens, 3) clinical drug design and screening, and 4) promoting the personalization and precision of CRC diagnosis and treatment. Owing to the continuous improvements in AI technology, specifically in terms of image recognition and natural language extraction, AI is bound to play an increasingly important role in the field of CRC treatment (**Table 1**). The rapid development of the internet has provided AI unlimited possibilities: First, Imler et al. [144] designed a quality-measuring AI system. Their system can monitor colonoscopy results from many institutions simultaneously, using blinded, paired, and annotated expert manual reviews as a reference standard. As this system can be put into practice, improving detection rates and controlling costs will be a reality for potential CRC patients. Second, AI can be integrated with mobile devices. Marzuki et al. [145] from Malaysia released an AI-supported mobile app, called ColorApp, on the Google store to share information regarding CRC. This app uses the nominal group technique, targets community educationists and clinicians, as well as community representatives, and enables users to receive current information and perform simple analysis. Third, AI can provide personalized healthcare as a virtual assistant for individuals and families. Some digital devices exist that can measure a user's heart rate and blood pressure in real time. AI can be used to promote the integration of services and data, even make a preliminary diagnosis, which will lead to more streamlined and efficient care pathways. It is evident that AI can make drastic changes to the landscape of the healthcare system and replace the need for a medical consultation in some cases [146].

In recent years, the use of AI in cancer diagnosis and treatment has become a hot topic among medical researchers, and developments in computer hardware have enabled this narrow field to become fertile ground for clinicians. However, training a computer to "think" like a human is a complex task that depends on various factors. The continued development of AI technology still faces many limitations. First, AI diagnosis lacks reliable guidelines and gold standards. In many cases, pathologists provide inconsistent judgments regarding the same pathological section (particularly early lesions), but such inconsistencies can be reduced by providing supportive evidence regarding the signs and symptoms of various cases. When an AI system diagnoses pathological sections, it only focuses on external input criteria, neglecting other information regarding the patient, which could lead to overdiagnosis [147]. Second, a lack of stratification of image signal strength limits the accurate diagnosis of tumors. There are many immune landscapes for cancer, which implies that imaging signals must be differentiated in more subtle ways to provide more accurate guidance for immunotherapy. Third, developing an AI system is expensive and difficult. During the training of a deep learning network, a large number of training samples and verification samples are required to improve accuracy. Even if an improved algorithm is developed to handle small sample sizes, its accuracy will inevitably be impacted [95]. Similarly, based on the quantity of the training sample, training processes require powerful computer configurations and long training times. Machine maintenance is also excessive. Furthermore, because AI training methods are extremely complex, nonprofessionals can only conduct auxiliary diagnosis and treatments based on exploited functions, which makes it difficult to update databases and algorithms when encountering novel cases. This significantly affects system development and popularization. Fourth, internet equipped with AI faces issues in terms of user screening and privacy protection. Increasing heterogeneous data sources and the richness of user data strongly increases the possibility of anonymized data reidentification. A suitable technical solution to mitigate the challenge of preserving privacy while answering the increasing need of data-driven science for accessing large genomic phenotypic datasets is nonexistent [148].

However, the general application prospects of AI in medicine are optimistic. We believe that in the near future, AI will be closely integrated with the various aspects of medicine and promote the progress of medicine to a greater extent.

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Table 1. The application of AI in CRC diagnosis and treatment

Types of AI	Authors/ Year	Type of experiment	Purpose	Sample size	All types of AI used	Results	Ref.
ANN (Artificial neural network)	Wan et al./2019	Retrospective	Detection the cfDNAs in CRC patients	546 CRC and 271 non-cancer controls	ANN	AUC 0.92 Sensitivity 85% Specificity 85%	[86]
	Chang et al./2011	Prospective	Finding miRNAs that can predict tumor status in stage II CRC	20 paired stage II tumor and normal tissues		Median accuracy: miR-139-5p 90.9% miR-31 90.9% miR-19b-1 100%	[93]
	Afshar et al./2019	Prospective	Identification of CRC-miRNAs biomarkers	371 patients and 150 controls		AUC 1	[97]
	Peng et al./2016	Prospective	Prediction of OS and DFS of stage IIA CRC patients	117 stage IIA CRC patients		Accuracy 87.9% Sensitivity 53.8% Specificity 97.8%	[128]
	Saghapour et al./2017	Retrospective	Prediction of metastasis of advanced CRC	54 specimens from database		Sensitivity 100% Specificity 95.8%	[135]
	Zhang et al./2019	Prospective	Detection of genetic mutations in colon cancer	312 CRC tissue samples	CP-ANN (Counter propagationartificial neural network)	Accuracy 93.8% Sensitivity 100% Specificity 87.5%	[75]
	Amirkhah et al./2015	Retrospective	Prediction of CRC-associated miRNAs and construction of interactive network	204 functional interactions	ANN and Naïve Bayes	AUC 0.956 Sensitivity 93% Specificity 86.1%	[94]
CNN (Convolutional neural network)	Gregor et al./2018	Retrospective	Improving the adenoma detection rate	More than 2000 patients	CNN	Accuracy 96.4% AMC 0.991	[47]
	Zhang et al./2017	Retrospective	Automatic Detection and Classification of Colorectal Polyps	215 polyps		Precision 87.3% recall rate 87.6% accuracy 85.9%	[48]
	Akbari et al./2018	Retrospective	A method of polyp accurate segmentation	200 images		Accuracy 97.7% Specificity 74.8% Sensiticity 99.3%	[53]
	Blanes-Vidal et al./2019	Prospective	Automatical detection of polyps during capsule endoscopy	255 patients		Accuracy 96.4% Sensitivity 97.1% Specificity 93.3%	[56]
	Eycke et al./2018	Retrospective	Separating the glands from the epithelium in the images	165 HE images and 4 sets of IMC images		Accuracy 91.2%	[67]
	Ito et al./2019	Prospective	Assistance on diagnose of stage 1b colon cancer	190 colon lesion images		Accuracy 67.5% Sensitivity 87.2% Specificity 89%	[78]
	Haj-Hassan et al./2017	Prospective	Prediction of 3 types of tissue associated with CRC progression by pathological biopsy	30 CRC patients		Accuracy 99.2%	[80]
	Rathore et al./2017	Retrospective	Multi-step glandular segmentation model	3 datasets		Accuracy 98% and 95% respectly	[82]
	Weis et al./2018	Prospective	Detection of tumor budding-associated TNM stage	20 CRC patients			[91]
	Shi et al./2019	Prospective	Prediction of chemoradiation therapy response in rectal cancer	51 patients		pCR accuracy 86% Good response (GR) accuracy 93%	[115]

	Kather et al./2019	Retrospective	Prediction of OS and DFS of CRC from image informations	86 CRC tissue slides		Accuracy 94%	[130]
	Geesink et al./2019	Prospective	Classification of Tumor-stroma ratio (TSR) for rectal cancer whole-slide images	129 rectal adenocarcinoma patients		Accuracy 94.6%	[131]
	Skrede et al./2020	Retrospective	Searching for prognosis markers of CRC	920 patients		Accuracy 76% Sensitivity 69% Specificity 66%	[132]
	Zhou et al./2019	Prospective	Automatic identification of pelvic metastatic lymph nodes from CRC tissues	301 patients		AUC 0.886	[138]
	Korsuk et al./2016	Retrospective	Classification of nuclei and detection of tumor through pathology images	100 colon cancer specimes stained with HE	SC-CNN (Spatially constrained convolutional neural network)	Accuracy 78.1%	[65]
	Xuan et al./2018	Retrospective	Prediction of miRNA-diseases	Data from dbDEMC, miRCancer and PhenomiR	DCNN (Dual convolutional neural network)	Average AUC 0.538	[96]
	Ding et al./2019	Retrospective	Diagnosis of metastatic lymph node for preoperative assessment	414 rectal cancer patients	Faster R-CNN (Faster region-based convolutional neural network)	r value 0.912	[100]
	Lu et al./2018	Prospective	Assistance on MRI diagnosis of lymph node metastasis of CRC	414 patients		AUC 0.912	[139]
SVM (Support vector machine)	Takemura et al./2012	Retrospective	Predicion of the histology of colorectal tumors	371 colorectal lesions	SVM	Accuracy 97.8% sensitivity 97.8% specificity 97.9%	[49]
	Rathore et al./2015	Prospective	Classification of normal and malignant colon pathology samples	174 colon biopsy images		Detection accuracy 95.40% Grading accuracy 93.47%	[62]
	Rathore et al./2015	Prospective	Classification of colon biopsy images	174 colon biopsy images		Accuracy 98.07%	[63]
	Yang et al./2019	Prospective	Classification of colon patholoty images through accurate color and spatial information	180 pathology images		Accuracy 83.1% Sensitivity 81.9% Specificity 84.2%	[64]
	Soares et al./2017	Retrospective	Classification of CRC samples and normal samples by fluorescence wavelength	dataset including 12,341 wavelengths		Sensitivity 87% Specificity 95%	[68]
	Xu et al./2017	Retrospective	Prediction on risk of recurrence of colon cancer and their prognosis	5 microarray datasets of colon cancer samples		Accuracy 92%	[73]
	Xu et al./2018	Prospective	Screening early CRC by copy-number variation (CNV) in plasma	70 samples		Sensitivity 91.7% Specificity 88.9%	[79]
	Gupta et al./2019	Retrospective	Prediction of TNM stage and prognosis of CRC	4021 CRC patients		F-measure 0.89 Accuracy 84% AUC 0.82	[89]
	Villanueva et al./2019	Prospective	Classification of clinical CRC patients based on miRNA screening	297 patients		AUC 0.92 Sensitivity 85% Specificity 90%	[98]
	Ichimasa et al./2018	Retrospective	Prediction of the need for additional surgery after endoscopic resection of T1 CRC	690 patients		Accuracy 100% Sensitivity 69% Specificity 66%	[102]

	Zhi et al./2018	Retrospective	Screening the differentially expressed genes (DEGs) for CRC metastasis	Dataset from The Cancer Genome Atlas database		Precision 98%-100%	[136]
	Ding et al./2019	Retrospective	Classification and integration of biomarkers	Information from Gene Expression Omnibus (GEO) database	RFE-SVM (Recursive feature elimination-SVM), RF etc.	Several models' accuracy over 80%	[122]
CAD (Computer-aided diagnosis)	Stefanescu et al./2016	Retrospective	Diagnosis for advanced colorectal cancer in confocal laser endomicroscopy	1035 images	CAD	accuracy error 15.5%	[58]
	Tamai et al./2017	Prospective	Classification of colorectal lesions for magnifying narrow-band imaging	121 lesions		Sensitivity 83.9% Specificity 82.6%	[60]
	Kominami et al./2016	Prospective	Prediction of histologic diagnoses of colorectal lesions	41 patients	Real-time CAD and SVM	Accuracy 93.2% Sensitivity 93.0% Specificity 93.3%	[50]
	Mori et al./2018	Prospective	Prediction of histologic diagnoses of colorectal lesions after application of NBI	791 patients	Real-time CAD	pathologic prediction rate 98.1%	[51]
	Takeda et al./2017	Retrospective	Diagonsis for invasive colorectal cancer through endocytoscopy images	375 lesions	EC-CAD (Endocytoscopy computer-aided diagnosis)	Accuracy 94.1% Sensitivity 89.4% Specificity 98.9%	[59]
RF (random forest)	Song et al./2019	Retrospective	Classification of stages of CRC	1000 samples	RF	Accuracy more than 90%	[81]
	Ferrari et al./2019	Prospective	Classification of pCR and NR of locally-advanced rectal cancer patients after neoadjuvant chemotherapy	55 patients		pCR AUC 0.86 NR AUC 0.83	[114]
	Oyaga-Iriarte et al./2019	Prospective	Prediction of drug toxicity in metastatic CRC patients	20 CRC patients	RF, SVM and BSLR (Backward stepwise logistic regression)	Accuracy: leukopenia 76% neutropenia 75% diarrhea 91%	[116]
	Lee et al./2019	Retrospective	Measuring the specificity of the drug to the target	Information from patent searching	RF, DT (Decision tree) and Naïve Bayes	AUC: test set validation 0.859 cross-validation 0.839	[123]
	Grundner et al./2018	Retrospective	Prediction of CRC clinical outcome		RF and neural network	Accuracy: relapse 71% RCT-R 70%	[127]
	Takamatsu et al./2019	Retrospective	Prediction of lymph nodes metastasis of early CRC	397 T1 CRC patients	RF and SML (Supervised machine learning)	AUC 0.938 Sensitivity 80% Specificity 94%	[137]
Surgical robot	Spanheimer et al./2017	Retrospective	Robot-assisted surgery	71 patients	Surgical robot	Lower conversion rate: 0% to 7%	[104]
	Yang et al./2018	Prospective	Robot-assisted surgery	300 patients		Advantage in pelvic autonomic nerve protection	[106]
Waston	Kim et al./2019	Prospective	Providing individualized and accurate diagnosis and treatment plan	61 CRC patients	Wason	concordance rate 88.4%	[118]
	Miyano et al./2019		Whole genome sequencing and interpretation of the data for less turnaround time				[119]

	Akturk et al./2018	Prospective	Measuring the meaning of life and symptom management in cancer patients undergoing chemotherapy	158 patients	Watson's Human Caring Model	posttest score 164.21±36.5 General Symptom Inventory score 55.06±13.19	[120]
Others	Fernandez et al./2016	Prospective	Automatical detection of polyps during colonoscopy	24 patients	Energy map	Accuracy 70.4 Specificity 72.4%	[45]
	Hilsden et al./2018	Retrospective	Screening precancerous lesions of colon cancer through basic patient informations	17,676 individuals	ColonFlag	odds ratio 2.0 Specificity 95%	[69]
	Gupta et al./2019	Prospective	Analyse system for enrichment calculation of epithelial circulating tumor cells (CTCs) in blood	32 young healthy donors	CellMax	Clinical sensitivity 80% Clinical specificity 80%	[70]
	Hu et al./2015	Prospective	Classification of CRC based on gene information	53 colon cancer patients	S-Kohonen	Accuracy 91%	[72]
	Shahbazy et al./2016	Retrospective	Detection the TNM stage and DFS of CRC	289 CRC patients	SKN (Supervised Kohonen network)	TNM stage F-meature 0.89 DFS accuracy 84%, AUC 0.82	[88]
	Sylvain Martel et al./2016		Cancer cell targeted drug delivery		Cancer-Fighting Nanorobots		[109, 110]
	Cruz et al./2018	Retrospective	Detection of drug semi-inhibitory concentration	18,850 organic compounds	CADD (Computer-aided drug design)	overall predictability accuracies more than 63%	[111]
	Berishvili et al./2018	Retrospective	Design of multi-target drugs	Compounds datas from ChEMBL database v.23	DNN (Deep neural network)	AUC 0.96	[112]
	Lin et al./2019	Retrospective	Providing diagnosis and prescription of Chinese medicine	261 CRC cases	Neural network analysis	Similarity to medical records 81.9%	[113]
	Keshava et al./2019	Prospective	Identifying subpopulations for patients based on pharmacological response	327 patients	SEABED (SEgmentation And Biomarker Enrichment of Differential treatment response)		[121]
	Pacheco et al./2019	Retrospective	Network-based drug target prediction targeting cancer-specific metabolism	Information from database	Rfastcormics (Fastcormics RNA-seq workflow)	Accuracy above 94%	[124]
	Horta et al./2018	Retrospective	Assessment of the necessity of co-management in internal and surgical department	Electronic clinical health records of CRC patients	Takagi-Sugeno fuzzy modelling	AUC 0.81 Accuracy 77% Sensitivity 74% Specificity 78%	[126]
	Ge et al./2019	Prospective	Analysing the nvasion of immune cells in tumor microenvironment	404 CRC and 40 adjacent non-tumorous tissues	CIBERSORT	concordance index: TNM stage I-II 0.69 stage III-IV 0.71 AUC over 0.67	[142]
	Reichling et al./2020	Retrospective	Automatical quantification of the lymphocyte density and surface area	Database of 1018 patients	LASSO (Least absolute shrinkage and selection operator)	less than 10% relapse risk	[143]

Notes: CNN: A kind of deep feedforward neural network composed of convolutional layer and pooling layer. Its artificial neurons can simultaneously respond to a part of surrounding units in the coverage area, which has excellent performance for large-scale image processing. ANN: A mathematical model of distributed parallel information processing that mimics the behavioral characteristics of animal neural networks. It is widely used to information process and storage, and has a certain ability of self-learning and self-adaptation. CAD: A method that combines imaging and medical image processing technology with the computational power of computers to assist the detection of lesions and improve the accuracy of diagnosis. SVM: A stratified discriminant model optimized by dual theory, which shows many unique advantages in solving small sample, nonlinear and high-dimensional pattern recognition. RF: An ensemble learning method that takes decision tree as the basic unit, which integrates multiple classification results before output, and can process variable input samples with excellent accuracy. Naïve Bayes: A commonly used supervised learning algorithm based on Bayesian theory, which is characterized with multivariate classification, biased and unbiased class probabability, no iteration and high learning efficiency. Watson: A technology platform that uses cognitive systems to reveal insights from unstructured data through natural language processing and machine learning, with the steps of understanding, learning, reasoning and interaction. Surgical robot: Surgical robot is classified into dominant type and auxiliary type. It can improve the success rate of surgery by learning surgical skills, skill decomposition and analysis, and surgical process analysis and learning through machine learning.

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