ISSN 2644-3236 (online)

Artificial Intelligence in *Gastroenterology*

Artif Intell Gastroenterol 2021 February 28; 2(1): 1-9

Published by Baishideng Publishing Group Inc

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Artificial Intelligence in Gastroenterology

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Bimonthly Volume 2 Number 1 February 28, 2021

MINIREVIEWS

Artificial Intelligence in Gastroenterology

Bimonthly Volume 2 Number 1 February 28, 2021

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ABOUT COVER

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AIMS AND SCOPE

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

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

INDEXING/ABSTRACTING

There is currently no indexing.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
Artificial Intelligence in Gastroenterology

ISSN
ISSN 2644-3236 (online)

LAUNCH DATE
July 28, 2020

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Rajvinder Singh, Ferruccio Bonino

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2644-3236/editorialboard.htm

PUBLICATION DATE
February 28, 2021

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Artificial Intelligence in Gastroenterology

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Artif Intell Gastroenterol 2021 February 28; 2(1): 1-9

DOI: 10.35712/aig.v2.i1.1

ISSN 2644-3236 (online)

MINIREVIEWS

Artificial intelligence and machine learning could support drug development for hepatitis A virus internal ribosomal entry sites

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Author contributions: Kanda T performed the majority of the writing and prepared the figures and tables; Sasaki R performed data acquisition and writing; Masuzaki R provided input in writing the paper; Moriyama M designed the outline and coordinated the writing of the paper; all authors have read and approve the final manuscript.

Supported by The Japan Agency for Medical Research and Development, No. JP20fk0210075.

Conflict-of-interest statement: There is no conflict of interest associated with any authors who contributed their efforts to this manuscript.

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Abstract

Hepatitis A virus (HAV) infection is still an important health issue worldwide. Although several effective HAV vaccines are available, it is difficult to perform universal vaccination in certain countries. Therefore, it may be better to develop antivirals against HAV for the prevention of severe hepatitis A. We found that several drugs potentially inhibit HAV internal ribosomal entry site-dependent translation and HAV replication. Artificial intelligence and machine learning could also support screening of anti-HAV drugs, using drug repositioning and drug rescue approaches.

Key Words: Artificial intelligence; Hepatitis A virus internal ribosomal entry sites; Cap-independent translation; Antivirals; Severe hepatitis A; Glucose-regulated protein 78

Core Tip: In certain areas, it is difficult to perform universal hepatitis A virus (HAV) vaccination. We found that several drugs potentially inhibit HAV internal ribosomal entry sites-dependent translation and HAV replication. After the application of machine and deep learning, artificial intelligence identified effective anti-HAV drugs more quickly, using drug repositioning and drug rescue.

Citation: Kanda T, Sasaki R, Masuzaki R, Moriyama M. Artificial intelligence and machine learning could support drug development for hepatitis A virus internal ribosomal entry sites. *Artif Intell Gastroenterol* 2021; 2(1): 1-9

URL: https://www.wjgnet.com/2644-3236/full/v2/i1/1.htm

DOI: https://dx.doi.org/10.35712/aig.v2.i1.1

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Japan

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): E

Received: October 15, 2020
Peer-review started: October 15, 2020
First decision: December 17, 2020
Revised: December 29, 2020
Accepted: February 12, 2021
Article in press: February 12, 2021
Published online: February 28, 2021

P-Reviewer: Raiter A, Ravaioli F
S-Editor: Wang JL
L-Editor: A
P-Editor: Li JH

INTRODUCTION

Infection with hepatitis A virus (HAV) can lead to acute hepatitis, occasionally resulting in acute liver failure, which is associated with death or liver transplantation[1,2]. In developing countries, HAV generally infects humans in childhood, and people have immunity against HAV without HAV vaccination[3]. In India, however, the prevalence of anti-HAV antibodies is lower now in adolescents and young adults (approximately 55% in 5-15 years in India) than before (approximately 90%)[3]. In some developed countries where there are no universal vaccination programs, such as Japan, people have less immunity against HAV than levels observed in the past[4,5].

HAV infects humans through the fecal-oral route when HAV-contaminated foods and water are ingested[6]. Recently, hepatitis A has also been recognized as a sexually transmitted disease[7]. Several effective HAV vaccines are available, but they are relatively expensive, and in some countries, it is difficult to perform universal vaccination[4,5]. Therefore, to prevent severe hepatitis A, it may be better to develop antivirals against HAV[8].

Recently, information and communication technology, and artificial intelligence (AI) have played roles in daily clinical practice[9,10]. AI also plays an important role in drug discovery[11]. With the progress of machine learning methods and the accumulation of pharmacological data, AI has become a powerful data mining tool in the area of drug discovery, such as *in silico* screening, quantitative structure-activity relationship (QSAR) analysis, *de novo* drug design, and *in silico* evaluation of absorption, distribution, metabolism, excretion and toxicity[12].

Structure-based drug design is becoming an essential tool for faster, more cost-efficient drug discovery, compared to traditional methods[13]. The combination of AI and deep learning, which is a family of machine learning models that use artificial neural networks, may be a more powerful tool for drug discovery. The associations of machine learning, deep learning and AI are shown in Figure 1. Moreover, network-based *in silico* drug efficacy screening allows us to predict novel drug-disease associations, which may provide us with drug repositioning or drug rescue information[14]. In this minireview article, we discuss the recent involvement of AI in drug discovery and its application in the development of antivirals against HAV in the near future.

HAV INTERNAL RIBOSOMAL ENTRY SITE-DEPENDENT TRANSLATION AND HAV REPLICATION

Translation of HAV protein is performed in a cap-independent manner under the control of the internal ribosomal entry site (IRES), which is mainly located at 5' untranslated region (5'UTR)[15]. It was reported that the HAV 5'UTR was more than 25-fold less active than the encephalomyocarditis virus IRES in producing translated proteins[16]. Thus, the relatively weaker activity of the HAV IRES may be due to a reduced affinity for several cellular translation factors[16]. Mutations within the HAV 5'UTR could enhance cap-independent translation in African green monkey kidney BS-C-1 cells[17]. Further studies are needed to identify specific mutations related to the severity of hepatitis A[18-20], although among HAV strains from HAV outbreaks in Korea and Japan, we did not identify specific mutations associated with severe hepatitis A in the HAV 5'UTR[21,22]. We also demonstrated that the inhibition of HAV IRES activity by small interfering RNAs (siRNAs) targeting HAV IRES could lead to the suppression of HAV replication[23]. Therefore, HAV IRES is an attractive target of antivirals against HAV.

IMPORTANT FACTORS INTERACTING WITH HAV IRES

HAV is a nonenveloped and enveloped positive-sense single-stranded RNA virus approximately 7.6 kb in length[24,25]. The HAV genome includes a 5'UTR, one open reading frame encoding structural (VP4, VP2, VP3, VP1 and 2A) and nonstructural proteins (2B, 2C, 3A, 3B, 3C and 3D) and a 3'UTR[26].

Among HAV proteins, HAV proteinase 3C suppressed HAV IRES-dependent translation[27]. Furthermore, HAV 3C cleaves the polypyrimidine tract-binding protein (PTB), which interacts with the HAV IRES[27,28]. Among host proteins, autoantigen La[27], glyceraldehyde-3-phosphate dehydrogenase[29], PTB[28], poly(C) binding protein

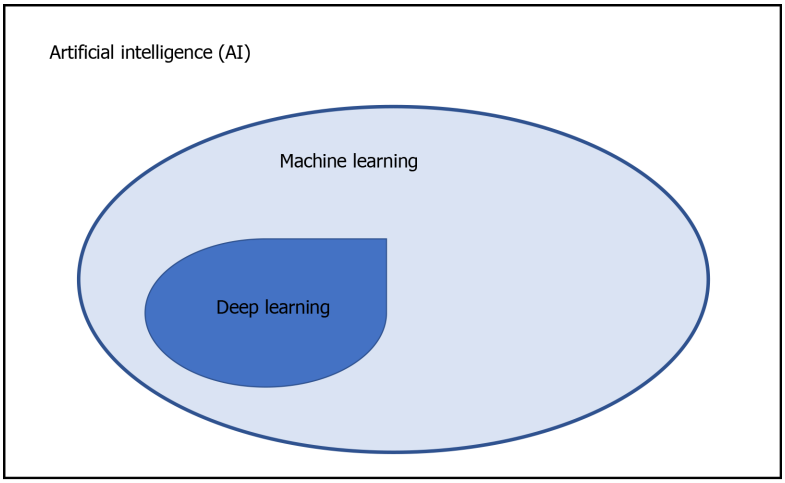

Figure 1 Association of artificial intelligence, machine learning and deep learning.

2[30], polyadenylate-binding protein-1[31], eukaryotic translation initiation factor 4E[32] and eukaryotic translation initiation factor 4E[33] are reported to interact with HAV IRES.

We demonstrated that siRNA against cellular cofactors for HAV IRES could inhibit HAV IRES-mediated translation[34]. The Janus kinase (JAK) inhibitors SD-1029 and AG490 could reduce La protein expression and inhibit HAV IRES-mediated translation as well as HAV replication[34]. The JAK2 inhibitor AZD1480 could reduce La expression and inhibit HAV IRES activity and HAV replication[35]. We also reported that the sirtuin inhibitor sirtinol[36] and broad-spectrum antivirals, such as amantadine[20,37,38], interferon-alpha[38] and interferon-lambda (interleukin-29)[39], could inhibit HAV IRES-mediated translation and HAV replication. Thus, *in vitro* drug screening with human hepatocytes revealed that several drugs inhibit HAV replication through the inhibition of HAV IRES activity.

BIOINFORMATICS AND CHEMINFORMATICS

Bioinformatics and cheminformatics are newer strategies to screen and design various drug candidates for HAV, as performed for severe acute respiratory syndrome coronavirus 2 in the coronavirus disease 2019-era[40]. Das *et al*[41] performed a genome-wide CRISPR screen and identified 39 candidate essential hepatovirus host factors, which form 4 clusters as follows: HAV IRES-mediated translation, chaperone activity, mitochondrial integrity and ganglioside synthesis. This strategy seems to result in the generation of more accurate approaches and techniques for HAV management.

STRUCTURE-BASED DRUG DESIGN

Crystallization of HAV IRES and formation of its drug modification

HAV needs a HAV 3C protease to form its viral replication complex. X-ray structures were reported for HAV 3C protease with HAV 3C protease inhibitor *N*-benzyloxycarbonyl-l-serine-β-lactone (1a), resulting in a lead compound that was further developed to produce a potent inhibitor of HAV 3C protease through the alkylation of the sulfur atom at the active site Cys172[42]. Furthermore, soaking *N*-iodoacetyl-valine-phenylalanine-amide, which inhibited HAV 3C protease activity, into HAV 3C–1a crystals through the modification of His102 $N^{\varepsilon 2}$-alkylated protein could lead to the successful utilization of this new crystal form in the study of enzyme–inhibitor interactions in the proteolytic active site[42]. In general, antivirals are used after hepatitis virus infects the liver. It may be better to prevent infection rather than to treat HAV.

Koirala *et al*[43] also reported a 2.84-Å resolution crystal structure of HAV IRES domain V in complex with a synthetic antibody fragment - a crystallization chaperone. This is useful for drug repositioning to compare other picornaviral HAV structures with those of HAV.

AI, MACHINE LEARNING AND DEEP LEARNING

AI and machine learning can contribute to drug development for viral infection by improving the speed and efficiency of repurposing and proposing new potent molecules to inhibit viral replication[40]. Both AI and machine learning can also be employed to make network-based predictions of drug-target interactions[44] or associations between gene expression and HAV infection[45]. This information is crucial to feed into AI and machine learning systems for the development of potent anti-HAV drugs. Although new drug discovery typically takes more than 10 years[46], this method may be useful for drug repositioning and drug rescue, which allows us to develop anti-HAV drugs more quickly. For example, the hepatitis C virus (HCV) NS5B polymerase inhibitor sofosbuvir and its derivatives could suppress HAV replication[47,48].

Many human proteins are involved in viral replication and pathogenesis[8,48]. The advantage of host-targeted antivirals is that the target is abundant. Another advantage is that they are less prone to resistance than those directly targeting the virus[8,49]. We and others also reported that host-targeted antivirals are useful for the suppression of HAV replication[8,34,35,50-53]. We would like to apply AI, machine learning and deep learning methods for drug repositioning and rescue to discover anti-HAV drug candidates (Figure 2). AI, machine learning and deep learning methods may also be useful for the avoidance of drug side effects.

MACHINE LEARNING AND DRUG DEVELOPMENT FOR HEPATITIS VIRUSES AND GLUCOSE-REGULATED PROTEIN 78

Hepatitis B virus

Qureshi *et al*[54] developed virus-specific as well as general QSAR models and computed approximately 18000 chemical descriptors (1D, 2D and 3D), including geometric, constitutional, electrostatic, topological, hydrophobic and binary fingerprints, using PaDEL, an open-source software to calculate molecular descriptors and fingerprints[54]. They also employed SVMlight software (Freely available at http://svmlight.joachims.org) for machine learning. After attribute selection, there were 15 relevant descriptors for HBV. Arora *et al*[55] performed a QSAR study based on a series of anti-hepatitis B virus (HBV) agents, namely, a series of novel bis(Lamino acid) ester prodrugs of 9-[2-(phosphonomethoxy)ethyl]adenine, a similar series of compounds comprising 2-amino-6-arylthio-9-[2-(phosphonoethoxy)ethyl] purine bis(2,2,2-trifluoroethyl) esters, and a series of 1-isopropylsulfonyl-2-amine benzimidazoles. These systems may also be useful for the development of anti-HAV drugs.

Deep learning has been applied for the diagnosis and treatment of chronic hepatitis B. Compared with two-dimensional shared wave elastography and fibrosis biomarkers, deep learning radiomics of elastography is valuable and practical as a noninvasive accurate diagnosis of liver fibrosis in HBV-infected patients[56]. Analysis of the quasispecies pattern of HBV genomes by the combination of deep sequencing and machine learning is also useful for the prediction of hepatocellular carcinoma (HCC) and direct therapeutic strategies[57,58]. A valid systematic approach based on big data mining and genome-wide RNA-seq data may be imperative to further investigate the pathogenic mechanism and identify biomarkers for drug design[59].

HCV

Weidlich *et al*[60] developed SAR with advanced machine learning methods and performed *in vitro* antiviral assays, resulting in the identification of the candesartan cilexetil, which is used to treat hypertension, as an HCV NS5B inhibitor. Using a support vector machine (SVM), three classification models were built in HCV NS3 protease inhibitors[61] or HCV NS5B polymerase inhibitors[62]. Qin *et al*[63] reported that the combination of the best sub- and whole dataset SVM models can be used as reliable lead design tools for new NS3/4A protease inhibitors.

Wei *et al*[64] reported that the multiple QSAR method is useful in predicting chemical-protein interactions for the discovery of multitarget inhibitors for the treatment of HIV/HCV coinfection. This strategy may be useful for the treatment of the cooccurrence of HAV infection and chronic liver disease[65].

Combination information from yeast-based library screening, next-generation sequencing, and structure-based modeling in a supervised machine learning approach

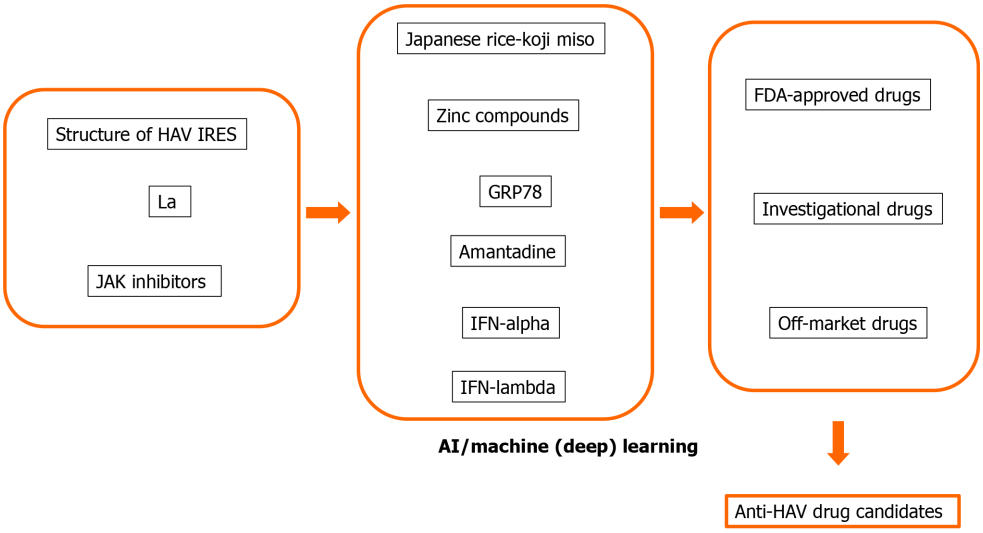

Figure 2 Drug screening and drug discovery for anti-hepatitis A virus using artificial intelligence-based drug repositioning and rescue.
HAV: Hepatitis A virus; AI: Artificial intelligence; IRES: Internal ribosomal entry-site; La: Lupus La protein/SSB; JAK: Janus kinase; GRP: Glucose-regulated protein; IFN: Interferon; FDA: Food and Drug Administration.

is useful for the comprehensive sequence-energetics-function mapping of the specificity landscape of the HCV NS3/4A protease, whose function-site-specific cleavages of the viral polyprotein are a key determinant of viral fitness[66]. Deep learning recurrent neural network models could be used to identify patients with HCV-related cirrhosis with a high risk of developing HCC for risk-based HCC outreach and surveillance strategies[67]. Deep learning should also be helpful for the development of antivirals.

Glucose-regulated protein 78

We previously found that glucose-regulated protein 78 (GRP78) is an antiviral target for HAV (Table 1)[50-52]. Computational drug discovery using the structure of HAV and GRP78 may lead to the discovery of new anti-HAV drugs or drug repositioning and drug repurposing for anti-HAV drugs[68-71].

CONCLUSION

We found that several drugs potentially inhibit HAV IRES-dependent translation and HAV replication. Approaches that utilize AI, machine learning and deep learning methods could have the most promise in the discovery of new anti-HAV drugs. A systematic approach based on big data mining with AI is also useful for the development of anti-HAV drugs[71].

Table 1 Target and mechanism of anti-hepatitis A virus candidates

Target or mechanism	Drug	Ref.
La antigen	SD-1029, AG490	Jiang *et al*[34]
JAK2-STAT3	AZD1480	Jiang *et al*[35]
GRP78	Japanese rice-koji miso extracts	Shubin *et al*[50]; Choi *et al*[51]
GRP78	Zinc sulfate	Ogawa *et al*[52]
Inflammatory cytokines	Zinc chloride	Mo *et al*[53]

La: Lupus La protein/SSB; JAK: Janus kinase; STAT: Signal transducer and activator of transcription; GRP78: Glucose-regulated protein 78.

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Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
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ISSN 2644-3236 (online)

Artificial Intelligence in *Gastroenterology*

Artif Intell Gastroenterol 2021 April 28; 2(2): 10-68

Published by Baishideng Publishing Group Inc

A I G

Artificial Intelligence in Gastroenterology

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AIMS AND SCOPE

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

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

INDEXING/ABSTRACTING

There is currently no indexing.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
Artificial Intelligence in Gastroenterology

ISSN
ISSN 2644-3236 (online)

LAUNCH DATE
July 28, 2020

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Rajvinder Singh, Ferruccio Bonino

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2644-3236/editorialboard.htm

PUBLICATION DATE
April 28, 2021

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Artif Intell Gastroenterol 2021 April 28; 2(2): 10-26

DOI: 10.35712/aig.v2.i2.10

ISSN 2644-3236 (online)

REVIEW

Artificial intelligence in rectal cancer

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Author contributions: Yakar M and Etiz D collected data and wrote the manuscript; Etiz D formatted and revised the article.

Conflict-of-interest statement: No conflict of interest has been declared by the authors.

Manuscript source: Invited manuscript

Specialty type: Oncology

Country/Territory of origin: Turkey

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

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Abstract

Accurate and rapid diagnosis is essential for correct treatment in rectal cancer. Determining the optimal treatment plan for a patient with rectal cancer is a complex process, and the oncological results and toxicity are not the same in every patient with the same treatment at the same stage. In recent years, the increasing interest in artificial intelligence in all fields of science has also led to the development of innovative tools in oncology. Artificial intelligence studies have increased in many steps from diagnosis to follow-up in rectal cancer. It is thought that artificial intelligence will provide convenience in many ways from personalized treatment to reducing the workload of the physician. Prediction algorithms can be standardized by sharing data between centers, diversifying data, and creating big data.

Key Words: Rectal cancer; Artificial intelligence; Deep learning; Machine learning

Core Tip: There is a growing interest in the application of artificial intelligence in healthcare to improve disease diagnosis, management, and the development of effective treatments. Considering the large number of patients diagnosed with rectum cancer and a significant amount of data, artificial intelligence is an important tool to improve diagnosis and treatment, follow-up in rectal cancer, develop personalized medicine, improve the quality of life of patients, and reduce unnecessary health expenses.

Citation: Yakar M, Etiz D. Artificial intelligence in rectal cancer. *Artif Intell Gastroenterol* 2021; 2(2): 10-26

Grade C (Good): C
Grade D (Fair): D, D
Grade E (Poor): E

Received: January 23, 2021
Peer-review started: January 23, 2021
First decision: February 10, 2021
Revised: March 3, 2021
Accepted: March 15, 2021
Article in press: March 15, 2021
Published online: April 28, 2021

P-Reviewer: Atsawarungruangkit A, Chen P, Shen F, Wang RF
S-Editor: Wang JL
L-Editor: Filipodia
P-Editor: Li JH

URL: https://www.wjgnet.com/2644-3236/full/v2/i2/10.htm
DOI: https://dx.doi.org/10.35712/aig.v2.i2.10

INTRODUCTION

Artificial intelligence (AI) is the computer science that tries to imitate human-like intelligence in machines by using computer software and algorithms to perform certain tasks without direct human stimuli[1,2]. Machine learning (ML) is a subset of AI that uses data-driven algorithms that learn to imitate human behavior based on the previous example or experience[3]. Deep learning (DL) is an ML technique that uses deep neural networks to create a model. Increasing computing power and reducing financial barriers led to the emergence of the DL field[4].

AI has entered our lives as support in every field. In medicine, it helps clinical processes and management of medical data and information. AI applications assist physicians in diagnosis, research, treatment, and prognosis evaluation of the disease[5]. Cancer is the most common cause of death in developed countries, and it is estimated that the number of cases will increase even more in aging populations[6,7]. Therefore, cancer research will continue to be the top priority for saving lives in the next decade.

In oncology, there are typical clinical questions such as 'Which patients have the highest risk of toxicity?' and 'What is the probability of local control and survival in this patient?'. Although clinical studies exist as the gold standard for answers to these questions, clinical studies are costly, slow, and limited to reachable patients. By using the available data, future clinical studies can be better planned, and new findings can be obtained. Evidence-based medicine is based on randomized controlled trials designed with a large patient population. However, the number of clinical and biological parameters that need to be investigated to obtain precise results is increasing day by day[8].

New and separate approaches are required for all patient subpopulations. Clinicians should use all diagnostic tools (radiological imaging, metabolic imaging, blood and genetic testing, *etc.*) to decide on the appropriate combination of therapy (radiotherapy, chemotherapy, targeted therapy, and immunotherapy). In oncology , AI, a new methodology that provides information using the large data available, has begun to be used to support clinical decisions[9]. It is important to combine a large and heterogeneous amount of data and create accurate models. Today, AI in oncology has entered our lives in early detection, diagnosis, treatment, and patient follow-up.

Although AI can take place in every step from patient consultation to patient follow-up in rectal cancer and can contribute to the clinician and the society, there are still many challenges and problems to be solved. Big data sets should be created for AI first, and these data sets should be improved. The development of prediction tools with a wide variety of variables and models limits the comparability of existing studies and the use of standards. Prediction algorithms can be standardized by sharing data between centers, diversifying data, and creating big data. In addition, the models can be made clinically applicable by updating the models by entering new data into the models. Today, the accuracy and quality of the data is also of great importance, as no AI algorithm can fix the problems in training data.

Colorectal cancer is the fourth most common type of cancer worldwide, with approximately 800000 new cases diagnosed each year and accounting for approximately 10% of all cancers[10]. Determining the optimal treatment plan for a patient with rectal cancer is a complex process. In addition to decisions regarding the purpose of rectal cancer surgery, the possible functional consequences of treatment, including the possibility of preserving normal bowel function and genitourinary function, should be considered. Achieving treatment goals and minimal impact on the quality of life can be challenging at the same time, especially for patients with distal rectal cancer. Careful patient selection in terms of specific treatment options and the use of sequential multimodality therapy combining chemoradiotherapy (CRT), chemotherapy (ChT), and surgical treatment are recommended for most patients[11].

In this review, the role of AI in the diagnosis, treatment, and follow-up of rectal cancer is discussed.

AI IN DIAGNOSIS OF RECTAL CANCER

AI in the detection of lymph node metastasis

Rectal cancers constitute the majority of gastrointestinal tumors. Among the metastatic spreading routes of rectal cancer, lymph node (LN) metastasis is the most important due to its high risk of local recurrence, which leads to poor prognosis[12]. LN metastasis is an important factor in treatment selection and in predicting prognosis. Preoperative evaluation of metastatic LNs is critical in determining the optimal treatment strategies of rectal cancer cases. Magnetic resonance (MR) imaging is widely used in clinical practice for the diagnosis of metastatic LNs in rectal cancer. MR is considered superior to computed tomography (CT) for better separation of soft tissue. Radiologists often evaluate their shape, boundaries, and signal intensities to identify metastatic LN[13]. However, correct evaluation in a short time is a great challenge, especially when considering clinics with a high number of cases. Also, when the same MR image is evaluated by different radiologists, very different results can be obtained, which weakens the sensitivity of LN staging[14-17]. As a result, it is often difficult to accurately determine the presence of LN metastasis. In recent years, the development of DL technology has greatly improved image recognition capability, making it possible to identify specific target areas within an image and allow images to be classified according to specified target features[18].

According to some studies, although the AI system is more successful than senior physicians in the diagnosis of solid tumors, such as lung, breast, prostate, and thyroid cancer, few studies have yet been reported on the determination of metastatic LN[19-25]. In the literature, there are studies in which LN metastases have been detected with AI in some cancers such as lung, oral cavity, breast, stomach, and thyroid cancer[26-30].

In the study conducted by Ding *et al*[18] enrolling 414 cases diagnosed with rectal cancer by collecting data from six centers, MR images of the cases were evaluated. Faster region-based convolutional neural network (Faster R-CNN), a new AI algorithm, was evaluated in the study. Patients who underwent surgery with a diagnosis of rectal cancer, whose patient data could be accessed, who did not receive preoperative RT or ChT, and who had MR images at the stage of diagnosis, were included in the study. Radiologist-based diagnosis and pathologist-based diagnosis were compared with the Faster R-CNN system. The number of metastatic LNs diagnosed between two of the three groups was evaluated using the pair-wise correlation analysis. A statistically significant correlation was found in the comparison of both groups [radiologist - Faster R-CNN ($P < 0.001$), pathologist - radiologist ($P = 0.011$), and pathologist - Faster R-CNN ($P < 0.001$). In Faster R-CNN, radiologist, and pathologist LN staging, consistency control was performed between groups, and the highest consistency was found among the Faster R-CNN - radiologist diagnosis ($P = 0.018$). Among the Faster R-CNN - pathologist diagnosis, the P value was 0.039. Among the radiologist - pathologist diagnosis, the P value was 0.043[18].

In another study by Ding *et al*[13], Faster R-CNN was evaluated for metastatic LN prediction, and it aimed to create mathematical nomograms for preoperative metastatic LN prediction. In the prediction of metastatic LN with Faster R-CNN, the MR images of 545 rectal cancer cases who did not receive preoperative RT or ChT were divided into training and validation groups at the rate of 2:1. While creating the nomogram, 183 cases were used as an outcome variable for the presence of LN metastasis, and 153 cases were used as validation for the level of LN metastasis (N1 or N2). Variables were age, gender, preoperatively differentiate grade, metastatic LN obtained by MR, metastatic LN obtained by postoperative pathology, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9. Important variables in predicting metastatic LN positivity with Faster R-CNN in univariate analysis were tumor differentiation grade and CEA level ($P < 0.05$) and age and tumor differentiation gradient in multivariate analysis ($P < 0.001$). Variables determined as important variables in multivariate analysis in MR-based and Faster R-CNN-based metastatic LN prediction were used in nomogram formation; in the MR-based nomogram and the Faster R-CNN-based nomogram, area under curve (AUC) and 95% confidence interval (CI) were found to be 0.856 (0.808-0.905) and 0.862 (0.816-0.909), respectively. According to this study, the Faster R-CNN nomogram appears to be suitable and reliable for predicting the presence of metastatic lymph nodes preoperatively[13].

Lu *et al*[31] evaluated 28080 MR images of 351 rectal cancer cases with Faster R-CNN in their study. Radiologist diagnosis and Faster R-CNN diagnosis were compared using receiver operating characteristic curves (ROC), and the Faster R-CNN ROC was found to be 0.912. It was accepted as a more effective and more objective method. According to the study, the diagnosis was made in 20 s per case with Faster R-CNN, while radiologists made the diagnosis in 600 s per case[31].

The diagnosis of metastatic LN in rectal cancer is very important for treatment decisions and prognosis. The diagnosis of metastatic LN by MR is largely based on the subjective interpretation of the radiologist. Therefore, it lacks objectivity and reproducibility, although it has a variable diagnostic accuracy. Therefore, using AI systems in the diagnosis phase can contribute to the ability of radiologists to diagnose metastatic LN correctly and in a shorter time and to make a more accurate treatment decision with more accurate tumor, node, metastasis (TNM) staging.

AI in the detection of t stage and tumor differentiation

Choosing the most appropriate treatment is important in rectal cancer. A correct preoperative stage is important for the surgical and neoadjuvant CRT decision. Generally, pathological type, tumor differentiation, infiltration depth, and presence of lymph node metastasis determine the prognosis of the tumor. Therefore, understanding the pathological features of the tumor is very important for the clinical treatment decision[32]. Radiomic analysis is a tool developed to assess tumor heterogeneity. Radiomics is a noninvasive method that includes high-quality image acquisition, high-throughput quantitative feature extraction, high-dimensional feature extraction, and diagnostic, prognostic, or predictive model generation. Radiomic models using medical images and clinical data have potential in making clinical decision[33]. The MRI-based radiomic model has been used to differentiate cancer from benign tissue and reflect the histological features of rectal cancer[34].

In the study conducted by Ma *et al*[35] with 152 rectal cancer cases, it aimed to predict the pathological characteristics of the tumor from the MR-based radiomic model. Tumor delineation was performed using 3T MR and high resolution T2-weighted images, and 1029 radiomic features were extracted. Multilayer perceptron, logistic regression (LR), support vector machine (SVM), decision tree (DT), random forest, and K-nearest neighbor (KNN) have been trained and used five-fold cross-validation to create prediction models. The best performance of the radiomics model for the degree of differentiation, T stage, and N stage was obtained by SVM (AUC, 0.862; 95%CI: 0.750–0.967; sensitivity, 83.3%; specificity, 85.0%), multilayer perceptron (AUC, 0.809; 95%CI: 0.690–0.905; sensitivity, 76.2%; specificity, 74.1%), and random forest (AUC, 0.746; 95%CI: 0.622-0.872; sensitivity, 79.3%; specificity, 72.2%). This study demonstrated that the high-resolution T2-weighted images–based radiomics model could serve as pretreatment biomarkers in predicting pathological features of rectal cancer[35].

AI in detection of distant metastasis

Although advances in treatment strategies and multidisciplinary treatment modalities have reduced local recurrences, distant metastasis continues to be the main cause of treatment failure in patients with rectal cancer[6]. The most common metastasis site is the liver, and liver metastasis develops in 26.5% of cases within 5 years from diagnosis[36]. At the stage of diagnosis, there is no liver metastasis in staging, but metachronous liver metastasis (MLM) that develops after initial staging and treatment is thought to be caused by occult metastases and micrometastases[37,38].

The main treatment strategy for early detected MLM is surgical resection, providing better prognosis and survival as well as a chance for cure compared to other treatments. However, a significant portion of patients with MLM may have lost their surgical chances by the time it is detected[39]. Although studies are reporting that some variables increase the risk of MLM, there is still no definite marker that can be used to predict the cases that will develop MLM[40]. Radiomics, which have come to the forefront recently, are obtained by using automated high-throughput extraction of many quantitative properties, offering the chance to capture intratumoral heterogeneity in a noninvasive manner[41].

Liang *et al*[42] predicted MLM by using MR radiomics with ML in a total of 108 rectal cancer cases with 54 MLM and 54 nonmetastatic patients. Radiomics were obtained from venous phase and T2-weighted MR images, and 2058 radiomic properties were evaluated by two separate ML techniques (SVM; LR). After determining the optimal radiomic properties, four groups of models were created: A model containing five radiomic features from T2 weighted MR images ($Model_{T2}$), a model containing eight radiomic features from venous phase images ($Model_{VP}$), a model containing the sum of these radiomics, *i.e.* 13 radiomics ($Model_{combined}$), and a model containing 22 optimal radiomics ($Model_{optimal}$). $Model_{optimal}$ was determined as the best prediction model with the LR algorithm, and its accuracy, sensitivity, specificity, and AUC were 0.80, 0.83, 0.76, and 0.87, respectively[42].

Peritoneal carcinomatosis (PC) has a poor prognosis and is considered a terminal stage. PC is present at diagnosis in 5%-10% of the cases diagnosed with colorectal cancer and in 25%-44% of recurrent disease. While a median survival of 33 mo can be achieved with cytoreductive surgery and hyperthermic intraperitoneal ChT, it is < 10 mo if incomplete cytoreductive surgery and diffuse PC are present[43]. Survival rates can also be high with minimally invasive surgery if PC can be detected early. To predict synchronous PC cases, Yuan *et al*[44] evaluated 19814 tomography images obtained from 54 PC and 76 non-PC cases in training, and 7837 images obtained from 40 cases as the test group. Using the ResNet-three dimensional (3D) algorithm + SVM algorithm, an accuracy rate of 94.1% was obtained, AUC: 0.92 (0.91-0.94), sensitivity 93.7%, specificity 94.4%, positive predictive value 93.7%, and the negative predictive value was found to be 94.4%. The performance of the algorithm was determined to be better than routine contrast-enhanced CT (AUC: 0.791 *vs* AUC: 0.92)[44].

Distant metastasis detection can be made more accurately in the earlier period by supporting the physician with the prediction models having high accuracy and this can reduce the cost of treatment while increasing survival rates.

AI IN RECTAL CANCER TREATMENT AND RESPONSE TO TREATMENT

Contouring in radiotherapy

Contouring is an important step that is routinely performed in RT to determine the treatment target and organs at risk (OAR). In a typical clinical workflow, the radiation oncologist needs to contour this target volume and OAR on the simulation images. Contouring is generally performed on CT and less commonly on MR images in clinics where MR guided RT is applied. This contouring process can take hours per patient[45]. AI can be used both to minimize the differences between physicians and to shorten the duration of this step in RT planning.

Target volume contouring: MR plays an important role in the diagnosis and treatment of rectal cancer[46]. It guides the physician in identifying the primary tumor, especially in RT planning. Also, MR-based planning increases local control and complete response rates, with the potential to facilitate individualized treatment plans for dose escalation[47,48]. Also, defining and contouring gross tumor volume (GTV) is time-consuming, and differences in target volume contouring among physicians may cause variability in treatment and different oncological results[49]. Although the application of Atlas-based automatic segmentation algorithms can reduce the identification time, these methods have low performance in rectal cancer[50]. The main advantage of DL methods is that they automatically create the most suitable model from the training data sets. In recent years, DL methods have also started to be used in RT steps. Tumor contouring with CNNs has been extensively studied in lung and head and neck cancers and a reduction in contouring time per patient of up to 10 min was observed compared to the contouring time of the physician[51-53].

In rectum cancer, contouring of GTV and clinical target volume (CTV) were performed using MR and CT images. Wang *et al*[54] created a DL-based autosegmentation algorithm for GTV delineation using MR (3 Tesla, T2-weighted) images of 93 locally advanced rectal cancer cases. The model was trained in two phases that are tumor recognition and tumor segmentation. Data is divided into 90% training and 10% validation groups for 10-fold cross-validation. Hausdorff distance (HD), average surface distance (ASD), Dice index (DSC), and Jaccard index (JSC) were used to compare and evaluate automatic and manual contouring. For the validation data set, DSC, JSC, HD and ASD (mean ± SD) were 0.74 ± 0.14, 0.60 ± 0.16, 20.44 ± 13.35, and 3.25 ± 1.69 mm, respectively. In the manual contouring of two radiation oncologists, DSC, JSC, HD and ASD (mean ± SD) were 0.71 ± 0.13, 0.57 ± 0.15, 14.91 ± 7.62, and 2.67 ± 1.46 mm, respectively. There was no statistically significant difference between the DL-based autosegmentation and manual contouring in terms of DSC (P = 0.42), JSC (P = 0.35), HD (P = 0.079), and ASD (P = 0.16) values. Before postprocess (erosion and dilation), that is, correction of contours and removing small isolated points, a statistically significant difference (P = 0.0027) was found only in HD. According to this study, results close to manual contouring can be obtained with DL-based algorithms using T2-weighted MR images[54].

In another study by Trebeschi *et al*[55], tumor contouring was performed using multiparametric MR images. The study included 140 locally advanced rectal cancer cases, and each case was contoured by two experienced radiologists. In this study, the CNN algorithm was used to function as a voxel classifier. CNN was trained using the

voxel values of the region with and without tumor in MR. In the independent validation data set, the DSC value was determined as 0.68 and 0.70 according to CNN and both radiologists. The AUC value for both radiologists was found to be 0.99. This study showed that DL can perform the correct localization and segmentation of rectal cancer in MRI in most patients[55].

Song *et al*[56] evaluated CTV contouring with CNN in 199 rectal cancer cases. For training, validation, and testing, 98 cases, 38 cases, and 63 cases were used, respectively. While volumetric DCS showed the volumetric overlap between automatic segmentation and manual contouring, surface DCS showed the overlap between automatic segmentation and manual contouring surfaces. Two CNN techniques were used in the present study that were DeepLabv3 + and ResUNet, and the volumetric DSC and surface DCS of CTV were 0.88 *vs* 0.87 (P = 0.0005) and 0.79 *vs* 0.78 (P = 0.008), respectively. According to this study, high quality and shorter CTV contouring can be performed with CNNs[56]. Target volume contouring studies with AI in rectum cancer are summarized in Table 1.

Contouring of OAR: In radiotherapy, it is necessary to make the contouring of OAR correctly to protect them and to evaluate the toxicity correctly. To fully benefit from the advantages of technological developments in RT planning and devices, OAR must be defined correctly. This step can become a rate limiting step in clinics with a high number of patients. Also, there may be differences among the practitioners, and due to significant anatomical changes (edema, tumor response, weight loss, *etc.*) during the treatment, it may be necessary to make a new plan with new contouring during the treatment. AI, particularly CNN, is a potential tool to reduce the physician's workload and set a standard in contouring. In recent years, DL methods have been widely used in medical applications, and CNN has been used in contouring OAR in head-neck, lung, and prostate cancer[57-59]. There are also studies on this subject in rectal cancer.

OAR contouring was also evaluated in the study performed by Song *et al*[56] for CTV contouring. As OAR, small intestine, bladder, and femoral heads were contoured. With ResUNet, both volumetric and surface DSC values in femoral head contouring and surface DSC values in bladder contouring were found to be statistically more significant, and contouring performance was better. Higher volumetric and surface DSC were obtained with DeepLabv3 + for the small intestine[56].

Men *et al*[60] conducted a segmentation study using deep dilated CNN based DL technique in both CTV and OAR (bladder, femoral heads, small intestine, and colon). CT images of 278 rectal cancer cases were included in the study. Images of 218 randomly selected cases were used for training, and images of the remaining 60 cases were used for validation. In this study, DSC was also evaluated and for CTV, bladder, left femoral head, right femoral head, small intestine, and colon as 87.7%, 93.4%, 92.1%, 92.3%, 65.3%, and 61.8%. CTV and OAR contouring time per case was found to be 45 s on average[60].

In another study conducted by Men *et al*[61], the effect of the patient's position on segmentation accuracy was investigated with CNN. The study included 50 supine and 50 prone cases with planning CT, and three different models were trained: Patients in the same position, patients in different positions, and patients in both positions. Performance evaluation regarding segmentation was performed using DSC and HD for CTV, bladder, and femurs. While the model trained in different positions compared to the model trained in the same position was statistically significantly better for CTV and bladder (P < 0.05), it was found to be P > 0.05 in femur segmentation. DSC values were 0.84 *vs* 0.74, 0.88 *vs* 0.85, and 0.91 *vs* 0.91 for CTV, bladder, and femurs, respectively. The accuracy rates for the model trained in both positions were similar (P > 0.05). The DSC was 0.84, 0.88, and 0.91 for CTV, bladder, and femur, respectively. According to this study, while the patient position is important for CTV and bladder in segmentation with the CNN model, it was not found to be an important factor for the femur[61]. Studies are summarized in Table 1.

In RT, while providing effective treatment for the tumor, protection of OAR is very important in terms of acute and late side effects. For this, it is an important step to define the tumor volume and OAR correctly and accurately. However, this step requires intensive labor and time and can be rate-limiting. Creating models with DL and using them in clinical practice will ensure standardization among physicians in contouring and accelerate this step.

Radiotherapy planning

Treatment planning is an important step in the RT workflow. Treatment planning has become more sophisticated over the past few decades with the help of computer science, allowing for the minimization of normal tissue damage while providing

Table 1 Target volume and organs at risk contouring with artificial intelligence

Ref.	Number of patients	Imaging method	Contouring	Artificial intelligence method	Results
Wang *et al*[54], 2018	93	MR (3 Tesla, T2 - weighted)	GTV, CTV	CNN	Between deep learning-based autosegmentation and manual contouring DSC (P = 0.42), JSC (P = 0.35), HD (P = 0.079), and ASD (P = 0.16); Before postprocess process only in HD (P = 0.0027).
Trebeschi *et al*[55], 2017	140	Multiparametric MRI (1.5 Tesla, T2-weighted)	GTV	CNN	According to CNN and both radiologists in independent validation data set DSC: 0.68 and 0.70; For both radiologists AUC: 0.99.
Song *et al*[56], 2020	199	CT (3 mm section thickness)	CTV and OAR	CNNs (DeepLabv3+ and ResUNet)	CTV segmentation better with DeepLabv3+ than ResUNet (volumetric DSC, 0.88 *vs* 0.87, P = 0.0005; surface DSC, 0.79 *vs* 0.78, P = 0.008); DeepLabv3+ model segmentation was better in the small intestine, with the ResUNet model, bladder and femoral heads segmentation results were better. In both models, the OAR manual correction time was 4 min.
Men *et al*[60], 2017	278	CT (5 mm section thickness)	CTV and OAR	CNN (DDCNN)	DSC values; CTV: 87.7%, bladder: 93.4%, left femoral head: 92.1%, right femoral head: 92.3%, small intestine: 65.3%, colon 61.8%.
Men *et al*[61], 2018	100	CT (3 mm section thickness)	CTV and OAR	CNN	CTV and bladder contouring were better in the model trained in the same position than the model trained in a different position (P < 0.05). No statistically significant difference between femoral heads (P > 0.05). No statistical difference between accuracy rates in CTV, bladder, and femoral heads segmentation in the model trained in both positions (P > 0.05).

AUC: Area under the curve; ASD: Average surface distance; CNN: Convolutional neural network; CT: Computed tomography; CTV: Clinical target volume; DDCNN: Deep dilated convolutional neural network; DSC: Dice similarity coefficient; GTV: Gross tumor volume; HD: Hausdorff distance; JSC: Jaccard index; MRI: Magnetic resonance imaging; OAR: Organs at risk.

adequate tumor dose. As a result, treatment planning has become more labor-intensive and takes hours and sometimes even days for planners. In RT planning, many algorithms have been developed to support planners, and these algorithms focus on automating the planning process and/or optimizing dosimetric changes. These algorithms have contributed to the improvement of treatment planning efficiency and quality[62]. Planning workflow starts with determining dosimetric requirements regarding target volume and OARs and makes decisions about basic planning parameters, including beam energy, number, and angles, *etc*., based on the needs of each case. While creating a minimally acceptable plan can be quick, improving a plan is much more difficult. Also, the plan may need to be improved according to the mid-plan result evaluation of the physicians, which causes increased effort and time. Automatic treatment planning systems, from simple automation to AI, are gradually taking their place in planning systems.

The knowledge-based planning system helps to use the previous planning information in the database with ML methods in obtaining the best dose distribution for target volume and OAR. Knowledge-based treatment planning algorithms use geometric and dosimetric information to estimate doses for new patients using the information found in training data. The dose volume histogram prediction model was created by using a knowledge-based treatment planning system, using 80 plans in training, and evaluating 70 plans in the test with simultaneous integrated boost and VMAT techniques. Using this model, the multileaf collimator sequences of 70 clinically validated plans were re-optimized. While doing this, parameters such as field geometry and photon energy were not changed. Dosimetric results were evaluated by comparing dose volume histogram data as homogeneity index, conformal index, hot spots (volumes taking more than 107% of the prescribed dose), mean dose, femoral heads, and bladder mean ($Dmean_{mesane}$, $Dmean_{femoralhead}$) and 50% of the dose ($D50\%_{bladder}$, $D50\%_{femoral\ head}$). Similar conformal index was obtained when comparing the original plan (1.00 ± 0.05 for planning target volume $(PTV)_{boost}$ and 1.03 ± 0.02 for PTV) and the knowledge-based plan (0.99 ± 0.04 for PTV_{boost} and 1.03 ± 0.02 for PTV). Better homogeneity index values were obtained in the knowledge-based plan (0.05 ± 0.01 for PTV_{boost} and 0.26 ± 0.01 for PTV) compared to the original plan (0.06 ± 0.01 for PTVboost and 0.26 ± 0.01 for PTV) (P < 0.05). It has been shown that V_{107}% values in the original plan were higher than the knowledge-based plan. The knowledge-based plan achieved a statistically significant decrease in $D_{50}\%_{femoral\ head}$, $Dmean_{femoralhead}$, D_{50}%

$_{bladder}$, and $Dmean_{mesane}$ values. According to this study, the knowledge-based planning system provided a statistically significant advantage in some dosimetric data compared to the original plans[63].

Zhou *et al*[64] aimed to develop a DL model for intensity-modulated RT, which provides an estimation of 3D voxel-wise dose distribution. Of the 122 post-op intensity-modulated RT treated cases, the plans of 100 cases were used for training-validation, and the plans of 22 cases were used for testing. To estimate 3D dose distributions, a 3D-DL model named U-Res-Net_B was created[60]. No statistically significant difference was found between the original plans and the DL model named U-Res-Net_B in terms of dosimetric parameters (homogeneity index, conformal index, V50, and V45 for PTV and OARs). The DSC value of the model was higher than 0.9 for most isodose volumes, and the ratio of 3D gamma passing ranged from 0.81 to 0.90 for PTV and OAR. This study has developed a DL model by considering beam configuration input; this model has shown that it has potential in terms of automated planning for easier clinical evaluation of more comprehensive cases[64].

Evaluation of chemoradiotherapy response

In locally advanced rectal cancer, neoadjuvant CRT improves local control, disease-free survival, and sphincter preservation rates[65]. However, tumor regression patterns after neoadjuvant CRT vary widely, from the pathological complete response (pCR) to disease progression. Although cases with pCR have the best survival and tumor control, neoadjuvant CRT can provide pCR in only 10%-30% of cases in locally advanced rectal cancer[66]. Some studies have shown that cases with pCR have low recurrence rates, and therefore less invasive alternative surgical treatments, such as sphincter-sparing local excision or a watch-and-wait approach, may be more appropriate[67-70]. Therefore, it is very important to determine the cases that are likely to have a complete clinical response before surgery.

MR, which enables the evaluation of the therapeutic response noninvasively, is promising in the early prediction of pCR. MR images taken at different times of the CRT, including before, during, and after treatment, can be analyzed separately or in combination to provide anatomical and functional information. With the advancement of MR imaging technology, several different sequences can be included in the MR protocol within a reasonable imaging time (< 30 min), and this multiparametric MR can provide comprehensive information to facilitate quantitative radiomic analysis for prediction of tumor response[71]. Radiomics extracts hundreds of quantitative image features and then uses advanced statistical analysis to classify different groups. Nie *et al*[72] predicted patients with pCR after CRT was completed with 80%-90% prediction accuracy of pretreatment multiparametric MRI-based radiomic analysis.

Shi *et al*[71] predicted the treatment response with DL from the radiomics they obtained from the MR images taken before treatment and in the middle of treatment (3-4 wk after the start of treatment) in CRT cases with a diagnosis of locally advanced rectal cancer. Of the 51 cases included in the study, 45 cases pre-treatment, 41 cases mid-treatment, and 35 cases both pre-treatment and mid-treatment MR images were available, and the MR protocol was specified as T2, diffusion-weighted imaging with b-values of 0 and 800 s/mm^2 and dynamic contrast-enhanced. In the surgical specimen performed after CRT, the response of the case depending on the tumor regression grade was determined. Total tumor volume and mean apparent diffusion coefficient (ADC) were measured on MRI. Using Haralick's Gray Level Co-occurrence Matrix was used to distinguish cases with and without pCR, cases with and without good response by applying radiomics using texture, and histogram parameters and CNN. Tumor volume decreased in mid-treatment MRI compared to before, and ADC increased. In predicting the cases with and without pCR with their radiomic features, AUC values were found to be 0.80, 0.82, and 0.86 when the pre-treatment MR, mid-treatment MR, and both MR, respectively, were evaluated together. In cases that respond well and those that do not, these rates were 0.91, 0.92, and 0.93, respectively. When MRIs before and during treatment were evaluated together, AUC was found to be 0.83 in DL prediction of cases with and without pCR[71].

A study conducted by Fu *et al*[73] aimed to obtain and compare handcrafted and DL-based radiomic features from pre-treatment diffusion-weighted imaging-MR images. Forty-three cases that underwent CRT with the diagnosis of locally advanced rectal cancer were included in the study. MRI was taken before treatment in all patients, and total mesorectal excision was applied 6-12 wk after the CRT. GTV from MR images was contoured by an experienced radiation oncologist. Postsurgical cases were grouped as responsive (n = 22) and unresponsive (n = 21). Handcrafted and DL-based radiomic features were extracted from diffusion-weighted imaging ADC map using traditional computer-aided diagnostic methods and pretrained CNN, respectively. The

ROC curve (AUC) of the model created with handcrafted radiomic features was 0.64, while that of the DL-based model was 0.73. Its statistical significance was found to be better ($P < 0.05$). According to this study, radiomic features obtained from MR images and the algorithm created using DL were shown to be better in predicting CRT response[73].

In another study by Shayesteh *et al*[74], 98 cases diagnosed with rectal cancer were included in the study, and MRI was performed 1 wk before the CRT. Radiomics such as density, shape, and texture features were extracted from MR images. For training and validation, 53 and 45 cases, respectively, were used. SVM, Bayesian network, neural network, and KNN algorithms were used one by one and together for predicting response to CRT. Prediction performance was evaluated by AUC. When the algorithms were evaluated separately, the best result was obtained with the Bayesian network algorithm, and the AUC and accuracy rate were 0.75 and 80.9%, respectively. When the algorithms (SVM, neural network, Bayesian network, KNN) were evaluated together, the AUC and accuracy rate were 0.97 and 92.8%, respectively. According to this study, the prediction process can be improved when algorithms are used together[74].

In another study conducted with 89 cases diagnosed with locally advanced rectal cancer, 66 cases were included in the training group and 23 cases were included in the test group, and resistance prediction to CRT was evaluated. Radiomics obtained from pre-treatment MR, ADC images, and clinical features of the cases were evaluated with the Random Forest Classifier (RFC) algorithm. Of 133 radiomic features and nine clinical features (entropy$_{mean}$, inverse variance energy$_{mean}$, small area emphasis, ADC$_{min}$, ADC$_{mean}$, sd Ga02, small gradient emphasis, age, and size) were determined as ten important variables. With the RFC algorithm, cases resistant to CRT were estimated with an accuracy rate of 91.3% (88.9% sensitivity and 92.8% specificity, AUC: 0.83)[75]. According to this study in predicting the response to CRT, when the radiomic and clinical parameters are evaluated together, predictions with high accuracy rates can be obtained. If these resistant cases can be predicted, treatment strategies can be changed, and oncological outcomes can be improved.

In another study conducted with 55 cases diagnosed with locally advanced rectal cancer, radiomics obtained from MRI images taken before, during, and after CRT were evaluated by the RFC algorithm for treatment response prediction. Images of 28 cases from 55 cases were used in the training, and images of 27 cases were used to evaluate the performance of the algorithm. pCR was obtained in 16 cases from all cases, and good results were obtained with the RFC algorithm in predicting pCR with AI (AUC: 0.86, 95%CI: 0.70-0.94). In the prediction of unresponsive cases, AUC was 0.83 (95%CI: 0.71-0.92) with the RFC algorithm[76].

In the study conducted by Bibault *et al*[77] with 95 cases diagnosed with T2-4N0-1 rectal cancer, radiomics (1683 radiomic features per case) obtained from CT images before CRT were evaluated together with clinical and treatment data, and the response prediction was made with AI. While radiomics were used with deep neural network and SVM, prediction models were created using only TNM staging in linear regression. pCR was obtained in a total of 23 cases. In prediction with deep neural network, SVM, and LR algorithms, the accuracy rates were 80.0%, 71.5%, and 69.5%, respectively[77]. In another study, artificial neural network, Naïve Bayes Classifier, KNN, SVM, and multiple LR models were evaluated in the response prediction of 270 locally advanced rectal cancer patients who underwent CRT. The most important factors affecting pCR were post CRT CEA level, the time between CRT and surgery, ChT regimen, clinical nodal status, and nodal stage. The accuracy rates for artificial neural network, KNN, SVM, Naïve Bayes Classifier, and multiple LR were 88%, 80%, 71%, 80%, and 77%, respectively[78]. Studies evaluating the CRT response with AI in rectal cancer are summarized in Table 2.

Shen *et al*[79] predicted response to CRT in 169 rectal cancer cases using positron emission tomography (PET)-CT radiomics. A total of 68 features were excluded from the metabolic active tumor site. Estimation was made with the RF algorithm, and the ROC algorithm was used to evaluate the performance. After CRT, pCR was obtained in 22 (13%) cases, and 42 radiomics features were included in the algorithm. Accordingly, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 81.8%, 97.3%, 81.8%, 97.3%, and 95.3%, respectively[79].

While the correct classification of cases in which pCR is provided helps to identify less invasive therapeutic strategies such as mucosectomy or wait-and-watch, early prediction of cases that do not respond to CRT will also allow these cases to be directed to more effective treatments.

Table 2 Studies of chemoradiotherapy response prediction with artificial intelligence

Ref.	Number of patients	Parameters evaluated	Imaging method	Technique used	Results
Shi *et al*[71], 2019	51 (90% cases for training and the remaining 10% for testing)	Tumor volume, mean ADC, radiomic	MRI (Pre-CRT and mid-CRT) (T2-DWI, DCE)	CNN	(1) pCR response prediction: (a) Pre-CRT with MR AUC: 0.80; (b) Mid-CRT with MR AUC: 0.82; and (c) Pre- and mid-CRT MR together AUC: 0.86; and (2) Good response to CRT: predicting yes/no: (a) Pre-CRT with MR AUC: 0.91; (b) Mid-CRT with MR AUC: 0.92; and (c) Pre-- and mid-CRT MR together AUC: 0.93.
Fu *et al*[73], 2020	43	Radiomic	MRI (Pre-CRT, DWI)	Handcrafted traditional computer-aided diagnostic method *vs* deep learning	Deep learning model with handcrafted model CRT response prediction AUC values: 0.64 *vs* 0.73 ($P < 0.05$)
Shayesteh *et al*[74], 2019	98 (53 training and 45 validation set)	Radiomic	MRI (1 wk before CRT) (3 Tesla, T2W-weighted)	Machine learning (SVM, BN, NN, KNN)	AUC for the BN algorithm: 74%, accuracy: 79%; When four algorithms were used together, AUC: 97.8% and accuracy rate 92.8%.
Yang *et al*[75], 2019	89 (66 training and 23 testing)	Radiomic and clinical features	MRI (Pre-CRT) (3 Tesla, T2W, 3 mm section thickness)	RFC	Predicting the accuracy of tumor resistance with RFC 91.3%, AUC: 0.83.
Ferrari *et al*[76], 2019	55 (28 training, 27 validation)	Radiomic	MR (Pre, Mid, Post RT) (3 Tesla, T2W, 2 mm section thickness)	RFC	(1) Prediction of cases with pCR by RFC; AUC: 0.86; and (2) Prediction of unresponsive cases with RFC; AUC 0.83.
Bibault *et al*[77], 2018	95	Radiomic, clinical variables	CT	DNN, SVM, LR	CRT response prediction accuracy rates; DNN: 80%; SVM: 71.5% LR: 69.5%.
Huang *et al*[78], 2020	270 (236 training, 34 validation)	Clinical variables	-	ANN, KNN, SVM, NBC, MLR	pCR prediction accuracy rates and AUC values; ANN: 88%, 0.84 KNN: 80%, 0.74 SVM: 71%, 0.76 NBC: 80%, 0.63 MLR: 83%, 0.77.

ADC: Apparent diffusion coefficient; ANN: Artificial neural network; AUC: Area under the curve; BN: Bayesian network; CNN: Convolutional neural network; CRT: Chemoradiotherapy; CT: Computed tomography; DCE: Dynamic contrast-enhanced; DNN: Deep neural network; DWI: Diffusion-weighted imaging; KNN: K-nearest neighbors; LR: Linear regression; MLR: Multiple logistic regression; MRI: Magnetic resonance imaging; NBC: Naïve bayes classifier; NN: Neural network; pCR: Pathological complete response; RFC: Random forest classifier; SVM: Support vector machine.

Prediction of KRAS mutation in rectal cancer

Kirsten rat sarcoma (KRAS) mutations, which occur in approximately 30%–40% of colorectal cancer, have been indicated as a highly specific negative biomarker for the antibody-targeted therapies to the epidermal growth factor receptor[80]. Metastatic colorectal cancers with KRAS mutations are resistant to anti-epidermal growth factor receptor targeted therapy. Therefore, the KRAS mutation test has been recommended by the National Comprehensive Cancer Network guidelines to guide targeted therapy for cases diagnosed with metastatic colorectal cancer[81].

Determination of the KRAS mutation is usually made by pathological examination of the tumor tissue. However, intratumor heterogeneity or heterogeneity of KRAS mutation that can occur between different tumor regions limits histological approaches[82]. Moreover, the inability to determine mutation status due to poor DNA quality of biopsy samples, difficult to access tissue samples from metastatic colorectal cancers, repeated tumor sampling, and relatively high costs also limit the feasibility of molecular tests to monitor targeted therapy[83]. Therefore, a relatively simple and noninvasive method for KRAS mutations can be helpful for personalized treatment strategies.

In a study by Cui *et al*[84], 304 cases with rectal cancer diagnosis from center I (training dataset, $n = 231$; internal validation dataset, $n = 91$) and 86 cases from center II were included as an external validation dataset. It aimed to predict KRAS mutation from T2-weighted image-based radiomics. Subsequently, three classification methods, *i.e.* LR, decision tree, and SVM algorithm, were applied to develop the radiomics signature for KRAS prediction in the training dataset. The predictive performance was evaluated by ROC analysis. A total of seven radiomics properties were accepted as important variables for KRAS prediction, and the best predictor was determined as the SVM. The AUC was found to be 0.722 (95%CI: 0.654-0.790)[84].

AI IN FOLLOW-UP IN RECTAL CANCER

Treatment toxicity

Effective toxicity estimation and evaluation schemes are required to limit RT-related side effects. High-tech devices and planning systems provide submillimetric precision. However, while giving the desired dose to the target volume, the OARs in its immediate neighborhood may be affected, leading to RT-induced toxicity. Acute toxicity occurs during treatment or within 3 mo of completion of treatment and usually, full recovery takes weeks to months. Late side effects such as fibrosis or RT-induced oncogenesis are generally irreversible and considered progressive over time. When planning RT, its potential benefits should be weighed against the possibility of damaging healthy organs and tissues to maximize the curative response while minimizing the possibility of normal tissue complications. On the other hand, the target volume should not be compromised to preserve OARs. In addition to complex dosimetric data, AI provides the clinician with the ability to predict complications by integrating higher-level information such as detailed clinical and comorbidity data into a more comprehensive and quantitative model[85].

Dosimetric parameters include dose volume histogram parameters and threshold doses such as maximum point doses. Nondosimetric factors include other variables such as age, gender, and histopathology. Normal tissue complication probability and tumor control probability prediction models focused on using dosimetric parameters alone[86,87]. Also, the necessity of using nondosimetric parameters has been emphasized in the Quantitative Analysis of Normal Tissue Effects in the Clinic[88]. Data-driven approaches, on the other hand, aim to determine the model that best fits the input data (called properties or independent variables) and output data (called the response or dependent variable). Toxicity predictors can be examined roughly in three parts as dosimetric, clinical, and image-based.

In rectum cancer RT, toxicity can be predicted in advance with AI-based models, and appropriate dose-area restrictions, additional treatment planning (simultaneous CT, *etc.*), and prophylactic medical support treatments can be reviewed. There are AI studies that predicted rectal toxicity in prostate and cervical cancer radiotherapy, but there are no studies predicting toxicity with AI in rectal cancer radiotherapy[89-91]. Oyaga-Iriarte *et al*[92] conducted a study to predict irinotecan toxicity in metastatic colorectal cancer with ML models, and leukopenia was estimated with 76% accuracy, neutropenia 75%, and diarrhea 91%.

The development of prediction tools with a wide variety of variables and models limits the comparability and standard use of existing toxicity studies. Toxicity estimation algorithms can be standardized by sharing data between centers and creating big data. The application of such models is valuable in many different ways for both patients and clinicians.

Survival

In oncological treatments, forecasting is very important in the treatment decision-making process because accurate survival prediction is critical in making palliative/curative treatment decisions. Also, the prediction of remaining life expectancy can be an incentive for patients to live a fuller or more fulfilling life. Survival statistics assist oncologists in making treatment decisions, but these are data from large and heterogeneous groups and are not well suited to predict what will happen to a specific patient. AI algorithms for the prediction of RT and ChT response have received considerable attention recently. In cases diagnosed with cancer, predicting survival is important in improving treatment and providing information to patients and clinicians. Considering the data set of rectal cancer patients with specific demographic, tumor, and treatment information, it is an important issue whether the patient's survival or recurrence can be predicted by any parameter. Today, many hospitals store data in digital media. By evaluating these large data sets with AI techniques, it may be possible to predict treatment outcomes of patients, plan personalized medicine, improve corporate performance, and regulate health insurance.

In a study conducted by Zhao *et al*[93], survival prediction was made with an ML method in cases with metastatic rectal cancer, and 4098 cases were used in training and 3107 cases were used as test data. A survival prediction nomogram was created. While creating the prediction model, lasso (least absolute shrinkage and selection operator), an ML technique that can lead to superior performance compared to traditional multivariate regression, was used. The model was designed to predict 3-year overall survival. The ML model formed the basis of the nomogram. Important

variables used in the nomogram were age, Charlson-Deyo score, tumor grade, pre-op CEA, liver metastasis, bone metastasis, brain metastasis, lung metastasis, peritoneal metastasis, presence of primary surgery, surgery for the metastatic area, the number of metastatic lymph nodes, and the presence of ChT. The c-index was used to evaluate the performance of the ML technique. Internally validated c-index values were 0.816 (95%CI: 0.813-0.818), 0.789 (95%CI: 0.786-0.790), and 0.778 (95%CI: 0.775-0.780) for 1-, 2-, and 3-year survival, respectively. External validated c-index was 0.811, 0.779, and 0.778 for 1-, 2-, and 3-year survival, respectively[93]. There was great variation in overall survival times in cases diagnosed with metastatic rectal cancer. Accurate models with ML methods can assist patients and clinicians in setting expectations and clinical decisions in this challenging patient group.

Pham *et al*[94] used AI to discover DNp73 expression in terms of 5-year overall survival and prognosis in their study with 143 cases diagnosed with rectal cancer. Ten different CNN algorithms were used, and each immunochemical image was resized. For the algorithm, 90% of these images were used in training and 10% as test data, and the accuracy rates of ten algorithms varied between 90%-96%[94].

Li *et al*[95] conducted a study with 84 patients diagnosed with locally advanced rectal cancer and predicted survival with radiomics obtained from PET, CT, and PET-CT images with CNN. They compared the CNN method evaluated in the study with the Cox proportional-hazards model and random survival forests method. C-index was used in the performance evaluation of the methods. C-indexes of models created with radiomics obtained from PET, CT, and PET-CT images for Cox proportional-hazards, random survival forests, and CNN were 0.53-0.58-0.60 *vs* 0.58-0.61-0.58 and 0.62-0.60-0.64 respectively, and the best performance was obtained when CNN and PET-CT were used together[95].

In the study conducted by Oliveira *et al*[96] to predict the 1-, 2-, 3-, 4-, and 5-year survival of cases with rectal and colon cancer, they evaluated 2221 cases in the test for colon cancer, 20061 cases in training, 551 cases in the test for rectal cancer, and 4962 cases in training. Important variables for colon cancer were determined as age, CEA, CS site-specific factor 2, TNM stage, localization of the primary tumor, and regional lymph nodes. For rectal cancer, important variables were age, tumor extension, tumor size, TNM staging, surgery of the primary tumor, and gender. ML performance was evaluated by the accuracy rate and AUC. Accuracy rates and AUC for predicting survival for colon cancer for 1-, 2-, 3-, 4-, and 5-years were 95.6% (AUC: 0.980), 96.2% (0.984), 96.4% (0.988), 96.6% (0.988), and 96.4% (0.985), respectively, and their mean was 96.2% (0.984). Accuracy rates and AUC for predicting 1-, 2-, 3-, 4-, and 5-year survival for rectal cancer were 94.4% (AUC: 0.957), 94.4% (0.960), 94.0% (0.961), 93.8% (0.963), and 94.5% (0.971), respectively, with a mean of 94.1% (0.960)[96].

Accurate survival prediction in cancer patients remains a problem due to the increasing heterogeneity and complexity of cancer, treatment options, and different patient characteristics (age, Karnofsky Performance Status Scale, comorbid diseases, *etc*.). If reliable predictions can be achieved with AI, it can help with personalized care and medicine. Studies on AI-based survival prediction are increasing day by day in the literature, and there is still no standard algorithm.

CONCLUSION

In recent years, the increasing interest in AI in all fields of science has led to the development of innovative tools in oncology. The development of prediction tools with a wide variety of variables and models limits the comparison of existing studies and the use of standards.

In order to improve long-term prognosis, it is important to predict the overall survival of patients with a diagnosis of rectal cancer and progression of the disease receiving multimodal treatment. With the evaluation of clinical, radiological, genetic, dosimetric, and epidemiological factors using AI, it is possible to perform accurate predictions to achieve personalized treatment. Given high treatment costs, potential serious toxicity, harms of early progression, and low survival in cases of ineffective treatment, predictive systems with AI are promising. Multicenter studies with large data sets can provide algorithms with higher accuracy rates.

AI technology develops day by day in the realization of human behaviors in oncology and offers more efficient, faster, and lower cost solutions. Both AI and robotic potential are enormous in the follow-up and treatment of rectal cancer. AI and robotics are on the way to becoming a part of our health ecosystem.

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Artificial Intelligence in Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

Artif Intell Gastroenterol 2021 April 28; 2(2): 27-41

DOI: 10.35712/aig.v2.i2.27

ISSN 2644-3236 (online)

REVIEW

Artificial intelligence in gastrointestinal radiology: A review with special focus on recent development of magnetic resonance and computed tomography

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Author contributions: Chu YW and Chang KP conceived the idea for the manuscript; Chang KP and Lin SH reviewed the literature and drafted the manuscript; Chu YW drafted and finally approved the manuscript.

Supported by Ministry of Science and Technology, No. 109-2321-B-005-024 and No. 109-2320-B-039-005; National Chung Hsing University and Chung-Shan Medical University, No. NCHU-CSMU 10911; China Medical University Hospital, No. DMR-109-258; and ChangHua Christian Hospital and National Chung Hsing University, No. NCHU-CCH-11006.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

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Abstract

Artificial intelligence (AI), particularly the deep learning technology, have been proven influential to radiology in the recent decade. Its ability in image classification, segmentation, detection and reconstruction tasks have substantially assisted diagnostic radiology, and has even been viewed as having the potential to perform better than radiologists in some tasks. Gastrointestinal radiology, an important subspecialty dealing with complex anatomy and various modalities including endoscopy, have especially attracted the attention of AI researchers and engineers worldwide. Consequently, recently many tools have been developed for

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Taiwan

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

Received: January 27, 2021
Peer-review started: January 27, 2021
First decision: March 7, 2021
Revised: March 21, 2021
Accepted: April 20, 2021
Article in press: April 20, 2021
Published online: April 28, 2021

P-Reviewer: Lu G, Lui TK
S-Editor: Wang JL
L-Editor: A
P-Editor: Li JH

lesion detection and image construction in gastrointestinal radiology, particularly in the fields for which public databases are available, such as diagnostic abdominal magnetic resonance imaging (MRI) and computed tomography (CT). This review will provide a framework for understanding recent advancements of AI in gastrointestinal radiology, with a special focus on hepatic and pancreatobiliary diagnostic radiology with MRI and CT. For fields where AI is less developed, this review will also explain the difficulty in AI model training and possible strategies to overcome the technical issues. The authors' insights of possible future development will be addressed in the last section.

Key Words: Artificial intelligence; Deep learning; Image diagnosis; Radiology; Magnetic resonance imaging; Computed tomography

Core Tip: Gastrointestinal radiology is a subspecialty that is important and complex, and is thus a popular subject in artificial intelligence (AI). Recently many deep-learning based diagnosis assistance tool have been developed in gastrointestinal radiology, particularly in diagnostic abdominal magnetic resonance imaging (MRI) and computed tomography (CT). Herein we will review recent advance of AI in gastrointestinal radiology, with a special focus on abdominal MRI and CT. Current difficulty in less-developed fields will be explained as well.

Citation: Chang KP, Lin SH, Chu YW. Artificial intelligence in gastrointestinal radiology: A review with special focus on recent development of magnetic resonance and computed tomography. *Artif Intell Gastroenterol* 2021; 2(2): 27-41
URL: https://www.wjgnet.com/2644-3236/full/v2/i2/27.htm
DOI: https://dx.doi.org/10.35712/aig.v2.i2.27

INTRODUCTION

The field of gastrointestinal radiology includes diagnostic radiology and interventional radiology. In the practice of diagnostic gastrointestinal radiology, various imaging tools are applied for the diagnosis of lesions in the abdominal cavity. These tools include X-ray used in abdominal plain film[1], angiography and abdominal computed tomography (CT)[2], magnetic resonance used in abdominal magnetic resonance imaging (MRI)[3,4], and ultrasound used in abdominal sonography[5]. For some diagnostic tasks, intravenous contrasts are used to enhance lesions for study. Contrast-enhanced, three-phase CT is the standard for examination of liver tumors and many other lesion types[6]. Contrast-enhanced ultrasound and MRI, though less frequently used, have some clinical use in examination of pancreatic lesions and inflammatory bowel disease[7-9]. Please refer to Ripollés *et al*[7] for example of contrast-enhanced ultrasound for diagnosis for Crohn's disease.

Artificial intelligence (AI) have been influential in radiology recently, because it has potential to reduce workloads of radiologists, and diagnostic radiology tools stated above have provided feasible ground for machine learning model development. Potential of machine learning models to reduce radiologist workload come from its better stability, higher work efficiency, and better accuracy in some selected tasks[10] than human workers. Deep learning has proven its suitability for different imaging methods, and radiology and has been widely used in image classification, segmentation, detection, and reconstruction tasks[11]. There are some optimistic radiologists who are willing to let AI assist them in their work so that they can enhance their role in other places[12,13]. Of course, there are also pessimistic radiologists who worry that the development of AI systems will replace radiologists[14].

The most significant shortcoming of machine learning algorithms require a lot of data[15]. At the same time, the lack of unified standard training data will lead to a decrease in the efficiency of AI learning, but it is difficult for doctors to label a large amount of accurate data in complex diseases. In addition, the algorithm may learn false correlations, which may also lead to overfitting. At the same time, it is difficult

for AI to explain the causality in the observation dataset. Semi-supervised learning is between supervised learning and unsupervised learning. In the training process, a small amount of labeled data and a large amount of unlabeled data are used at the same time. The development of semi-supervised learning algorithms is mainly because data labeling is very expensive or impossible in some fields[16-18]. The development of semi-supervised learning can also simultaneously solve the problems of a large number of labeling and overfitting.

INTERVENTIONAL RADIOLOGY

Interventional radiology uses imaging techniques in diagnostic radiology to treat diseases or take specimens. The practice of interventional procedures in gastrointestinal radiology can be best exemplified by the treatment solid organ tumors. Among the most-frequently used non-surgical treatment procedures of hepatocellular carcinoma (HCC) are transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA). In TACE[19], liver tumors are first highlighted by angiography, and then embolized by particles coated with chemotherapeutic drugs. In RFA[20], the lesion is located by ultrasound rather than angiography and ablated by radiofrequency heating. In addition to liver cancer, any solid organ tumors with rich vasculature can be treated with this procedure. For example, pancreatic neuroendocrine tumors are frequently hypervascular, therefore are sometimes treated by embolization since last century[21,22], especially in patients with multiple endocrine neoplasia type 1 syndrome, where multiple tumors may make resection unfeasible[23]. are also widely applied in some of pancreatic tumors, such as neuroendocrine tumors. Application of RFA, which does not require rich vasculature, is even more versatile than TACE. There are reports of successful radiofrequency ablation on unresectable pancreatic cancer[24,25], and even intra-abdominal sarcomas such as gastrointestinal stromal tumor[26].

Interventional radiology also has broad application on non-tumor diseases, especially in vascular diseases. The best well-known example is emergent management of gastrointestinal bleeding, where the bleeding artery can be visualized by angiography, and embolized[27,28]. A similar approach can be also applied to thrombotic diseases such as Budd-Chiari syndrome or celiac artery occlusion[29,30]. In management of these disorders, the vessels are visualized and dilated with stents or dissolved with thrombolytic agents. Applications of interventional radiology are numerous and still developing, so a thorough review is out of scope of this article.

Both diagnostic and interventional gastrointestinal radiology can be done endoscopically. For example, in endoscopic ultrasound (EUS), the ultrasound probe is inserted through an endoscope to visualize lesions that are not easily accessible by abdominal sonography[31,32]. Biopsy and other interventional procedures can then be done to the visualized lesion *via* the endoscope, as exemplified in publications by Williams *et al*[33]. and Kahaleh *et al*[34]. Endoscopic radiological images are more difficult to be collected in large amount, because like in EUS, most image from endoscopic procedures are manually captured with custom angle of the endoscopist, rather than in an automatic and standard manner. Therefore, unlike in development of AI in regular diagnostic radiology, in which large scale public dataset, such as pancreas CT dataset from The Cancer Imaging Archive[35-37], and Beyond the Cranial Vault Abdomen data set[38,39], are readily available, most AI studies in endoscopic radiology still requires collection and processing of multihospital data. Moreover, lack of standardization and technical difficulty can make researchers reluctant or afraid to make image public. For example, in the study of computer-aided diagnosis of gastrointestinal stromal tumors by Li *et al*[40], the authors made the research possible only after collecting data from 19 hospitals, and did not publish the dataset. To our knowledge, there is only one well-known, public database of endoscopic ultrasound, published in 2020[41], and we hope that more database will be available in the following decade. In the present situation, due to less available resource, endoscopic radiology is less developed, so in this review article, we will focus on non-endoscopic radiological examination, particularly on CT and MRI.

DEEP LEARNING IN RADIOLOGY: ACHIEVING STATE OF THE ART IN LESION DETECTION

In the last five years, there have been marked progress in deep learning-assisted lesion detection for radiology, particularly in computed tomography. The progress can be exemplified by the DeepLesion tool developed by National Institutes of Health[42], which claims to detect all types of lesion in computed tomography regardless of the organ, with a sensitivity of 81.1% and five false-positives per case. DeepLesion was published along with an immense dataset with 32120 CT slices. With this annotated database in hand as a powerful tool, researchers refined lesion detection algorithm at an accelerated pace. For example, with the DeepLesion dataset, researchers from Chinese Academy of Sciences were able to develop the MVP-Net tool[43] by feature pyramid network, which claims to be 5.65% more sensitive than DeepLesion. With more developed advancements in deep learning algorithms and more databases available, we can expect that universal lesion detection in computed tomography will reach clinical use in reasonable time. An example of lesion detection in DeepLesion can be found in Yan *et al*[42].

For MRI, recent advancements are much less pronounced. Due to complex and variable sequencing techniques used in MRI, such as perfusion weighted imaging and T2* used in in stroke protocol[44] and diffusion weighted imaging[45] used in various organs, development of an universal, organ-neutral lesion detection algorithm is very difficult, if not impossible. Nonetheless, for individual organs, there is still marked progression. For example, using a deep learning algorithm, Amit *et al*[46] developed a tool for lesion detection in breast MRI. Later, in 2019, with the application of deep learning on T1-weighted, fat-suppressed MR images, Kijowski *et al*[47] further extended the technology to predict breast lesion type. Though not as effective as in breast lesion detection, the application of deep learning on musculoskeletal system MRI has achieved marked success for the detection of variable lesions, such as fracture, deformity, and metastatic disease. There are numerous studies about lesion detection on MRI in other organs, but it is beyond the scope of this review article.

Given the fact that there are on an average five false-positive lesions detected by DeepLesion, deep learning algorithms trained by radiographs are prone to over-detecting lesions. Researchers are aware of this problem and have tried to overcome it by various technologies. The most-used and earliest method applied is multi-view convolutional networks (CNN), wherein native 3D shapes are recognized from their rendered 2D views[48]. By using multi-view CNN, Setio *et al*[49], Kang *et al*[50] and El-Regaily *et al*[51] reported significant reduction of false-positive lesions in the lung with computed tomography, thus making this algorithm the most effective detection training tool for lung image. Recent results of the use of multi-view CNN in lung lesion detection are shown in Table 1.

In addition to lung computer tomography, multi-view CNN has been used with other imaging subjects as well. It is also used to increase specificity in mammographic image classification[52] and longitudinal multiple sclerosis lesion segmentation[53]. Besides multi-view CNN, masking techniques during neural network training are also used to reduce false positive lesions. For example, Zlocha *et al*[54] used dense masks to improve the performance of RetinaNet[55], and the researchers developing ULDor tool[56] used pseudo mask to reduce false positivity in universal lesion detector.

Taken together, in recent years, deep learning for lesion detection in technology has shown great progress. In the next section, we will focus on how these technical advancements have benefited the diagnosis of gastrointestinal lesions.

DISEASE DIAGNOSIS AND PREDICTION IN GASTROENTEROLOGY

Cholangiographic diagnosis

One of the most advanced achievement in gastrointestinal radiology is the non-invasive evaluation of for the bile ducts. Before the era of image reconstruction and advanced endoscopy, visualization and diagnosis of lesions causing biliary disease usually required quite invasive procedures such as transhepatic cholangiography[57]. In late 20th century, with the advancements in endoscopy, it was replaced by endoscopic methods like retrograde cholangiopancreatography (ERCP)[58] and EUS cholangiography[59,60]. For achieving both treatment and diagnosis, endoscopic procedure maybe necessary and appropriate, but for the sole purpose of diagnosis, such as visualization of lesions in primary sclerosing cholangitis (PSC)[61] and

Table 1 Recent results in usage of multi-view convolutional networks in lung lesion detection

Dataset	Toolset	AUC	Ref.
LIDC	ConvNets (2D)	0.996	Setio *et al*[49], 2016
LIDC	Inception-Resnet (3D)	0.99	Kang *et al*[50], 2017
LIDC	MatConvNet (2D)	0.94	El-Regaily *et al*[51], 2020

LIDC: Lexington Infectious Disease Consultants; AUC: Area under the curve.

choledochal cyst[62], endoscopic procedure maybe too invasive and inconvenient for patients.

Therefore, in the last three decades, with the increasing demand of non-invasive procedures and the progress of digital image reconstruction technologies, some radiology visualization tools, such as magnetic resonance cholangiopancreatography (MRCP)[63] and CT cholangiography[64], have been developed and achieved clinical importance. For diagnostic problems, the precision of non-invasive examination has become comparable to that of endoscopic procedure. MRCP achieved diagnostic accuracy of up to 97% in the diagnosis of choledocholithiasis as early as 2000[65]. In 2011, MRCP even rivaled the performance of pathologic examination, with an accuracy of 82.9% in predicting carcinomatous biliary obstruction[66]. In the meantime, CT cholangiography also reached the status of standard care in some situations, such as preoperative biliary anatomy assessment when MRCP is inconclusive[67].

These noninvasive diagnostic examinations are, of course, far from perfect. Despite early success, in some studies between 2010 and 2020, the sensitivity of MRCP for choledocholithiasis was reportedly inferior to that of EUS[68]. This outcome may be attributed to subjectivity and inter-observer variability of interpretation, because, even though it is less demanding than ERCP, the radiological assessment of the bile duct and pancreas still requires high level of expertise to interpret[69]. For more demanding tasks, such as detection and classification of pancreatic lesions[70,71], the performance of noninvasive tests can be even more disappointing.

To cope with the problem of interpretation difficulty in noninvasive cholangiopancreatography, researchers began to use variable deep learning methods in an attempt to achieve more subjective and sensitive lesion detection in the bile ducts and pancreas. For example, Ringe *et al*[72] developed a transfer learning-based system for automated detection of PSC, achieving a sensitivity of 95%. If this system is used clinically, radiologists can avoid all-manual interpretation for difficult PSC detection, thus reducing possible the inter-observer disagreement. Some of researchers also used deep learning to improve image reconstruction and segmentation in the pancreatobiliary region, to reduce pitfall in traditional MRCP and CT cholangiography. For example, Tang *et al*[73] used deep learning to improve highlighting of periampullary regions in MRI, which can be difficult with traditional MRCP method. Al-Oudat *et al*[74] used Denoising Convolutional Neural Networks for better construction of intrahepatic biliary segmentation in MRI image.

Besides its utility in noninvasive examination, deep learning can also benefit imaging difficulty in endoscopic procedure. By a segmentation algorithm trained by D-LinkNet34 and U-Net, Huang *et al*[75] developed a system to evaluate stone removal difficulty of ERCP. By training on a deep learning model using ultrasound images and videos, Zhang *et al*[76] developed a system to recognize pancreas segments and stations in EUS. With globally increasing computing power and maturing deep learning technology, we can expect radiological pancreaticobiliary system assessment to continuously improve in the future.

Detection and classification of solid organ tumor

Imaging studies, such as abdominal contrasted CT scan and contrast enhanced ultrasound, are crucial for the evaluation of solid organ tumor diagnosis, such as liver cancer, pancreatic cancer, and other solid organ tumors. The best example is screening for HCC in patients with cirrhosis[77]. Image diagnosis of liver tumor is crucial and effective to the point that HCC can be diagnosed by three-phase contrasted CT[78] alone, without the need of a biopsy[79]. Despite being less accurate, image diagnosis is helpful in more difficult-to-diagnose tumor types, such as focal nodular hyperplasia and hepatocellular adenoma[80-82]. CT diagnosis is also crucial and sensitive for pancreas cancer diagnosis[83] and prediction of malignant change in cystic lesion[84].

The first problem in image diagnosis is that, even with state-of-the-art, highly sensitive technique, it can have less than ideal specificity. For example, image appearance of intrahepatic cholangiocarcinoma (ICC) can mimic HCC both in contrast-enhanced CT[85] and contrast-enhanced ultrasound[86]. Since the long-term outcome and treatment strategy are significantly different between HCC and ICC[87,88], this can be a severe misdiagnosis that impacts prognosis. Some vascular tumors like epithelioid hemangioendothelioma[89,90] and sclerosed hemangioma[91] may also mimic epithelial malignancy, making the image diagnosis even less specific. Moreover, because of a large volume of abdominal CT and MRI done for liver cancer screening, the workload is quite a lot for radiologists[92,93]. Pancreatic cancer is more problematic, since inflammatory process such as autoimmune pancreatitis can mimic adenocarcinoma, causing diagnostic difficulty in CT and MRI[94,95]. Less prevalent tumor types, such as acinar cell carcinoma of pancreas, can be even more challenging[96]. Therefore, there is strong demand for automatic tumor classification algorithm for abdominal imaging, to improve the accuracy of tumor classification and reduce radiologists' workload.

Of the two purposes stated above, the most recent development was on assisted lesion detection to relieve radiologists' workload. Using watershed transform and Gaussian mixture, Das *et al*[97] developed a tool that they claimed can detect hemangioma, HCC and metastatic carcinoma with a classification accuracy of 99.38%; however, they did not consider ICC in their differential diagnosis, therefore, this tool can be used only for screening, and not for final tumor diagnosis. Vorontsov *et al*[98] used fully convolutional network for the detection of liver metastatic colorectal cancer, with a sensitivity of up to 85%. There are several other developed for liver tumor detection and segmentation with variable success[99,100]. For automatic pancreatic cancer detection, there are also variable success. Li *et al*[101] developed a computer aided diagnosis model by Dual threshold principal component analysis for pancreas cancer on PET/CT image, with an accuracy of up to 87.72%. By using faster region-based CNN on CT image, Liu *et al*[102] built a diagnosis system which detected pancreatic cancer with an area under the curve (AUC) of 0.9632. These studies are only some examples of AI detection of digestive system cancer in medical images. For a more detailed discussion, readers can refer to the other review article focused on this subject[103].

Few researchers have published results about detailed tumor classification based on abdominal imaging. By training convolution CNN with both MRI image and clinical data, Zhen *et al*[104]'s model achieved AUC of up to 0.985 in the classification of malignant tumors as hepatocellular carcinoma, metastatic carcinoma or other primary malignancies. Yasaka *et al*[105] attempted automatic classification of liver tumor into five classes (HCC, other malignancy, indeterminate masses, and two classes of benign lesions) using CNN, and achieved an accuracy of 0.84. Scope of these classification tools are summarized in Table 2. Due to limited literature available, it is too early to predict whether automatic radiological tumor classification will be comparable to pathologic diagnosis, but the recent results seem promising, and would be a good subject for further research.

Intelligent assistance on endoscopic radiology

Endoscopic radiological procedures, such as EUS and ERCP, can be very difficult to perform and interpret, and require a lot of training to achieve competence[106], particularly if combined with interventional procedures like ampullectomy or biopsy[107,108]. Artificial intelligence assistance to reduce difficulty and allow for a reasonable learning curve is therefore desired for these procedures.

Due to the limited availability of public image database of EUS and ERCP, the development of AI models for these modalities is, as stated in a previous review article, still in its infancy[109]. There are, however, already some promising results in assistance of endoscopic radiological procedure. The most pronounced progress is with depth assessment in EUS. EUS imaging for evaluation of tumor depth is crucial in predicting the safety of endoscopic submucosal dissection[110]; however, the image diagnosis can be subjective, and requires much expertise. Cho *et al*[111] developed a tool using deep learning that predicts tumor depth in EUS with a claimed AOC of 0.887. For less sophisticated tasks such as detection of pancreatic cancer in EUS, the result is even better, with a claimed AOC of 0.940[112]. Therefore, it is evident that deep learning-assisted diagnosis can be a reliable tool.

In summary, AI has proven helpful in radiological diagnosis. Although few of the tools described above have reached clinical use, with current development, we can expect AI-assisted diagnosis to advance further in few years, and it may eventually become relevant to everyday clinical practice.

Table 2 Classification scope for recent deep learning-based tumor classification tools

Ref.	HCC	ICC	Metastatic carcinoma	Other malignancy	Benign tumors
Das *et al*[97], 2019	O	X	O	X	O
Vorontsov *et al*[98], 2019	X	X	O	X	X
Zhen *et al*[104], 2020	O	O	O	O	X
Yasaka *et al*[105], 2018	O	O	O	O	O

HCC: Hepatocellular carcinoma; ICC: Intrahepatic cholangiocarcinoma. X: Yes; O: No.

MAIN CHALLENGES AND PITFALLS OF THE APPLICATION OF AI IN RADIOLOGY

Although AI has made a lot of contributions in radiology, there are still some challenges and pitfalls, and AI experts should be cautious when working with radiologists. One of the biggest challenges is the availability of data. Ordinary deep learning algorithms will be learned through millions of training datasets, but it is difficult for the medical field to have such a large amount of data, and even if there are a large number of training datasets, there is currently no unified classification standard[113,114]. If the training dataset is too small, multiple neuron training through deep learning will easily lead to overfitting[115,116] and will show poor accuracy in independent tests. How to choose the right amount of model depth to adapt to a smaller training dataset will be the biggest challenge for AI engineers. In addition, generative adversarial networks[117] is also very suitable for small training datasets. At the same time, the establishment of a large number of training databases can also effectively help improve the efficiency of AI. Physicians and engineers work together to establish an open database and set uniform standards, which can also enhance AI applicability in radiology and pathology.

In addition, some diseases (usually rare diseases) have a problem of extreme disparity in the classification ratio, which is called imbalanced data. Imbalanced data training is more difficult, which usually leads to high accuracy but poor results, because the machine only needs to guess more. The classification, you can get a good-looking accuracy. Although there are good solutions already available[118], these are still important challenges for using AI with rare diseases.

Finally, when an AI model that can be used clinically is to be developed, proper verification settings must be ensured in the experimental verification of the model. Lack of sufficient verification can lead to untrustworthy models[119]. It is common that the training dataset and the test dataset are not extensive at the time of collection, thus resulting in poor results in practical applications.

FUTURE OF AI IN GASTROINTESTINAL RADIOLOGY

With advanced deep learning algorithm, computers can assist clinicians to make an accurate diagnostic decision by providing the right information. For difficulties in endoscopic and interventional procedure, however, information alone is of little help. Complete automation of a manual procedure must be assisted by both deep learning and robotics. For example, there have been marked advancements in robot-assisted endoscopy devices[120]. If these robots can be combined with an intelligent system that detect lesions *via* ultrasound[112], then it would have a potential to automatically take procure a biopsy sample from the lesion, or perform a surgical procedure, thus eliminating the difficulties of endoscopic and surgical technique.

The other factor that would augment the power of intelligent system is the development of radiological technology itself. The best example would be combination of radiology and endoscopic robotic capsule[121,122]. Recently, with the assistance of neural network, trajectory control and image visualization of endoscopic robotic capsules have been more automatic than they were previously[123]. In the future, if the size of ultrasound probe or other radiological device can be reduced to nanoscale, with an intelligent robotic capsule and intelligent ultrasound probe, fully automated detection and management of any lesion accessible by endoscopic capsules would be possible. Possible path to fully automatic diagnosis and intervention in

gastroenterology by combining artificial intelligence with various technologies is shown in Figure 1.

The problems inherent to AI itself, that is, data acquisition and annotation, will also be solved by recent technical developments in deep learning models. The best sample would be using unsupervised learning or semi-supervised learning[16,18] to decrease or eliminate the need for radiologist annotation, making development of models faster. For research topics with large public database and well-developed models, such as abdominal CT, transfer learning with pre-trained model and included clinical data can also make training easier, more precise, and faster[124]. In addition to improvement of deep learning model itself, the advancement of advanced deep learning algorithm will enable in-vivo live visualization of lesion detection in endoscope[125], which will be a powerful, clinically applicable function. LeNet-5 architecture can be found in publication by Lecun *et al*[126].

However, areas with less data availability, such as EUS, cannot be advanced with AI technology alone. For developments of these areas, international collaboration for collection of multi-center image database and clinical data must be done to overcome data scarcity and facilitate precise training and evaluation of models. These multi-center database of image and clinical data will not only benefit model training, but also validation of previous models. Because multi-center data can be more unbiased than data from single source, validation or re-training by multi-center data may improve precision of models by eliminating sampling bias.

With future advancement in data science, deep learning algorithm and medical robotics, AI can play important role in gastrointestinal radiology in the future and may lead a medial revolution.

CONCLUSION

As demonstrated in the assistance of liver tumor diagnosis and cholangiography, AI has the potential to reduce radiology workload and improve diagnostic specificity, thus making radiologic diagnoses faster and more reliable. In some tasks like the detection of a malignant stricture, we can even hope for machine diagnosis to surpass human diagnosis, making fully automated diagnosis possible. Conversely, for fields where training data collection is more difficult, such as endoscopic ultrasound, training deep learning models would still be slow using today's technology.

To overcome the problem of lack of technical advancement due to limited data in these areas, particularly in endoscopic procedure, two approaches maybe used. The first solution is to use algorithms that are designed to increase data availability in small medical dataset, such as generative adversarial network and transfer learning. The other suggestion is to build public, global endoscopic image library for model training. In conclusion, though a lot have to be done to make AI universally successful in gastrointestinal radiology, the researchers and developers actually already have the facility to deal with the difficult aspects of this task. Therefore, it is reasonable to expect more scientific advancements and clinical use of AI in the coming decade.

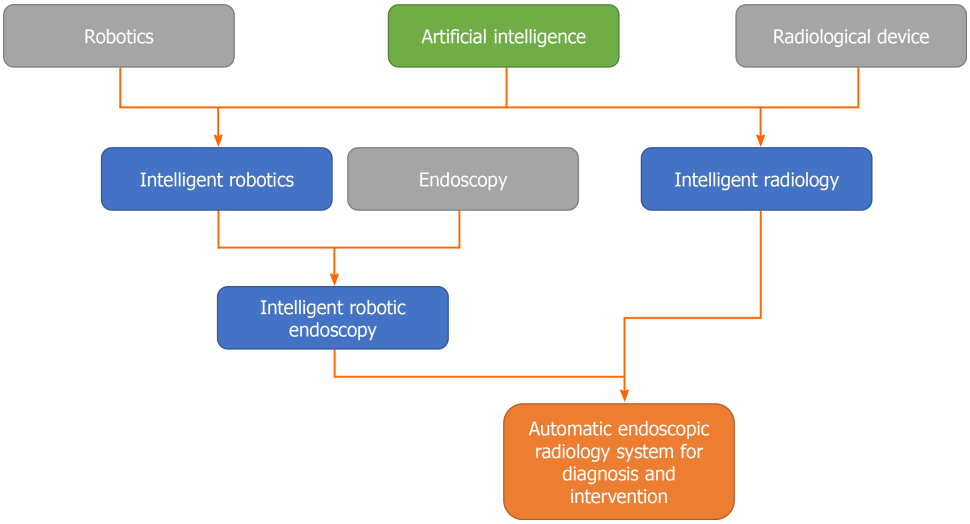

Figure 1 Illustration of a possible path to automatic diagnostic and interventional system in gastroenterology.

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Artificial Intelligence in Gastroenterology

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Artif Intell Gastroenterol 2021 April 28; 2(2): 42-55

DOI: 10.35712/aig.v2.i2.42

ISSN 2644-3236 (online)

MINIREVIEWS

Clinical value of artificial intelligence in hepatocellular carcinoma: Current status and prospect

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Author contributions: Yu F proposed the idea; Yi PS and Hu CJ wrote the manuscript; Yi PS and Hu CJ contributed equally to this work; Li CH performed the electronic searching and abstracted the data.

Supported by Project of Science and Technology Department of Sichuan Province, No. 2018JY050; and Nanchong Science and Technology Bureau Project, No. 18SXHZ0336.

Conflict-of-interest statement: The authors declare that they have no competing interests.

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Abstract

Hepatocellular carcinoma (HCC) is the most commonly diagnosed type of liver cancer and the fourth leading cause of cancer-related mortality worldwide. The early identification of HCC and effective treatments for it have been challenging. Due to the sufficient compensatory ability of early patients and its nonspecific symptoms, HCC is more likely to escape diagnosis in the incipient stage, during which patients can achieve a more satisfying overall survival if they undergo resection or liver transplantation. Patients at advanced stages can profit from radical therapies in a limited way. In order to improve the unfavorable prognosis of HCC, diagnostic ability and treatment efficiency must be improved. The past decade has seen rapid advancements in artificial intelligence, underlying its unique usefulness in almost every field, including that of medicine. Herein, we sought and reviewed studies that put emphasis on artificial intelligence and HCC.

Key Words: Hepatocellular carcinoma; Artificial intelligence; Diagnosis; Prognosis; Therapy; Genomic

Core Tip: We performed electronic searching in PubMed, Web of Science and EMBASE. Artificial intelligence (AI) or in-depth learning and hepatocellular carcinoma were used as mesh terms. We found that AI showed favorable results in

Manuscript source: Unsolicited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: China

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 6, 2021
Peer-review started: January 6, 2021
First decision: February 14, 2021
Revised: February 25, 2021
Accepted: March 15, 2021
Article in press: March 15, 2021
Published online: April 28, 2021

P-Reviewer: Simsek H
S-Editor: Wang JL
L-Editor: Filipodia
P-Editor: Li JH

early diagnosis and treatment response prediction and prognosis estimation in patients with hepatocellular carcinoma. The past decade has seen rapid advancements in AI, underlying its unique usefulness in almost every field, including that of medicine. Herein, we sought and reviewed studies, and we expect that AI will be an important complement to traditional diagnosis, treatment and prognosis estimation of hepatocellular carcinoma.

Citation: Yi PS, Hu CJ, Li CH, Yu F. Clinical value of artificial intelligence in hepatocellular carcinoma: Current status and prospect. *Artif Intell Gastroenterol* 2021; 2(2): 42-55
URL: https://www.wjgnet.com/2644-3236/full/v2/i2/42.htm
DOI: https://dx.doi.org/10.35712/aig.v2.i2.42

INTRODUCTION

According to GLOBOCAN 2018[1], liver cancer was the sixth most commonly diagnosed (4.7%) type of cancer and the fourth leading cause (8.2%) of cancer-related mortality. It has been estimated that there are approximately 841000 new liver cancer cases and 782000 liver cancer-related deaths annually. Hepatocellular carcinoma (HCC) accounts for the majority of primary liver carcinoma[1]. The widely accepted risks of HCC include chronic hepatitis B virus/hepatitis C virus infection, alcohol consumption, cirrhosis, aflatoxin intake as well as nonalcoholic fatty liver disease. Due to its atypical radiological appearance and the possibility of false-negative biopsy results, early-stage HCC is likely to be missed. Only a few HCC patients are suitable for radical resection, and even fewer can receive a liver transplant due to the limited availability. The high recurrence rate of HCC also undermines the benefits of surgery. Patients in intermediate and advanced stages can only benefit from noncurative treatments, including transarterial chemoembolization (TACE), radiofrequency ablation (RFA), targeted agents and systemic therapies, albeit in a limited way[2]. Managing HCC is a major challenge in the clinic.

In the past few years, rapid progress has been made in artificial intelligence (AI) due to improvements in computer science. AI techniques, including machine learning (ML), artificial neural networks (ANNs) and computer vision, were combined with surgery, radiology, bioinformatics and pharmaceuticals and played an innovative role in boosting the development of those techniques[3,4]. At present, AI is applied in drug design, patient monitoring, diagnostics and imaging, risk prediction and management, wearables and virtual assistants[5].

As AI is now frequently used in diagnosis, treatment and patient managing of many types of cancer, including lung, gastric, prostate and colon cancers[6-17], the assistance of AI in enhancing our diagnostic, therapeutic and prognostic ability to control HCC was not unexpected. In addition, the combination of AI and big data also performed much better than traditional methods[18].

Recent studies have exhibited promising applications of AI in HCC. In the present study, the latest developments in the use of AI in HCC were studied, and both methods and improvements were reviewed.

DIAGNOSTIC ASSISTANCE FROM AI

An HCC diagnosis is based mostly on imaging and laboratory tests. Radiological and nonradiological imaging holds a dominant position in the diagnosis, staging, therapeutic decisions and management of patients, while laboratory biomarkers [*e.g.*, α-fetoprotein (AFP)] offer some support. For certain patients, histological examination is recommended[19]. By introducing AI into the evidence-based diagnostic procedure, more accurate classification was provided to assist clinical determination. Recent developments were summarized in Table 1.

In a study in 2010, a total of 250 HCC patients, including 200 patients who underwent hepatectomy and 50 who underwent liver transplantation, were randomly divided into a test group (n = 75; 30%) and a training group (n = 175; 70%)[20]. Factors including serum AFP, preoperative tumor number, maximum tumor size and tumor volume were found by univariate analysis to be strongly related to tumor grade

Table 1 Recent developments in artificial intelligence assisted diagnosis

AI category	Data adopted	Advantages	Control	Ref.
ANN	Preoperative serum AFP, tumor number, size and volume	The ANN showed higher AUCs in identifying tumor grade (0.94) and MVI (0.92)	LR model (0.85 and 0.85)	[20]
CNN	Enhanced MRI	The CNN showed comparable accuracy (90%)	Traditional multiphase MRI (89%)	[24,25]
Open-source framework "caffe" based CNN model	DWI	CNN trained with three sets of b-values found better grading accuracy (80%)	CNN trained with different b-values (65%, 68%, 70%)	[26]
CNN	Nonenhanced MRI	The deeply supervised and pretrained CNN model performed better in characterizing HCC (accuracy 77.00 ± 1.00%)	CNN-based method pretrained by ImageNet (65.00 ± 1.58%)	[27]
DL-based segmentation model	Contrast-enhanced CT	The model with a combination of 2D multiphase strategy showed higher ability of segmenting active part from the tumors	Traditional CT estimation	[28-30]
RF based ML model	HE-stained histopathological images	The classifying model showed an AUC of 0.988 in the test set and 0.886 in the external validation set	-	[31]
1D CNN	Hyperspectral and HE-stained images	The models had a higher average AUC of 0.950	RF (0.939) and SVM (0.930) models	[33]
Shiny and Caret packages-based prediction model	Clinical and laboratorial information	The optimal model had an AUC of 0.943	Single factor-based predictors (0.766, 0.644 and 0.683)	[34]

1D: One-dimensional; 2D: Two-dimensional; AFP: α-fetoprotein; AI: Artificial intelligence; ANN: Artificial neural network; AUC: Area under the curve; CNN: Convolutional neural network; CT: Computed tomography; DL: Deep learning; DWI: Diffusion-weighted imaging; HE: Hematoxylin and eosin; LR: Logistic regression; ML: Machine learning; MRI: Magnetic resonance imaging; MVI: Microvascular invasion; SVM: Support vector machine; RF: Random forest.

and/or microvascular invasion. Those four factors were used to build both a traditionally used logistic regression (LR) model and an ANN, which was set as a 3-layer feedforward neural network with a learning rule of backpropagation of error, endowing the ANN with a capacity of reducing overall error. It was clear that ANN [area under the curve (AUC) = 0.94; 95% confidence interval (CI): 0.89-0.97] had a notably higher ($P < 0.001$) predictive ability for tumor grade than LR analysis (AUC = 0.85; 95%CI: 0.78-0.89). At the same time, its ability to predict microvascular invasion was also significantly stronger (AUC = 0.92, 0.85; 95%CI: 0.86-0.96, 0.74-0.89; $P < 0.001$). Compared with single factor prediction, which cannot effectively predict tumor grade and microvascular invasion[21-23], ANN provided a significantly improved ability to stratify tumors in a multidimensional way.

Magnetic resonance imaging (MRI) is highly valued in clinical diagnosis due to its outstanding ability to locate lesions. Recent research has shown the potential of deep-learning systems to distinguish HCC from other hepatic diseases, in which all 494 typical imaging features of six types of hepatic lesions were divided into a training set ($n = 434$) and a test set ($n = 60$)[24]. An AI model was used to classify hepatic lesions through multiphasic contrast-enhanced MRI scans. A custom convolutional neural network (CNN) with iteratively optimized architecture was trained by 43400 samples generated from 434 patients of the training set *via* augmentation techniques. The test set included 60 lesions (10 lesions from each category) randomly selected by Monte Carlo cross-validation. Eventually, the CNN consisted of three convolutional layers for generating filtered images, two maximum pooling layers for providing spatial invariance and two fully connected layers for outputting matched lesion types. As a result, a 90% sensitivity and an AUC of 0.992 for HCC classifying were observed in the test set, with an average 90% sensitivity and 98% specificity for a total of six classes of lesions. It had comparable efficiency to traditional multiphase MRI, which was reported to have an overall sensitivity of 89% and specificity of 96% for HCC[25].

Another recent study, in which imaging data was partitioned into a training and validation set (60 HCCs) and a fixed test set (40 HCCs), paid attention to the tumor grading potential of diffusion-weighted imaging[26]. An AI model was constructed based on an open-source deep-learning framework, "caffe", to grade HCC by diffusion-weighted imaging. Edmondson grade I and II HCCs were defined as low-grade ($n = 47$), while Edmondson grade III and IV HCCs were defined as high-grade (

n = 53). Diffusion-weighted imaging was performed with three sets of b-values (0, 100, 600 s/mm^2), logarithmically transformed into log maps and then extracted by a specifically designed two-dimensional CNN to collect spatially deep features for grading tumors. The two-dimensional CNN was established with two convolutional layers, two pooling layers, two fully connected layers and a softmax layer. A deeply supervised loss functioned as the cross-entropy loss of the proposed CNN, which combined the three loss functions of CNN in the three b-value images and the loss function of the concatenated deep features. In terms of grading accuracy, the proposed CNN (80%; AUC, 0.83) performed better than other CNNs derived from original b 0 (65%), b 100 (68%), b 600 (70%) images and an apparent diffusion coefficient map (72.5%).

Jian *et al*[27] reported a novel method of training a deep-learning HCC diagnosis model with nonenhanced MRI scans. A total of 112 HCC patients (115 HCC tissue samples) with histological HCC proofs and enhanced MRI scans (including precontrast phase, arterial phase, portal vein phase and delayed phase) were classified into four Edmondson grades and further defined as low-grade (Edmondson grades I and II) and high-grade (Edmondson grades III and IV) HCCs. A deep-learning framework was established in two steps. The first step was the pretraining process, in which the relationship between precontrast (nonenhanced) and enhanced MRI scans was identified in order to find out malignant characterizations of nonenhanced MRI scans. The identified characterizations were transferring-learnt using a supervised cross modal method in the second step. Results showed that the CNN-based method performed better in characterization than the traditional way, and the deeply supervised model pretrained by the cross modal from the three phases (precontrast, arterial and portal vein phase) performed the best compared with nonsupervised CNN and deeply supervised methods pretrained by the cross modal from two out of three phases (precontrast + arterial phase and precontrast + portal vein phase). This result revealed a new diagnostic approach for patients not receptive to enhanced imaging.

A deep-learning automatic segmentation model was built on multiphase computed tomography (CT) images to discriminate tumors from healthy liver tissue and further identify between active and necrotic tumor areas[28]. A total of 13 contrast-enhanced CT sequences from 7 HCC patients were manually segmented by four experts into 104 labeled CT scan slices, containing images captured before contrast agent injection and images reflecting the arterial phase and the portal venous phase. The U-Net architecture was configured in a hierarchical method to specially segment by applying separate networks for each type of specific tissue. Two opposite strategies were investigated: Dimensional MultiPhase strategy, in which single-phase images were processed in a multi-dimensional feature map and the MultiPhase Fusion strategy, in which each phase was independently processed and then merged into the final segmentation. The softmax was introduced in the final layers of the different networks. The weighted cross-entropy functioned as the cost to optimize the weights and balance classes problem. Finally, a commonly used Dice similarity coefficient was used to estimate segmentation quality. Results indicated a better competency of multiphase methods in segmenting the liver and active part of tumors as compared with single phase ones. Between the two multiphase methods, Dimensional MultiPhase outperformed MultiPhase Fusion in the segmentation of the liver (P = 0.004) and active part of the tumors (P = 0.005). Furthermore, the combination of two Dimensional MultiPhase methods displayed the highest ability in spotting active areas from tumor tissues, making it reliable (mean error rate = 13.0%) in estimating the necrosis rate in which traditional CT estimation is not[29,30]. With a more accurate assessment method, more beneficial clinical decisions may be made.

Histological examination provides solid evidence for the diagnosis, grading and prognosis analysis of HCC. Hematoxylin and eosin staining is the most common method used for biopsy. A total of 491 whole-slide hematoxylin and eosin-stained histopathological images of HCC and adjacent normal tissues downloaded from the Genomic Data Commons data portal were used for supervised training of ML classifier based on Breiman's random forest (RF)[31]. The 31 most valuable image features (IFs) identified from the training set by principal component-based analysis (PCA) were used during the establishment of the classification model. An external validation set of tissue microarray images from the West China Hospital was employed in addition to the randomly partitioned training (70%) and test (30%) sets. The IF classification model showed an AUC of 0.988 (95%CI: 0.975-1.000) in the test set, while that of the external validation set was 0.886 (95%CI: 0.844-0.929). This outstanding performance of the IF model indicates its possible applications in the future.

Hyperspectral imaging (HSI) was regarded as a promising diagnostic technique[32]. A one-dimensional CNN was designed to discriminate HCC from normal tissues through HSI images[33]. HCC samples were cut into two adjacent slices, one of which was hematoxylin and eosin-stained and the other one underwent HSI. A total of 14 sets of HSI images, each containing 107 images photographed under different wavelengths, were used in a leave-one-out cross-validation approach, resulting in 14 different models. The framework consisted of a convolution layer, a max-pooling layer and a fully connected layer. The convolution layer could extract features from HSI images supervised by annotated tumor areas on the paired hematoxylin and eosin-stained slice, with a rectified linear unit that was shown to avoid gradient vanishing and accelerate the training process. Extracted features were processed in the max-pooling layer to reduce dimension and classified afterward in the fully connected layer. The average accuracy, sensitivity, specificity and AUC of those models was 0.881, 0.871, 0.888 and 0.950, respectively. Further evaluation was carried out and exhibited a salient capacity of the one-dimensional CNN model as compared with the RF and support vector machine (SVM) models.

Information was extracted from 539 HCC patients and 1043 non-HCC patients to train and test a predictive ML framework developed using R version 3.4.3 and the Shiny and Caret packages[34]. Patients were randomly divided into the training (80%), development and test sets. Clinical information, including AFP, AFP-L3, des-g-carboxy prothrombin (commonly referred to as DCP), aspartate aminotransferase, alanine transaminase, platelet count, alkaline phosphatase, gamma-glutamyl transferase, albumin, total bilirubin, age, sex, height, body weight, hepatitis B surface antigen and hepatitis C virus antibody, was obtained for ML. The framework had several classifiers and two components. In the first component, a grid search was performed to select the best classifier and its specific hyperparameter, which would be introduced in the second component to output probabilities of HCC. Among a total of seven classifiers, gradient boosting showed an AUC of 0.940 as the highest one, with that of the optimal, based on the framework, classifier at 0.943; single-factor prediction using thresholds of 200 ng/mL for AFP, 40 mAu/mL for DCP and 15% for AFP-L325 performed AUCs of 0.766, 0.644 and 0.683, respectively.

THERAPY RESPONSE PREDICTION BY AI

Surgical resection remains the first-line treatment for early-stage patients, with 5-year survival in appropriately selected cases exceeding 70%. However, it has been reported that HCC diagnosis is usually delayed, especially in countries with limited screening resources[19]. Out of patients who miss the optimum surgical time window or are unsuitable for operative therapy, only a few benefit from loco-regional (*e.g.*, RFA), intra-arterial (*e.g.*, TACE), systemic and targeted therapies[2]. Thus, enhancing the accuracy of surgical indications and promoting treatment benefits of nonoperative therapies would effectively improve the clinical prognosis of patients. In the past years, some AI models with great potential were built, as referred in Table 2.

HCC has been estimated as the fourth highest cause of all cancer-related mortality worldwide[1], indicating a high malignancy and poor prognosis of HCC. Accurate prognostic prediction of tumor resection is needed to identify high-risk patients and enable more favorable clinical decisions. As Qiao *et al*[35] reported, the independent risk factors (including tumor size, number, AFP, microvascular invasion and tumor capsule) found by linear regression to be significantly related to survival were selected to assist in predicting the prognosis of early HCC after partial hepatectomy, both in a Cox model and using an ANN method. A feed-forward neural network was built as a perceptron with several layers, outputting a prognosis condition (survival or death) for certain time points. In addition to the training and cross-validation cohort in which patients from the Eastern Hepatobiliary Surgery Hospital were randomly selected, an external validation cohort was obtained from the First Affiliated Hospital of Fujian Medical University. AUCs demonstrated that the ANN (0.855) outperformed the Cox model (0.826), Tumor, Node, Metastasis 6th (0.639), Barcelona Clinic Liver Cancer (BCLC) (0.612) and HepatoPancreato-Biliary Association system (0.711), and consistent results were observed in the external validation cohort. It drew attention to the potential of the ANN model to provide clinical assistance and improve benefits of early-stage HCC patients.

AI models can also help identify predictive factors of surgery outcomes. In a multicenter retrospective study that included 976 BCLC 0-B HCC patients who underwent hepatectomy, Tsilimigras *et al*[36] generated homogeneous groups of

Table 2 Artificial intelligence models that can help in predicting therapy responses

AI	Data adopted	Advantages	Control	Ref.
ANN	Cox-identified risk factors	The ANN had the highest AUC (0.855)	Cox model, TNM 6th, BCLC and HPBA system (0.826, 0.639, 0.612, 0.711)	[35]
CART model	Clinical and laboratorial parameters	The model successfully identified pre- and postoperative prognosis predictive factors	-	[36]
Weka-based ANNs	Cox-identified risk factors (15 factors for DFS and 21 for OS)	The ANNs showed higher abilities of predicting DFS and OS	LR and decision tree model	[37,38]
Radiomics-based DL CEUS model	Contrast-enhanced ultrasound	The model showed an AUC of 0.93 in predicting therapy response to TACE	Radiomics-based time-intensity curve of CEUS model (0.80) and radiomics-based B-Mode images model (0.81)	[40]
Pretrained CNN "ResNet50"	Manually segmented CT images	The model showed AUCs for predicting CR, PR, SD and PD in training (0.97, 0.96, 0.95, 0.96) and validation (0.98, 0.96, 0.95, 0.94) cohorts	-	[41]
Automatic predictive CNN model	Quantitative CT and BCLC stage	The model had a better prediction accuracy of 74.2%	ML model based on BCLC stage (62.9%)	[42]
ANN	Clinical features	The models showed higher AUCs in predicting 1- and 2-yr DFS (0.94, 0.88) after RFA	Model built with 8 features for 1-yr DFS (0.80), and model built with 6 features for 2-yr DFS (0.76)	[45]

AI: Artificial intelligence; ANN: Artificial neural network; AUC: Area under the curve; BCLC: Barcelona Clinic Liver Cancer; CART: Classification and Regression Tree; CEUS: Contrast-enhanced ultrasound; CNN: Convolutional neural network; CR: Complete response; CT: Computed tomography; DFS: Disease-free survival; DL: Deep learning; HPBA: HepatoPancreato-Biliary Association; LR: Logistic regression; ML: Machine learning; OS: Overall survival; PD: Progressive disease; PR: Partial response; RFA: Radiofrequency ablation; SD: Stable disease; TACE: Transarterial chemoembolization; TNM: Tumor, Node, Metastasis; Weka: Waikato Environment for Knowledge Analysis.

patients based on their 5-year overall survival (OS) and identified clinical factors, which can be used to predict OS after resection using the nonparametric Classification and Regression Tree (CART) model based on pre- (preoperative CART model) and postoperative (postoperative CART model) factors. CART is a risk prediction model with a performance to recursively partition the 'covariate space'. As a result, the CART model successfully identified several prognosis predictive factors. Among BCLC-0/A patients, the CART model selected AFP and Charlson comorbidity score as the first and second most important preoperative factors and lymph vascular invasion as the best postoperative predictor of OS. Radiological tumor burden score and pathologic tumor burden score were selected as the best pre- and postoperative factors for predicting surgical outcomes for BCLC-B HCC patients.

Consecutive studies of Ho *et al*[37,38] have been reported in which AI models were predictively capable of classifying patients into different groups with distinctive disease-free survival (DFS) and OS after hepatic resection. Data from HCC patients who underwent liver resection were examined and merged for further construction of survival predictive models. The input variables were identified by the univariate Cox proportional hazard model to be closely related (log-rank test; $P < 0.05$) to DFS or OS. Eighty percent of the data were used for training, and the other 20% for validation, while no significantly different effect of input variables was observed between training and validation ($P > 0.05$). The proposed ANNs in both studies, which shared homologous structures based on the Waikato Environment for Knowledge Analysis software using a backpropagation algorithm, were framed with input, hidden and output layers. Each of the identified variables was inputted into one of the input neurons, and then a trial-and-error process was performed in the hidden layer to optimize its neuron numbers before generating DFS and OS status in the output layer, which contained only one neuron.

In the first reported study showing the capacity of the ANN to predict DFS based on 15 statistically significantly associated variables, two comparative models were tested: An LR and a decision tree model. The receiver operating characteristics curves and AUCs for the 1-, 3- and 5-year DFS models constructed using ANN, LR and decision tree demonstrated an acceptable and exceeding performance of the ANN model as compared with the LR and decision tree models.

In another study, attention was paid to OS after resection with 21 potential variables serving as inputs. An LR model was used for performance comparison. The accuracy, sensitivity, specificity and AUC of the ANN and LR models were calculated. As a result, the prediction performance of the ANN model was significantly stronger than that of the LR model. In both studies, the possible usage of the ANN as a clinical supplementary tool for decision-making was emphasized, suggesting it might be able to enhance the profit-risk ratio of HCC resection.

TACE has been widely accepted as the standard and effective treatment for HCC patients at the intermediate stage[39]. Recent studies have paid considerable attention to deep-learning and TACE, highlighting treatment response prediction and AI-assisted clinical decision-making.

Contrast-enhanced ultrasound (CEUS) and B-mode ultrasound images of 130 HCC patients who received first-time TACE treatment were obtained for retrospective analysis using AI, which was trained to predict patient response (objective-response and nonresponse) to TACE[40]. A total of three models were framed by applying CEUS images (deep-learning radiomics-based CEUS model), the time-intensity curve of CEUS (ML radiomics-based time-intensity curve of CEUS model) and B-mode images (ML radiomics-based B-Mode images model). AUCs were compared between the three models, and the hepatoma arterial-embolization prognostic score was used to predict the outcomes of patients with HCC undergoing TACE. In the training (n = 89; 68.5%) and validation (n = 41; 31.5%) cohorts, the three models markedly outperformed the hepatoma arterial-embolization prognostic score [AUC = 0.98 (0.92-0.99), 0.84 (0.74-0.90), 0.82 (0.73-0.91) and 0.623 in the training and 0.93 (0.80-0.98), 0.80 (0.64-0.90), 0.81 (0.67-0.95) and 0.617 in the validation cohorts for deep-learning radiomics-based CEUS model, ML radiomics-based time-intensity curve of CEUS model, ML radiomics-based B-Mode images model and hepatoma arterial-embolization prognostic score, respectively]. A high reproducibility of this predictive accuracy was displayed by robustness experiments performed in triplicate in both the training and validation cohorts. The predictive capability of human readers with a deep-learning feature map showed an advantage over that of ML radiomics-based time-intensity curve of CEUS model or ML radiomics-based B-Mode images model but not over that of deep-learning radiomics-based CEUS model.

In two analogous studies, the ML network displayed a strong ability to predict TACE therapy outcomes using CT images. Peng *et al*[41] trained a pretrained deep CNN, ResNet50, with manually segmented CT images to predict treatment response to TACE. Tumor regions of interest segmented by experienced radiologists were divided into one training set (n = 562) and two validation sets (n = 89; 138). The weights of earlier layers (1-174) in this network were frozen to prevent overfitting and speed up the training process. The trained model showed AUCs of 0.97 (0.97-0.98), 0.96 (0.96-0.97), 0.95 (0.94-0.96) and 0.96 (0.96-0.97) in the training cohort (n = 562), 0.98 (0.97-0.99), 0.96 (0.95-0.98), 0.95 (0.93-0.98) and 0.94 (0.90-0.98) in the validation cohort 1 (n = 89), and 0.97 (0.96-0.98) and 0.96 (0.94-0.98), 0.94 (0.92-0.97), 0.97 (0.95-0.98) in the validation cohort 2 (n = 138) for complete response, partial response, stable disease and progressive disease, respectively. Morshid *et al*[42] built a fully automated ML algorithm that can predict response to TACE using quantitative CT scan features and BCLC stage. A total of 105 HCC patients who had received TACE were defined by time to progression as TACE-susceptible (time to progression ≥ 14 wk) or TACE-refractory (time to progression < 14 wk). A total of five imaging features that were different between background liver and tumor were extracted, including tumor volume, maximum two-dimensional axial diameter of the background liver, small area low gray-level emphasis within the background liver, maximal correlation coefficient within the background liver and long-run high gray-level emphasis within the tumor. Those features were added to the AI model to promote prediction accuracy. Compared with the model based on the BCLC stage alone (prediction accuracy = 62.9%, 95%CI: 0.52-0.72), the model based on CT scan features and BCLC stage showed a better prediction accuracy of 74.2% (95%CI: 0.64-0.82).

Abajian *et al*[43] established an LR and an RF model to predict TACE treatment response using MRI scans. The quantitative European Association for the Study of the Liver response criteria were used to measure TACE response. A total of 36 patients were defined as treatment responders (8/36; 22.2%) and nonresponders (28/36; 77.8%) using a cut-off value of 65% changes in quantitative European Association for the Study of the Liver response criteria. During the training process of both models, five features, including cirrhosis, pre-TACE tumor signal intensity, pre-TACE number of tumors, performing method of TAC and existence of sorafenib treatment, were used in 30 different combinations to identify the most accurate predictive model. A leave-one-out cross-validation method was used for a predictive accuracy test. When trained on

all five features, the LR model displayed an accuracy of 72.0%, sensitivity of 50.0% and specificity of 78.6%, while an accuracy of 66.0%, sensitivity of 62.5% and specificity of 67.9% were validated for the RF model. Notably, these two models shared a best performance (accuracy 78%, sensitivity 62.5% and specificity 82.1%) when trained using only two (pre-TACE tumor signal intensity > 27.0 and presence of cirrhosis) of those five features but still remained inferior to that of MR scan using a baseline apparent diffusion coefficients value threshold of 0.83 × 10^{-3} mm^2/s, which demonstrated 91% sensitivity and 96% specificity to predict TACE response at 1 mo after treatment and an AUC of 0.965[44].

RFA is considered a viable option for HCC patients who are unsuitable for resection or on the waiting list for a liver transplant. A prognostic prediction ANN model was reported to be promising for clinical practice[45]. Patients were divided into a 1- (n = 252) and a 2-year (179) DFS group. A total of eight and six variables from a total of fifteen potential variables (total bilirubin, aspartate aminotransferase, alanine transaminase, albumin, platelet, age, gender, tumor size, tumor number, AFP, HCC treatment history, TACE, recurrence events after TACE, BCLC stages and liver cirrhosis events) were found to be significantly associated with 1- and 2-year DFS and were used as inputs for building prediction models, which was based on a multiple-layer perceptron structure and a backpropagation learning rule. This ANN model was designed with the ability of selecting structure depending on its predictive performance. Between two 1-year DFS models, the one built with 15 features (the accuracy, sensitivity, specificity, and AUC were 0.92, 0.87, 0.94 and 0.94, respectively) was better than the one with 8 significant features (the accuracy, sensitivity, specificity and AUC were 0.78, 0.37, 0.96 and 0.80, respectively). Consistently, a 2-year DFS model with 15 features (the accuracy, sensitivity, specificity and AUC were 0.86, 0.79, 0.91 and 0.88, respectively) showed a considerable advantage over that with 6 significant features (the accuracy, sensitivity, specificity and AUC were 0.68, 0.47, 0.84 and 0.76, respectively) and traditional methods including acoustic radiation force impulse elastography (AUC = 0.821; 95%CI: 0.747-0.895) and transient elastography(AUC 0.793; 95%CI: 0.712-0.874)[46,47]. Although some of the 15 features were evaluated by χ^2 test to be nonsignificantly related with 1- or 2-year DFS, the better outcome of models with all 15 features might have prompted their implicit roles in RFA response prediction.

PROGNOSIS ESTIMATION USING AI

In order to correctly identify the development characteristics and improve the outcomes of existing therapies, accurate prognostic information is indispensable. Individualized precise treatment based on risk and prognostic data would substantially enhance curing efficiency in HCC[48]. Table 3 displayed some of the effective models which can provide prognosis estimation.

Two deep-learning algorithms, CHOWDER and SCHMOWDER, which adopted whole-slide digitized histological slides of HCC patients that had undergone surgery were set up to predict OS after resection[49]. CHOWDER could automatically recognize survival-related patterns on the tiles derived from the slides and assess the risk score for each whole-slide digitized histological slide in three steps: Preprocessing, tile-scoring and prediction. SCHMOWDER has an identical preprocessing step as CHOWDER and a two-branch tile-scoring and predicting pipeline. The upper branch, which generated a representation of highly-probably tumoral tiles with an attention mechanism used, was trained by annotations from pathologists; the lower branch, which generated a representation of only a few tiles, was weakly supervised. Representations from the two branches were merged to calculate a survival risk score. The discriminatory capacities of the two models assessed by cross-validation were demonstrated as better than baseline factors (including microvascular invasion, serum AFP, largest nodule diameter and satellite nodules) and composite score by combining survival-related clinical, biological and pathological features.

In a prospective study including 442 patients with Child A or B cirrhosis, an HCC development prediction model based on ML algorithms, known as RF, was compared using conventional regression analysis[50]. Previously determined clinically relevant parameters (age, body mass index and presence of diabetes) and those identified by univariate analysis (AFP level, bilirubin, male gender, aspartate aminotransferase, alanine transaminase, Child-Pugh score and viral etiology) were selected to build a predictive regression model and an ML classifier. Multiple decision trees were constructed and used as "votes" to create the final classification prediction model. Cross-validated accuracy estimation and external validation in the hepatitis C antiviral

Table 3 Prognosis prediction models built with artificial intelligence algorithms

AI category	Data adopted	Advantages	Control	Ref.
DL algorithms CHOWDER and SCHMOWDER	Whole-slide digitized histological slide	C-indexes for survival prediction of SCHMOWDER and CHOWDER reached 0.78 and 0.75	Baseline factors and composite score	[49]
ML classifier	Previously determined relevant parameters and those identified by univariate analysis	The ML algorithm performed a c-statistic of 0.64 for HCC development prediction	Regression model (0.61) and the model built on the HALT-C cohort (0.60)	[50]
DL survival prediction model	RNA, miRNA and methylation data from TCGA	The DL model showed better potential in classifying HCC patients into two subgroups with different survival	PCA and the model built with manually inputted features	[51]
OS prediction model based on SVM-RFE algorithm	134 methylation sites identified using Cox regression and SVM-RFE algorithm	This algorithm showed a higher accuracy of classifying HCC patients	Traditionally set classifying methods based on DNA methylation	[54-56]
ANN	Mortality-related variables	The ANN showed higher AUCs (0.84 and 0.89) in predicting in-hospital and long-term mortality	LR model (0.76 and 0.77)	[57,58]

AI: Artificial intelligence; ANN: Artificial neural network; AUC: Area under the curve; DL: Deep learning; HALT-C: Hepatitis C antiviral long-term treatment against cirrhosis; HCC: Hepatocellular carcinoma; LR: Logistic regression; ML: Machine learning; OS: Overall survival; PCA: Principal component-based analysis; RFE: Recursive feature elimination; SVM: Support vector machine; TCGA: The Cancer Genome Atlas.

long-term treatment against cirrhosis trial cohort, which included 1050 patients, was conducted. The ML algorithm performed the best classifying characteristics with a c-statistic of 0.64 (95%CI: 0.60-0.69) compared with the regression model (0.61; 95%CI: 0.56-0.67) and the model built on the hepatitis C antiviral long-term treatment against cirrhosis cohort (0.60; 95%CI: 0.50-0.70), raising the possibility of prospectively predictive HCC development by ML.

Two HCC subgroups were found to have a notably discrepant prognosis by survival analysis and were focused on to build a deep-learning survival prediction model[51]. RNA, miRNA and methylation data from 360 HCC patients were collected from The Cancer Genome Atlas (TCGA) and were split to train an SVM model. Five additional confirmation datasets were obtained to estimate the predictive accuracy. TCGA HCC omics data were regarded as the input of the proposed autoencoder, in which three hidden layers with different numbers of nodes were implemented using the Python Keras library. The autoencoder was trained for ten epochs with a 50% dropout in the gradient descent algorithm. A total of 37 features of the TCGA omics data significantly (log-rank test, $P < 0.05$) associated with survival were identified by the autoencoder. With those features, a classification model using the SVM algorithm was built and validated in the test group and five additional groups of HCC patients. C-index, Brier score and log-rank test were carried out to evaluate the performance of the AI model, and two alternative methods, including PCA and a model based on 37 manually identified features from the omics data. The proposed model showed a clearly better potential than that of PCA and the model with manually-inputted features, and intended prediction robustness was validated in additional datasets.

Anomalous DNA methylation was found to be highly related to HCC[52,53] and able to predict survival in HCC patients that had undergone surgery[54]. DNA methylation data from 377 HCC samples and 50 adjacent normal tissue samples were obtained and analyzed using the ChAMP tool in *R* software. A total of 2785 sites from 40799 sites that had been methylated differently between HCC tissue and adjacent normal tissue were assessed *via* Cox regression and found to be significantly related to OS ($P < 0.05$). The SVM-recursive feature elimination algorithm behaved as a classifier to identify valuable sites that could be used to build a predictive model. Finally, 134 methylation sites were used to build the predictive model. A total of 163 patients were divided into a "high-risk" (died within 1 year after surgery, $n = 58$), "intermediate-risk" (survived 1-5 years after surgery, $n = 64$) and "low-risk" (survived > 5 years after surgery, $n = 41$) groups and were separated into a training ($n = 130$) and a test ($n = 33$) set. A total of 26 (78.8%) patients were successfully classified into the test set. Further validation of 19 paired HCC and normal tissue samples from the GSE77269 dataset in the Gene Expression Omnibus database demonstrated no incorrect classification of normal tissues and a similar ratio of HCC samples classified as "high-risk." Although this algorithm showed a higher accuracy of classifying HCC patients than some traditionally-set classifying methods based on DNA methylation[55,56], validation in a

larger sample size was needed.

Liao *et al*[31] built an IF-based prognosis prediction model (IF model) that can divide HCC patients who underwent resection into two groups, the high- and low-score groups, with a different OS according to the cut-off value of the training set. A total of 46 informative IFs, identified by Cox proportional hazard regression and an RF minimal depth algorithm, were found to be significantly ($P < 0.05$) associated with OS and were used to train the IF model. As a result, the IF model successfully distinguished patients with higher scores from those with lower scores in all three sets (log-rank test; $P < 0.0001$ in the training set, $P = 0.013$ in both the test and external validation sets), exhibiting a well-performed prognosis prediction ability. Furthermore, time-dependent receiver operating characteristics curves were used to compare the prognosis performance between the IF model and the Tumor, Node, Metastasis staging system, with no significant difference observed (adjusted $P = 0.848$-1.000) at each time point (1-9 years after treatment), indicating that the IF model may have a comparable predictive accuracy with that of the Tumor, Node, Metastasis staging system.

Two similarly framed ANN models, expected to respectively predict in-hospital and 5-year mortality in HCC, were trained with data from a large population of 22926 patients who had been diagnosed with HCC and had undergone resection[57,58]. The structure of ANNs consists of an input layer, a hidden layer and an output layer. To identify related variables, continuous and categorical variables were respectively tested by one-way analysis of variance and Fisher's exact test, and significant predictors ($P < 0.05$) were verified by univariate analysis. The following steps were repeated 1000 times: (1) Data were randomly divided into a training set ($n = 18341$; 80%) and a test set ($n = 4585$; 20%); (2) the LR and ANN models were established based on the training dataset; and (3) Paired *t*-tests were used to compare indices between the two models. Statistically in-hospital mortality-related variables, including age, gender, comorbidity (estimated by Charlson comorbidity index), hospital volume, surgeon volume and length of stay) were extracted by the ANN, and an outcome (death/survival) was generated. Compared to the LR model, the ANN showed a substantial advantage with a higher accuracy rate (97.28 *vs* 88.29, $P < 0.001$), a lower Hosmer-Lemeshow statistic (41.18 *vs* 54.53, $P < 0.001$) and a higher AUC (0.84 *vs* 76, $P < 0.001$). The other ANN model was built and tested similarly with six identical variables to predict 5-year mortality, and ANN was found to significantly outperform the LR model (accuracy rate 96.57% *vs* 87.96%; Hosmer-Lemeshow statistic 0.34 *vs* 0.45; AUC 88.51% *vs* 77.23%). Those two models combined with the deep-learning technique showed unique prognosis prediction performance, revealing their possible applicability in the prediction of in-hospital and long-term mortality.

OMICS RESEARCH PERFORMED WITH AI

Genomic data have exhibited efficient and unique advantages in both research and clinical experience. A recent study managed to correlate tumor samples and their original tissue types using an ML prediction model[59]. RNA-seq data of 14 tumors and at least 10 corresponding adjacent normal tissue samples for each tumor were downloaded from TCGA, Therapeutically Applicable Research to Generate Effective Treatments and the Genotype-Tissue Expression. An autoencoder neural network based on Pytorch with a rectifying activation function, dropout and normalization between layers was built. The mean squared error between the input and output was introduced as the loss function. After 10000 iterations for converging loss, the autoencoder demonstrated an outstanding ability to identify tissue sites for cancers with increasing accuracy in parallel with the mounting number of varying genes, noticeably surpassing the predominant PCA method, which identified only 8/14 cancers. In the distinction of HCC samples, the autoencoder with all features utilized showed a highly specific capacity of capturing biological information. This study provided a solid reference for further research in HCC and might be able to promote sample usage in a precise way.

A novel approach of seeking HCC-related genes by ML was established[60]. Gene expression profiles of 43 tumor and 52 normal tissue samples were downloaded from NCBI Gene Expression Omnibus. A maximum relevance-minimum redundancy (mRMR) method, referred to as mRMRe, was used to rank the features. The mRMR is a proven ML approach for phenotype classification; it can classify transcriptional features based on both the redundancy between features and their relevance to the target. An incremental feature selection method was combined with the mRMRe

algorithm, generating a possible feature subset for further analysis. A subset consisting of 117 features with a satisfying accuracy of 0.895 was finally selected as the criteria to distinguish HCC from non-HCC samples, in which several previously identified HCC-related genes (such as *MT1X*, *BMI1* and *CAP2*) were found, justifying the rationality of this model. Furthermore, some genes, such as *TACSTD2*, that were not considered to be HCC-related before (one of which was identified by protein-protein interaction) might be crucial during the pathogenesis of HCC, namely ubiquitin C was identified by this model.

CONCLUSION

AI showed a substantial enhancement throughout the pre- and postclinical process of HCC in terms of both investigation and treatment. Due to the low diagnostic rate of early-stage patients, its high recurrence rate and unsatisfactory treatment effectiveness, HCC is one of the deadliest types of cancer worldwide. The emerging and fast-developing techniques of AI offer the possibility of improving the survival of HCC patients. Brought by deep-learning methods, a higher accuracy of diagnosis and treatment response prediction combined with individual prognosis assessment could potentially improve the time and quality of survival for HCC patients to a considerable extent.

AI has also been used in a wider range of clinical practice. Hyer *et al*[61] released an ML approach to predict postsurgical prognosis. The novel method referred to as Complexity Score outperformed several currently used indices of prognosis estimation. Mueller-Breckenridge *et al*[62] identified two hepatitis B virus quasispecies by ultra-deep sequencing and developed a ML model to determine the viral variants and assist clinical decision-making with regards to anti-hepatitis B virus strategies. A newly-established ML model was reported as an alternative method in the prediction of liver fibrosis caused by chronic hepatitis C virus infection[63]. While none of those studies were directly related to HCC, their findings might significantly help preclinical prevention, early diagnosis and surgical planning.

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Artif Intell Gastroenterol 2021 April 28; 2(2): 56-68

DOI: 10.35712/aig.v2.i2.56

ISSN 2644-3236 (online)

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Artificial intelligence for pancreatic cancer detection: Recent development and future direction

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Author contributions: Laoveeravat P, Abhyankar PR, and Brenner AR equally contributed to this paper with conception and design of the study, literature review and analysis, drafting the manuscript; Gabr MM, Habr FG, and Atsawarungruangkit A provided critical revision, editing, and final approval of the final version.

Conflict-of-interest statement: No conflict of interest exists.

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Abstract

Artificial intelligence (AI) has been increasingly utilized in medical applications, especially in the field of gastroenterology. AI can assist gastroenterologists in imaging-based testing and prediction of clinical diagnosis, for examples, detecting polyps during colonoscopy, identifying small bowel lesions using capsule endoscopy images, and predicting liver diseases based on clinical parameters. With its high mortality rate, pancreatic cancer can highly benefit from AI since the early detection of small lesion is difficult with conventional imaging techniques and current biomarkers. Endoscopic ultrasound (EUS) is a main diagnostic tool with high sensitivity for pancreatic adenocarcinoma and pancreatic cystic lesion. The standard tumor markers have not been effective for diagnosis. There have been recent research studies in AI application in EUS and novel biomarkers to early detect and differentiate malignant pancreatic lesions. The findings are impressive compared to the available traditional methods. Herein, we aim to explore the utility of AI in EUS and novel serum and cyst fluid biomarkers for pancreatic cancer detection.

Key Words: Artificial intelligence; Machine learning; Deep learning; Endoscopic ultrasound; microRNA; Pancreatic cancer; Pancreatic cyst

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: United States

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): E

Received: January 26, 2021
Peer-review started: January 26, 2021
First decision: February 27, 2021
Revised: March 31, 2021
Accepted: April 20, 2021
Article in press: April 20, 2021
Published online: April 28, 2021

P-Reviewer: Jiménez Pérez M, Marescaux J, Vishnoi S
S-Editor: Wang JL
L-Editor: A
P-Editor: Li JH

Core Tip: Artificial intelligence (AI) aided endoscopic ultrasound (EUS) and microRNA analyses are sensitive and effective for pancreatic cancer detection with sensitivity of more than 95%. The size of pancreatic lesion does not affect the diagnostic performance by artificial intelligence. This will help overcome the delayed diagnosis and high mortality of pancreatic cancer. Recent studies showed that the speed of AI system in EUS can be performed in real time fashion. This will be adjunctive to the conventional EUS examination for future utility.

Citation: Laoveeravat P, Abhyankar PR, Brenner AR, Gabr MM, Habr FG, Atsawarungruangkit A. Artificial intelligence for pancreatic cancer detection: Recent development and future direction. *Artif Intell Gastroenterol* 2021; 2(2): 56-68
URL: https://www.wjgnet.com/2644-3236/full/v2/i2/56.htm
DOI: https://dx.doi.org/10.35712/aig.v2.i2.56

INTRODUCTION

Pancreatic cancer has been notorious for late detection and high mortality rate[1,2]. The main contributing factor is the difficulty of diagnosis from imaging studies[3]. Differentiation between benign disease like chronic pancreatitis and malignancy is challenging[4]. Malignant pancreatic diseases [*i.e.*, pancreatic ductal carcinoma, intraductal papillary mucinous neoplasms (IPMN), and mucinous cystic neoplasm] can present differently in radiologic imaging[3]. Endoscopic ultrasound (EUS) has been recognized as an effective method for detecting pancreatic cancer with a reasonable sensitivity but low specificity[5]. Compared to computed tomography (CT) and magnetic resonance imaging (MRI), EUS had a superior performance in small pancreatic tumors[6,7].

The use of computer aided diagnosis for cancer detection has been introduced since 1960[8]. In the past 10 years, the use of artificial intelligence (AI) has been exponentially increased in every field, including medicine[9-11]. Machine learning and deep learning are two major techniques in AI used for analyzing a large dataset and creating a predictive model[12-14]. The advance of AI in gastroenterology field has played an important role in pancreatic cancer regarding detection and survival prediction[15-17].

Given the emerging role of AI in this field, we conducted the systematic review on AI and pancreatic cancer with keywords of "artificial intelligence" and "pancreatic cancer" from PubMed and Institute of Electrical and Electronics Engineers databases. We aim to elaborate the advancement of AI application in pancreatic cancer detection by imaging studies focusing on endoscopic ultrasound and novel serum and cyst fluid marker analysis.

AI CONCEPT AND TERMINOLOGY

AI is the use of mathematical models and computer algorithms to mimic human intelligence. It has been increasingly used to predict risk and diagnose pancreatic cancer with imaging and personal health features[15,18-20]. Most medical AI is considered narrow AI, which focuses on single or limited tasks[19]. There are different AI techniques for creating predictive models, including machine learning and deep learning.

Machine learning is a subfield of AI that uses mathematical techniques to create a predictive model by recognizing patterns in the dataset without being explicitly programmed[18,19]. There are many machine learning algorithms available such as regression, decision trees, k-nearest neighbors, and neural network[21]. Machine learning shows great promise in medical research as it can detect complex patterns in a large dataset that human doctors would likely miss[22,23].

Deep learning, a subfield of machine learning, is basically a neural network with multiple hidden layers (usually a large number) to automatically detect higher-level features of input data. A neural network is also known as artificial neural network. As shown in Figure 1, neural network is a system of interconnected neurons with three type of layers: (1) Input layer; (2) Hidden layer; and (3) Output layer. Each layer

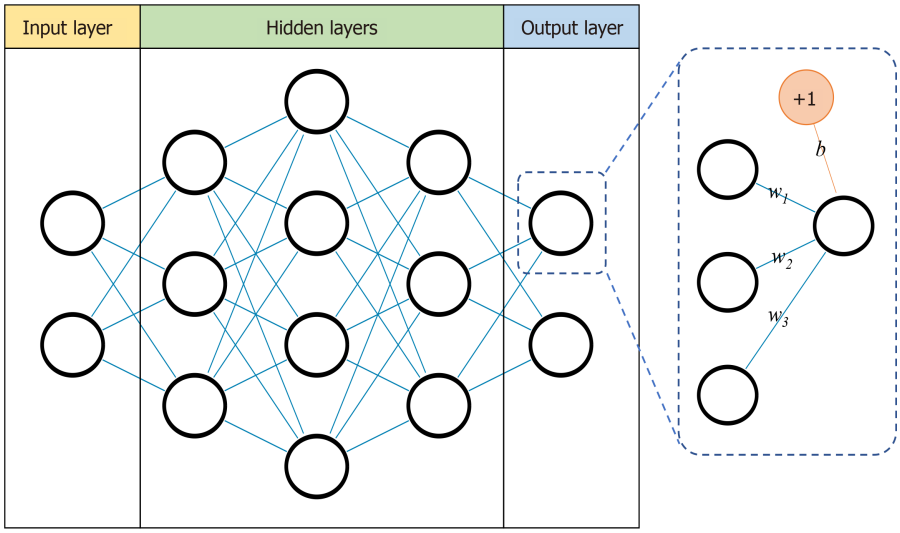

Figure 1 Neural network with input layer, hidden layers, and output layer. Each circle represents a neuron within the network. Within each neuron, weights and bias are applied to the input values to produce an output value. w: Weight; b: Bias.

amplifies certain aspects of the input that are important for discrimination by applying a weight to each input[24,25]. Besides requiring a large and well-annotated dataset, the major drawback of deep learning is a long training time, which could take hours or days. One method that can significantly improve the training time of deep learning is the use specialized hardware such as graphic processing unit or tensor processing unit[26].

A convolutional neural network (CNN) is a class of deep learning that apply a filter to capture the characteristic of the data. In image analysis, CNN use different filters to capture various aspects of the image[27,28]. The most significant advantage of CNN in the medical field is its ability to detect image features automatically and objectively, for instance, the detection of pancreatic cancer based on EUS images[19,29].

Three major types of machine learning problems are supervised learning, unsupervised learning, and reinforcement learning. Most machine learning problems in medicine are supervised learning, in which the response variable must be already known or labeled. To create a predictive model for solving supervised learning problem, the first step is the collection and annotation (label) of input data. The data is then divided into training and testing sets. The training data is used for training machine learning models, including applying different learning algorithms or architectures, optimizing model parameters, and selecting a final predictive model. Once the final predictive model is selected, the model will be evaluated using the testing data to assess the model performance on the data that has not been used before. These are common steps used to create a predictive model for both machine learning and deep learning[21,30]. In fact, the choice of using machine learning or deep learning usually depends on the type of inputs. Typically, CNN-based deep learning is the preferred choice for image classification. Additionally, deep learning model had a higher diagnostic ability than the subjective measurement of tumor feature values (tumor width, shape, and color) by doctors because of its objectivity[31-33].

APPLICATION OF AI IN IMAGING STUDIES FOR PANCREATIC CANCER DETECTION

Modern imaging modalities, including CT scan, MRI, ultrasound, and endoscopy, contain far more visual information than humans can distinguish with the naked eye[18]. Since 2010, significant progress has been achieved in applying AI to the gastroenterology imaging[15]. The pancreas is one of the most challenging organs in CT segmentation. Each patient produces more than 300 images that a radiologist must discern, creating intense reading efforts that sometimes succumb to unavoidable misdiagnosis[34]. Many machine learning and deep learning models have been created to aid physicians in making diagnosis based on medical imaging, including the detection of pancreatic neoplasms. There are two major types of AI systems used in the

detection of cancer: Computer-assisted detection (CADe) and computer-assisted diagnosis (CADx) and they serve different purposes. CADe systems are used for locating lesions in medical images. CADx systems characterize lesions and can distinguish between benign and malignant[35].

COMPUTED TOMOGRAPHY

CADx AI systems have been created with the analysis of segmented CT images of the pancreas. These systems work by creating an experimental group of image data and a control group of image data which are imported into a program. The data is fed through two matrices and a filter, statistics, and other data are applied. Then the pancreatic cancer and the normal control images are distinguished by data processing and statistical analysis[36].

An extension of CADx systems is the use of radiomics in CT images. Radiomics is an AI process that not only answers simple clinical questions (*e.g.*, benign or malignant), but can also be used to extract quantitative imaging features from radiology images to produce more detailed information about the areas of interest (*e.g.*, determining risk of malignancy in pre-malignant lesions)[18]. A study by Wei *et al*[37] used a machine learning based model to determine serous cystic neoplasms from non-serous cystic neoplasms based on 409 quantitative radiomic features from preoperative CT images. The model outperformed clinicians with an area under the receiver operating characteristic curve (AUC) of 0.84.

Segmentation of the pancreas in CT imaging is a difficult but essential task for a successful diagnosis of pancreatic cancer. The main challenges lie in its close proximity to other organs, shape variance and low contrast blurring[27,38-40]. Notably, the ideal type of CT imaging in patients with suspected pancreatic cancer is a contrast-enhanced, multidetector CT, which has sensitivity of 70% to 100% whereas traditional CT has an accuracy of 83.3%, sensitivity of 81.4%, and specificity of 43% for pancreatic adenocarcinoma detection[41].

Liu *et al*[42] used a faster region-based CNN (faster R-CNN) model to form a CADx to solve the challenging pancreas segmentation problem in CT images. Their faster R-CNN model assisted had an AUC of 0.96 and mean average precision of 0.7664, indicating a high discriminating ability and precision. Consequently, the time required to establish a diagnosis using their model was 3 s compared to 8 min by an imaging specialist. Another study used multi-scale segmentation-for-classification to detect pancreatic ductal adenocarcinoma (PDAC). This method functioned by performing tumor segmentation at the same time as tumor classification. This information was helpful for radiologists when determining tumor location. Their method reported a sensitivity of 94.1% and a specificity of 98.5%, implying that their model for tumor segmentation was strong in screening for PDAC[43]. Interestingly, Chu *et al*[44] used random forest algorithm to classify PDAC based on CT images. The overall accuracy, AUC, sensitivity, and specificity were 99.2%, 0.999, 100%, and 98.5%, respectively.

To classify pancreatic cancer, a custom method using a combination of support vector machine and random forest technology was applied to PET/CT images[45]. Their proposed model achieved accuracy of 96.47%, sensitivity of 95.23%, and specificity of 97.51%. They demonstrated that their model outperformed other models based on an external dataset.

MAGNETIC RESONANCE IMAGING

It is challenging to obtain multi-modal MRI images and then effectively fuse the information from these images due to the heterogeneity of the pancreas and the ill-defined tumor boundary[46-48]. PDAC diagnostic value by traditional MRI has an accuracy of 89.1%, sensitivity of 89.5.%, and specificity of 63.4%[41].

Barriers to machine learning algorithm development for MRI include limited availability of MRI data, reduced image quality, and unstandardized nature of MRI[49]. In addition, overfitting can be an issue due to small datasets in MRI and CNN studies[48]. However, CADx systems for the diagnosis of pancreatic cancer have been developed with MRI images. One study used a CNN was used for feature representation for IPMN diagnosis with MRI[47]. This approach led to a 30% improvement in specificity of IPMN diagnosis compared to single modality-based approaches (T1 or T2 imaging). The multi-modal fusion approach for IPMN detection had an accuracy of 82.80%, sensitivity of 83.55%, and specificity of 81.67%. It is only

needed to identify a single slice where pancreatic tissues could be obviously observed. Zhang *et al*[34] used support vector machine in combination with MRI detection to classify pediatric pancreatic cancer; their proposed model achieved a higher accuracy when compared to the normal detection algorithm. Corral *et al*[50] created a CNN which diagnosed intraductal papillary mucinous neoplasm (IPMN) on MRI images in 1.82 s with a sensitivity of 75% and specificity of 78%. Another study by Gao *et al*[51] created a deep learning model that graded pancreatic neuroendocrine tumors using MRI images, reaching an accuracy of 81.1% and AUC of 0.89. In a 2020 retrospective study, the research group assessed baseline CT images from 207 patients with proven PDAC and developed a machine learning model that used radiomics to predict molecular subtypes. The classification algorithm achieved a sensitivity, specificity and ROC-AUC of 0.84, 0.92, and 0.93, respectively[49]. Table 1 demonstrates the studies on CT and MRI of pancreatic cancer.

ULTRASONOGRAPHY

AI is used in transabdominal ultrasonography and endoscopic ultrasonography. In transabdominal ultrasonography, AI is used primarily for detecting liver fibrosis stage and chronic liver disease by using the histogram analysis and RGB-to-stiffness inverse mapping technique[19]. The role of transabdominal ultrasonography for pancreatic cancer detection is very minimal because the pancreas visualization is obscured by bowel gas. Due to this, there are no available studies in the evaluation of pancreatic cancer with transabdominal ultrasound.

ENDOSCOPIC ULTRASOUND

Among MRI, CT, and EUS, only EUS enables observation of the pancreas with high spatial resolution. EUS has higher tumor detection rates than contrast enhanced CT by allowing detection of the echo structure in lesions as small as 1 cm[52]. The sensitivity of EUS is superior to CT scan, 94% and 74%, respectively[5]. However, the accuracy of EUS is currently highly operator dependent.

There are previous studies on the application of AI in EUS for pancreatic cancer detection (Table 2). The overall accuracy of AI based approach were 80%-97% with sensitivity of 83%-100%. The findings are comparable to a sensitivity of 94% by endoscopist driven EUS according to the meta-analysis[5]. The first study of AI based EUS analyzed a single EUS image per patient obtained from the total of 21 patients[53]. Machine and human demonstrated a similar diagnostic performance. However, this study was done before the introduction of modern deep learning framework, which has demonstrated much better performance in general than earlier neural network architecture. Based on the observation that there is an age-related change of pancreas shape, Ozkan *et al*[54] used three different neural network models to classify pancreatic cancer in three age groups: Below 40, 40 to 60, and above 60. As a result, a higher performance was achieved by using a different model for each age group.

There were different techniques being used for image analyses and creating classification models in pancreatic cancer studies, including deep pocket inspection[55], support vector machine[56], region of interest, principal component analysis[57], neural network, and deep learning. We noticed that these requires were evolved with the major progress of AI development; machine learning techniques were used at the beginning and gradually evolved to CNN-based models (deep learning).

Interfering factors associated with misdetection of pancreatic cancer include chronic pancreatitis with more false negative results[4]. The compromised ability of pancreatic cancer detection in patients with chronic pancreatitis decreased to 54%-75%. Tonozuka *et al*[33] found that non-PDAC is the significant factor of misdetection which means the system tends to work towards preventing the overlooking of tumors than overdiagnosis of tumors. On the other hand, tumor size is not associated with misdetection. Thus, AI guided diagnosis can help with early detection of small tumor and prevent the progression of pancreatic cancer. Another consideration is that the control group with a few cases of mass forming pancreatitis makes the results not generalizable to the group of focal pancreatitis (pseudotumorous pancreatitis) as more included in Norton *et al*[53]. The main limitations of prior studies on AI-guided EUS diagnosis are small sample size. Data augmentation has been used to increase the number of images in later study[33]. Slow processing time and low-quality image are other constraints. They hinder the development of this approach to be real time

Table 1 Summary of studies assessing computed tomography and magnetic resonance using artificial intelligence-based approach for pancreatic cancer

Ref.	Overall dataset	Testing data	Model	Model performance on testing data					
				Accuracy (%)	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CT									
Zhu *et al*[43], 2019 (United States)	439 cases	23 cases	CNN	NA	NA	94.1	98.5	NA	NA
Liu *et al*[42], 2019 (China)	338 patients	100 patients	CNN	NA	0.9632	NA	NA	NA	NA
Chu *et al*[44], 2019 (China)	380 patients	125 patients	ML	99.2%	0.999	100	98.5	NA	NA
Li *et al*[75], 2018 (China)	206 patients	No separate testing data (10-fold CV)	CNN	72.8%[1]	NA	NA	NA	NA	NA
Wei *et al*[37], 2018 (China)	260 patients	60 patients	SVM	NA	0.837	66.7	81.8	NA	NA
MR									
Kaissis *et al*[49], 2020 (Germany)	207 patients	26 patients	ML	NA	0.93	84	92	NA	NA
Corral *et al*[50], 2019 (United States)	139 cases	No separate testing data (10-fold CV)	DL	NA	0.78[1]	92[1]	52%[1]	NA	NA
Gao *et al*[51], 2019 (China)	96 patients	No separate testing data (5-fold CV	DL	85.13[1]	0.9117[1]	NA	NA	NA	NA

[1]The performance was based on n-fold cross-validation on training data.

AUC: Area under the curve; CNN: Convolutional neural network; CT: Computed tomography; CV: Cross-validation; DL: Deep learning; IPMN: Intraductal papillary mucinous neoplasm; MR: Magnetic resonance; NA: Not available; NN: Neural network; NPV: Negative predictive value; PCA: Principal component analysis; PPV: Positive predictive value; SVM: Support vector machine.

analysis. Interestingly, real time EUS video using CNN for pancreas segmentation and station recognition has been studied[58]. The real-time system works as a monitoring safety net and remind endoscopist to make up the unobserved part. It can also increase trainee performance in learning how to detect pancreatic cancer using EUS, which can lead to the reduction of training time and cost.

AI also plays important role in two new EUS techniques, including contrast enhancing EUS (CE-EUS) and EUS elastography. CE-EUS is a technique that uses gas-containing contrast agents intravenously injected for better visualization and differential diagnosis of focal pancreatic lesions. A study found machine learning assisted CE- EUS provided higher sensitivity of 94% compared to 87.5% of qualitative CE-EUS without machine learning aid[59]. EUS elastography is a technique that measure the tissue stiffness, which help differentiate a mass from normal or inflammatory area. The real-time performance of neural network provided comparable efficacy to standard EUS elastography. The predictive performance of EUS elastography is similar to the b-mode EUS with AUCs of 0.94-0.965[60,61].

Regarding a real-time application, Marya *et al*[62] demonstrated the high accuracy of PDAC detection from other pancreatic diseases with AUC of 0.98. The author claimed that the speed of image processing is eligible for real-time system but it was not performed. Future application is warranted which can guide biopsy in patients with diffuse inflammation as chronic pancreatitis to avoid unnecessary biopsies.

AI has not only been studies in PDAC, but also in pancreatic cystic lesions. One study on the differentiation of malignant *vs* benign IPMN by EUS revealed the superior accuracy in identifying malignancy; 94% by AI *vs* 56% by the physician diagnosis performing EUS. However, the AI's prediction on EUS images was not performed during the EUS procedure in a real time. The real-time integration will help aid clinicians to make a clinical judgement[63]. EUS guided needle confocal laser endomicroscopy is a novel technique for pancreatic cystic lesions. A study was conducted in 15027 videos from 35 subjects with IPMN. The CNN algorithm for high grade dysplasia or adenocarcinoma diagnosis had higher sensitivity (83.3% *vs* 55.6%)

Table 2 Summary of endoscopic ultrasound using artificial intelligence-based approach studies pancreatic cancer and malignant pancreatic cyst detection

Ref.	Overall dataset	Testing data	Model	Model performance on testing data					
				Accuracy (%)	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Marya *et al*[62], 2020 (United States)	583 patients (1174461 images)	123 patients	CNN	NA	0.976	95	91	87	97
Tonozuka *et al*[33], 2020 (Japan)	139 patients (920 images)	47 patients (470 images)	CNN	NA	0.94	92.4	84.1	86.8	90.7
Ozkan *et al*[54], 2016 (Turkey)	332 images	72 images	NN	87.5	NA	83.3	93.33	NA	NA
Saftoiu *et al*[59], 2015 (Multicenter in Europe)	167 cases	15% of cases	NN	NA	NA	94.64	94.44	97.24	89.47
Zhu *et al*[56], 2013 (China)	388 images	50% of all data (200 trials)	SVM	93.86	NA	92.52	93.03	91.75	94.39
Zhang *et al*[55], 2010 (China)	216 patients	50% of all data (50 trials)	SVM	97.98	NA	94.32	99.45	98.65	97.77
Das *et al*[57], 2008 (United States)	319 images	50% of all data	NN	NA	0.93	93	92	87	96
Norton *et al*[53], 2001 (United States)	21 patients	4 patients	ML	80	NA	100	50	NA	NA
Elastography									
Saftoiu *et al*[61], 2012 (Multicenter in Europe)	258 cases	No separate testing data (10-fold CV)	NN	84.27[2]	0.94[2]	87.59[2]	82.94[2]	96.25[2]	57.22[2]
Saftoiu *et al*[60], 2008 (Denmark and Romania)	68 cases	No separate testing data (10-fold CV)	NN	NA	0.957[2]	NA	NA	NA	NA
IPMN									
Machicado *et al*[64], 2021 (United States)[1]	35 cases of EUS-nCLE (15027 frames)	No separate testing data (5-fold CV)	(1) CNN (segmentation); and (2) CNN (holistic)	(1) 82.9[2]; and (2) 85.7[2]	NA	(1) 83.3[2]; and (2) 83.3[2]	(1) 82.4[2]; and (2) 88.2[2]	(1) 83.3[2]; and (2) 88.2[2]	(1) 82.4[2]; and (2) 83.3[2]
Kuwahara *et al*[63], 2019 (Japan)	50 cases	No separate testing data (10-fold CV)	CNN	94[2]	NA	95.7[2]	92.6[2]	91.7[2]	96.2[2]

[1]Presented two designs of CNN algorithms: segmentation based model and holistic based model.
[2]The performance was based on n-fold cross-validation on training data.
AUC: Area under the receiver operating characteristic curve; CE-EUS: Contrast enhanced endoscopic ultrasound; CNN: Convolutional neural network; CV: Cross-validation; EUS-nCLE: Endoscopic ultrasound-guided needle based confocal laser endomicroscopy; IPMN: Intraductal papillary mucinous neoplasm; NA: Not available; NN: Neural network; NPV: Negative predictive value; PCA: Principal component analysis; PPV: Positive predictive value; SVM: Support vector machine.

and accuracy (82.9%-85.7% *vs* 68.6%-74.3%) than the Fukuoka and American Gastroenterology Association diagnostic criteria[64].

APPLICATION OF AI IN BIOMARKER ANALYSIS FOR PANCREATIC CANCER DETECTION

Conventional markers

The most used biomarker in monitoring pancreatic cancer is currently carbohydrate antigen (CA) 19-9[65]. It is usually used in monitoring progression and treatment of

pancreatic cancer due to the low specificity and sensitivity. The combined sensitivity and specificity were 78.2% and 82.8% respectively. The relatively low specificity and sensitivity, and low positive predictive value in asymptomatic patients, would indicate that CA19-9, would be a poor biomarker if applied as a screening test, causing unnecessary and wasteful workups for patients[66]. Another biomarker that has been explored is carcinoembryonic antigen (CEA), which exhibits an even poorer sensitivity and specificity for classifying pancreatic cancer than the CA19-9[65].

Some methods using more targeted screening have been suggested such as using multiple biomarkers together or screening only high-risk populations, but those have yet to be universally defined. A screening model was suggested to separate high risk populations into those with inherited pancreatic cancer and those who are at high risk for non-inherited. Even between those two categories non-inherited high-risk could only narrowed to individuals with new onset diabetes[66]. Using this as an example would still provide for a very large screening population with low sensitivity and specificity if only using CA19-9[67]. Other biomarkers have been identified that are present in early pancreatic adenocarcinoma but none of them alone have produced high enough quality data to prove even non-inferiority *vs* no screening, let alone CA19-9[66,68].

A study utilized neural network for multiple tumor marker analysis (CA19-9, CEA, and CA125) for pancreatic cancer diagnosis in 913 serum specimens. AUCs of neural network derived model was superior to logistic regression model with AUCs of 0.905 and 0.812, respectively. The diagnostic performance of single marker is lower than the AI model with AUCs of CA19-9, CA125, and CEA of 0.845, 0.795, and 0.800, respectively[69].

Kurita *et al*[70] used AI to differentiate between malignant and cystic lesions of the pancreas using a dataset consisting of biomarkers, sex, characteristics of cystic lesion, and cytology. It is worth noting that the authors clearly stated that the deep learning was used, but it is technically a neural network with two hidden layers; each layer contains nine nodes. In terms of discriminating performance of classifiers, their AI approach with an AUC of 0.966 well outperformed CEA (AUC = 0.719) and cytology (AUC = 0.739). Although this study is limited by its low sample size and retrospective nature, it showed that a predictive model based on a combination of biomarkers and other factors could achieve a higher performance in classifying the malignancy status of pancreatic cyst fluid in comparison to the use of single biomarker.

Novel biomarkers

In the past, conventional markers like CEA, CA72-4, CA125, and CA19-9, have been used to identify, differentiate, and monitor pancreatic cyst fluid. CA19-9 and CA125 can be used to assess for if a cyst has mucinous characteristics, while CEA can help to differentiate a malignant cyst from benign cyst[65,70]. Advances in genomic sequencing and identification have introduced the ability to isolate microRNA (miRNA) sequences in pancreatic cyst fluid and serum as potential biomarkers for pancreatic adenocarcinoma.

It was first suggested in 2010, that miRNA could be used as a marker for pancreatic adenocarcinoma. miRNA-21 and miRNA-155 in pancreatic juice were present in statistically significantly higher levels in pancreatic adenocarcinoma as compared to benign pancreatic cysts[71]. miRNA are exosome sequences that, in the setting of pancreatic adenocarcinoma, encode for proteins that are oncogenic or have tumor suppressor function. Several specific miRNAs have been identified to have a higher expression in pancreatic ductal adenocarcinoma, including miRNA-21 and miRNA-155[68]. These miRNAs are detected in the pancreatic juice. miRNAs are mostly expressed in pancreatic cyst fluid, but Yoshizawa *et al*[72] have gone on to examine miRNA in the urine. Looking the ratio of miR-3940-5p/miR-8069 in the urine of patients with pancreatic ductal adenocarcinoma, they found that an elevated ratio with an elevated CA19-9 better predicts pancreatic ductal adenocarcinoma than CA19-9 alone. These studies all examine the viability of miRNA in various types of fluid to detect disease states of the pancreas, none though utilize AI to determine which miRNA may produce the highest yield results. A limitation is that they represent small sample sizes with limited application at a population level.

Several studies have identified several miRNAs that potentially represent significant value in determining malignancy of pancreatic cystic lesion or identifying pancreatic adenocarcinoma at an early stage by AI, but each study has decided which miRNAs to utilize based on identifying and isolating very few sequences. Alizadeh *et al*[73], combined several AI and data mining techniques to best determine the miRNA sequences that have the greatest diagnostic and prognostic capabilities. Particle Swarm Optimization (PSO) and neural network, two forms of AI deep learning, identified a

set of five miRNAs: miR-663, miR-1469, miR-92a-2-5p, miR-125b-1-3p, and miR-532-5p. These were identified from 671 serum samples of patients with pancreatic ductal adenocarcinoma and healthy controls. This model had the greatest AUC score in differentiating pancreatic adenocarcinoma from controls with a sensitivity of 0.93, specificity of 0.92, and accuracy of 0.93.

Cao *et al*[74] employed machine learning to identify two panels of plasma miRNA to distinguish between chronic pancreatitis and pancreatic neoplasm from 361 plasma samples in China. Panel 1 consisted of miR-486-5p, miR-126-3p, and miR-106b-3p, and had an AUC of 0.891. Panel 2 consisted of miR-486-5p, miR-126-3p, miR-106b-3p, miR-938, miR26b-3p, and miR-1285, and had an AUC of 0.889. Both panels had a higher AUC than CA 19-9, which was 0.775.

The most robust path to create a new screening test for pancreatic adenocarcinoma must contain a combination of biomarkers and patient data to maximize both the sensitivity and sensitivity of the test[68,70,71,74]. AI creates the potential to assess patient characteristics, miRNA, and classical biomarkers, which allows for a comprehensive screening analysis of a patient. With the use of neural network and PSO, AI thinks, acts, and analyzes data at much faster speed and in more depth pattern recognition that forms the perfect environment for the development of high yield screening tests that have previously evaded us in diagnosing and screening for pancreatic cancer. Pancreatic juice for multiple exosomes of miRNA that are known to be associated with increased risk for pancreatic cancer, like oncogenes and tumor suppressor mutations, provides the opportunity to examine multiple pancreatic adenocarcinoma biomarkers with one test.

FUTURE PROSPECT

Pancreatic cancer is notorious for late detection. The studies on this area have been conducted mainly to identify the best approach for early detection by imaging studies and biomarkers. The advancement of EUS and the application of AI technology showed a promising performance. The modes of EUS: B-mode and elastography do not provide different accuracy and predictive value for pancreatic cancer. However, no data is available for EUS with contrast enhancement. B-mode which is generally used among centers can be the first step of AI implication. Ultimately, the data of imaging studies, biomarkers, and clinical parameters will be combined to build the sophisticated algorithm and implemented in the electronic medical records where clinicians use it as the predictive tool. There are a few limitations of AI application for EUS. First, the collection of EUS images as the big data is difficult. The collaboration of gastroenterologists, radiologists, and hospital administration will help facilitate the retrieval of images into the system. Multicenter participation is required to create the large dataset of EUS images of which it will optimize the efficiency of AI. The platform of dataset in one institution can be the good example that other centers can adopt and join the group. Second, the root of clinical decision based on AI results is possibly affected by the black box issue (inability to identify the ground of decision). Although there are ways that enable AI to be more interpretable, it is still an active area of research in computer science. Third, the diagnosis is most often made by examination of static images after EUS procedure. Further research on real-time implication of pancreatic malignant lesion diagnosis by AI method is warranted to aid clinician at the examination time to avoid unnecessary biopsy. Regarding biomarkers, although still a mainstay of current practice, the use of singular biomarkers like CA19-9, CEA, and CA-125, may soon become a thing of the past for pancreatic cancer detection. Recent studies showed that moving toward AI aided multiple fluid and serum analysis for biomarkers, like miRNA, potentially provide more sensitive and specific detection. AI not only provides a pathway for the computational, multilayered analysis of multiple patient variables and biomarkers, but also can provide indications for which of those EUS and biomarkers will be highest yield. Combining the knowledge in the field of and the capability of AI introduces a new world of exploration into both screening and diagnosis of pancreatic cancer. AI capabilities allow research to be more finely tuned and the implementation of the most effective method for research into developing screening and diagnostics for pancreatic adenocarcinoma and malignant pancreatic cysts.

CONCLUSION

AI applications for pancreatic cancer has are emerging. New studies come out and showed the promising results of AI in radiological imaging and biomarkers for pancreatic cancer detection. There are still some limitations which need to be addressed in the future studies before incorporating this technology in the clinical practice. The accuracy of AI aided EUS for pancreatic cancer diagnosis is high. However, it has been derived from the small training dataset. The generalizability needs to be considered before using it. Larger studies with population of various pancreatic diseases and third-party validation will demonstrate a greater confidence for adopting AI. For novel biomarkers, our review demonstrated that AI guided analysis of combination of candidate miRNAs have high predictive performance compared to standard tumor markers. The availability of miRNA testing is not widespread in every medical facility. To adopt this implication, further studies on the diagnostic performance are warranted to strongly support the evidence of utility.

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ISSN 2644-3236 (online)

Artificial Intelligence in *Gastroenterology*

Artif Intell Gastroenterol 2021 June 28; 2(3): 69-93

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Artificial Intelligence in Gastroenterology

Contents **Bimonthly Volume 2 Number 3 June 28, 2021**

MINIREVIEWS

Artificial Intelligence in Gastroenterology

Bimonthly Volume 2 Number 3 June 28, 2021

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

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

INDEXING/ABSTRACTING

There is currently no indexing.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Jia-Hui Li*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jin-Lei Wang*.

NAME OF JOURNAL
Artificial Intelligence in Gastroenterology

ISSN
ISSN 2644-3236 (online)

LAUNCH DATE
July 28, 2020

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Rajvinder Singh, Ferruccio Bonino

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2644-3236/editorialboard.htm

PUBLICATION DATE
June 28, 2021

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Artificial Intelligence in Gastroenterology

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Artif Intell Gastroenterol 2021 June 28; 2(3): 69-76

DOI: 10.35712/aig.v2.i3.69

ISSN 2644-3236 (online)

MINIREVIEWS

Artificial intelligence in gastrointestinal diseases

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Author contributions: Tanabe S designed the outline and coordinated the writing of the paper, performed the majority of the writing and editing, and prepared the figure and table; Perkins EJ performed the editing; Ono R and Sasaki H provided input into the writing the paper and performed the editing.

Supported by Japan Agency for Medical Research and Development (AMED), No. JP20ak0101093.

Conflict-of-interest statement: There is no conflict of interest associated with any of the senior author or other coauthors contributed their efforts in this manuscript.

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Abstract

Artificial intelligence (AI) applications are growing in medicine. It is important to understand the current state of the AI applications prior to utilizing in disease research and treatment. In this review, AI application in the diagnosis and treatment of gastrointestinal diseases are studied and summarized. In most cases, AI studies had large amounts of data, including images, to learn to distinguish disease characteristics according to a human's perspectives. The detailed pros and cons of utilizing AI approaches should be investigated in advance to ensure the safe application of AI in medicine. Evidence suggests that the collaborative usage of AI in both diagnosis and treatment of diseases will increase the precision and effectiveness of medicine. Recent progress in genome technology such as genome editing provides a specific example where AI has revealed the diagnostic and therapeutic possibilities of RNA detection and targeting.

Key Words: Artificial intelligence; Gastrointestinal disease; RNA; Therapeutic application; Inflammatory diseases

Core Tip: The application of artificial intelligence (AI) in the diagnosis and treatment of disease is a promising approach in medicine. The application of AI approaches in gastrointestinal diseases is summarized and reviewed. AI holds great promise in

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Japan

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): E, E

Received: January 27, 2021
Peer-review started: January 27, 2021
First decision: March 29, 2021
Revised: April 9, 2021
Accepted: June 4, 2021
Article in press: June 4, 2021
Published online: June 28, 2021

P-Reviewer: Eccher A, Hanada E, Liu Y
S-Editor: Gao CC
L-Editor: Filipodia
P-Editor: Li JH

medicine, but to safely and efficiently apply AI in medicine, the advantages and limitations should first be carefully considered.

Citation: Tanabe S, Perkins EJ, Ono R, Sasaki H. Artificial intelligence in gastrointestinal diseases. *Artif Intell Gastroenterol* 2021; 2(3): 69-76
URL: https://www.wjgnet.com/2644-3236/full/v2/i3/69.htm
DOI: https://dx.doi.org/10.35712/aig.v2.i3.69

INTRODUCTION

Recent studies have developed RNA editing using the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) system, which has made genome editing more accessible and has resulted in the development of many applications[1-3]. These new technologies have many advantages and disadvantages in their utilization, which are already being applied in medicinal situations. RNA editing has been recognized as a potential prognostic biomarker for cancer and prediction models have been developed with machine learning[4]. The utilization of artificial intelligence (AI) is rapidly expanding and is increasingly useful in understanding gastrointestinal (GI) diseases[5-7]. To better understand the use of AI-oriented diagnosis and treatment of diseases, it is important to determine how to raise the potential of AI and manage the human-AI interaction in diagnosis and therapeutics in diseases. AI technology has been combined with a massive amount of data to understand human activities[8]. Increasingly image data such as magnetic resonance imaging, X-ray, computed tomography scanning or endoscope in clinic will be utilized for the diagnosis of the diseases[9-12]. Currently, machine learning algorithms improve performance of gastrointestinal endoscopy by diagnosing the gastrointestinal diseases[13]. The application of AI has increased identification of patients with intestinal malignancies or premalignant lesions, and inflammatory or other nonmalignant diseases or lesions[14]. Computer-aided diagnosis (CAD) for colonoscopy would improve the quality of image-oriented diagnosis of colorectal cancer[15]. Classification of systems in AI-oriented disease management is summarized in Table 1.

APPLICATION OF AI IN DIAGNOSIS OF GASTROINTESTINAL DISEASES

There are several areas in which AI can advance the diagnosis of GI diseases. Diseases of interest for AI-oriented disease management are summarized in Figure 1.

AI application in inflammatory diseases

The diagnosis of GI diseases such as inflammatory bowel disease (IBD) including Crohn's disease, a chronic inflammatory condition in the GI tract, and ulcerative colitis, which occurs in the colon, includes several fundamental laboratory tests including measurement of hemoglobin, hematocrit, blood urea nitrogen, creatinine, liver enzymes and C-reactive protein[16].

AI application in tumor

Recent progress in AI has resulted in predictive tools for the diagnosis of GI cancer classification, where network-based machine learning in colorectal and bladder organoid models predicts drug responders and non-responders using network analysis of pharmacogenomics data and the patient's transcriptome[17]. Bioinformatic analyses of gene expression data have revealed common gene signatures in hypopharyngeal and esophageal squamous cell carcinoma, which may serve as diagnostic and therapeutic targets[18]. Balloon catheter tracking and visualization in GI tracking could be made more precise with AI guidance using image recognition [19]. Deep learning algorithms for image recognition can lead to more precise endoscopic diagnosis with improved sensitivity and specificity in upper GI tract diseases such as gastric cancer and Barrett's esophagus[20]. Convolutional neural networks (CNNs) have generated liver imaging features and shown promise in

Table 1 Classification of systems in artificial intelligence-oriented disease management

Disease of interest	Purpose of AI	User	Limitation of use	Ref.
Acute appendicitis	Diagnosis	Specialist	The study is designed in retrospective nature	Reismann *et al* [5]
Colon cancer	Diagnosis	Specialist	The design of the analysis is post hoc and the number of patients is limited	Reichling *et al* [6]
Ulcerative colitis	Diagnosis	Specialist	Long-term clinical prognosis is not clear	Maeda *et al*[7]
Spinal stenosis in degenerative lumbar kyphoscoliosis	Surgery navigation	Specialist	The number of patients is limited. Long-term follow-up data is needed	Ho *et al*[9]
Coronavirus infectious disease (COVID-19)	Screening, diagnosis	Specialist	Privacy of the patient data should be considered	Bhattacharya *et al*[10]
Diseases in general	Diagnosis	Specialist	The burden on specialists may increase	Karako *et al*[11]
Diseases in general	Screening	Specialist	Careful and thorough investigation is necessary	Shiyam Sundar *et al*[12]
Gastrointestinal disease	Diagnosis	Specialist	There is a difference in the definition of anomaly detection between the area of computer science and medical domain	de Lange *et al* [13]
Gastrointestinal disease, hepatic diseases	Diagnosis	Specialist	High-quality datasets are needed	Le Berre *et al* [14]
Colorectal cancer	Diagnosis	Specialist	The quality of previous study designs is limited, and practical usefulness of computer-associated diagnosis systems is unknown	Kudo *et al*[15]
Colorectal cancer, bladder cancer	Prediction of anti-cancer drug efficacy	Specialist	Further molecular layer profiling in organoids may be needed	Kong *et al*[17]
Hypopharyngeal squamous cell carcinoma, esophageal squamous cell carcinoma	Identification of diagnostic and therapeutic targets	Specialist	Further studies are needed to validate the findings of the study	Zhou *et al*[18]
Arterial stenosis, coronary arterial diseases, stricture of the gastrointestinal tract	Guiding of balloon catheter	Specialist	The systemic performance needs to be improved	Kim *et al*[19]
Gastrointestinal disease	Diagnosis	Specialist	Further studies are needed to improve the performance	Marlicz *et al*[20]
Colorectal cancer	Prediction of liver metastasis	Specialist	The investigation of another dataset is needed	Lee *et al*[21]
Colon cancer	Diagnosis	Specialist	The change of protein expression level needs to be investigated	Xue *et al*[22]
Gastrointestinal disease	Diagnosis	Specialist	Investigation and development of newly improved methods are encouraged	Borgli *et al*[23]
Gastrointestinal disease	Diagnosis	Specialist	Further development is needed	Adler and Bjarnason[24]
Upper gastrointestinal cancer	Diagnosis	Specialist	Only high-quality endoscopic images for the training and validation analyses were used	Luo *et al*[25]
Gastric cancer	Diagnosis	Specialist	The associations of the quality or the number of training images and the CNN accuracy needs to be examined	Hirasawa *et al* [26]
Gastrointestinal disease	Diagnosis	Specialist	The possibilities to improve the medical performance, to reduce the medical cost, and to improve the satisfaction of the patient and medical staff are unknown	Min *et al*[27]
Functional gastrointestinal disorder	Diagnosis	Specialist	Evaluation of the feasibility of AI on studies on the gut-brain-microbiome axis is needed	Mukhtar *et al* [28]
Colorectal cancer	Diagnosis	Specialist	The uncertainty about the true efficacy of CAD in "real-world" practice remains	Ahmad *et al*[29]
Colorectal cancer	Diagnosis	Specialist	Further accumulation of lesion images for training is needed	Yamada *et al* [30]
Small-bowel disease	Diagnosis	Specialist	Further multicenter, prospective studies and external validation are needed	Yang[31]

Colorectal cancer	Diagnosis	Specialist	Complaints of system malfunctions and reports of patient injuries could lead to lawsuits against stakeholders	Ciuti *et al*[32]
Cholangiocarcinoma, pancreatic adenocarcinoma	Diagnosis	Specialist	Case-control and single-center design, and the lack of an independent validation cohort should be considered	Urman *et al*[33]
Colorectal cancer	Screening	Specialist	The applicability to other types of cancer needs optimization	Misawa *et al*[34]
Gastrointestinal disease	Diagnosis	Specialist	Most studies were designed in retrospective manner. Ethical issues on misdiagnosis or misclassification need to be handled	Yang and Bang [35]
Gastrointestinal cancer	Prediction of microsatellite instability for immunotherapy	Specialist	Larger training cohorts are needed	Kather *et al*[36]
Colorectal cancer	Diagnosis	Specialist	The CNN architecture needs to be improved for colonoscopy	Azer[37]
Barrett esophagus cancer	Diagnosis	Specialist	The number of patients is limited. Further optimization is needed	Ebigbo *et al*[38]
Celiac disease	Diagnosis	Specialist	The preliminary results need to be followed-up with a real clinical setting	Tenório *et al*[39]
Esophageal squamous cell carcinoma	Prediction of prognosis	Specialist	Further experimental studies to verify the results are needed	Zhang *et al*[40]
Advanced rectal adenocarcinoma	Prediction of response to neoadjuvant chemoradiotherapy	Specialist	The size of the cohort is limited. The confirmation of the findings with another data set is needed	Ferrando *et al* [41]
Inflammatory bowel disease	Prediction of prognosis	Specialist	Interventional study to confirm the efficacy of the stratifying therapy is needed	Biasci *et al*[42]
Inflammatory bowel disease	Mapping	Specialist	The application of advanced natural language processing algorithms to the text-mining step may improve the current process	Sarntivijai *et al* [43]

AI: Artificial intelligence; CAD: Computer-aided diagnosis; CNN: Convolutional neural network.

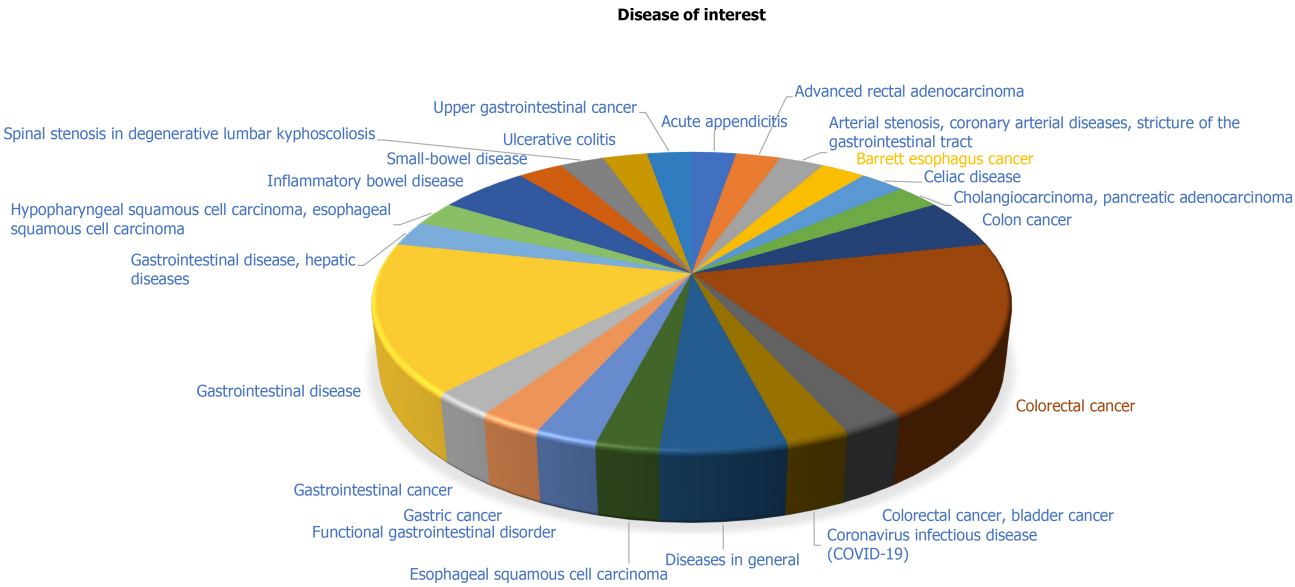

Figure 1 Disease of interest in references surveyed in artificial intelligence-oriented disease management. AI: Artificial intelligence; COVID-19: Coronavirus disease 2019.

predicting the metachronous liver metastasis in stage I-III colorectal cancer patients [21]. Deep learning of immunohistochemistry images of human colon tissues are used to improve the performance in detection of protein subcellular localization[22]. AI is poised to have a greater impact on GI endoscopy with publication of large datasets

including multi-class images and video datasets that are useful for AI deep learning [23]. It seems that the performance of capsule endoscopy for diagnosing small bowel disease is improved using AI approaches[24]. An AI deep learning algorithm that can diagnose upper GI cancers with clinical endoscopic imaging data has been developed and validated[25]. CNNs in AI deep learning using numerous endoscopic image data have been developed that can detect and diagnose gastric cancer[26].

AI application in other diseases and endoscopy

Min *et al*[27] pointed out that one drawback of AI approaches is the need for large datasets to train the system; therefore, the quality of CNN-based AI endoscopy is limited by the need for a large number of high-quality endoscopic images. Machine learning and AI are important to diagnose functional GI disorders and aid healthcare professionals and researchers[28]. Ahmad *et al*[29] suggested that the level of AI and CAD in colonoscopy has reached that of human expert performance. A real-time AI system with deep learning technology has been developed to diagnose colorectal cancer[30]. An AI-oriented automated CAD system can identify histologic inflammation associated with ulcerative colitis[7]. Reismann *et al*[5] used AI to identify biomarker signatures to diagnose and classify the pediatric acute appendicitis.

APPLICATION OF AI IN THERAPEUTICS OF GI DISEASES

The application of AI in therapeutics of GI diseases has been expanding. The roles of AI in capsule endoscopy and other recent advanced diagnostic technologies have increased in therapeutics of GI diseases[31,32]. AI analysis was implemented to build neural network models enabling the classification of patients with biliary strictures and identify potential biomarkers in human bile[33]. Machine learning on medical examination records has stimulated the development of preventative measures for colorectal cancer[34]. Retrospective and prospective clinical studies have been conducted to diagnose and predict the prognosis of GI diseases including gastroesophageal reflux disease, atrophic corpus gastritis, acute pancreatitis, acute lower GI bleeding, esophageal cancer, nonvariceal upper GI bleeding, ulcerative colitis after cytoapheresis therapy, IBD, lymph node metastasis in T1 colorectal cancer and postoperative distant metastasis in esophageal squamous cell carcinoma[35]. Kather *et al*[36] found that deep learning can be used to predict microsatellite instability from histology in GI cancer. Azer[37] developed CNN models that can detect and classify colorectal polyps, which may increase colonoscopy application in appropriate colorectal cancer therapeutics. AI-guided tissue analysis has been developed that predicts stage III colon cancer outcomes, which may improve patient care with pathologists' assistance[6]. Ebigbo *et al*[38] found that AI utilization can be used to classify the Barret esophagus cancer. An AI-based clinical decision-support system has been developed to diagnose celiac disease[39]. Bioinformatics analyses have identified important genes associated with the pathogenesis and prognosis of esophageal squamous cell carcinoma, which may contribute to the molecular-targeted therapy [40]. Long non-coding RNA signature has been identified in locally advanced rectal adenocarcinoma, which may predict the response to neoadjuvant chemoradiotherapy in the patients[41]. Machine learning has been utilized for identifying prognostic biomarkers in the whole blood of IBD patients to support the personalized therapy [42]. Ontology tools such as Experimental Factor Ontology or the Ontology of Biomedical Association may be useful for mining the disease-phenotype associations for IBD[43]. Since the responsiveness toward drug alters in cancer cell phenotypes such as epithelial-mesenchymal transition in diffuse-type gastric cancer, the AI application in the identification of cancer subtype would lead to establish therapeutic strategy[44,45]. The machine learning algorithms may be applied to the therapy of the GI diseases in terms of gut-brain axis[28,46].

FUTURE PERSPECTIVES OF AI APPLICATION IN GI DISEASES

Despite the rapid advances of the application of AI in GI diseases, there still remains some concern in terms of the precision of AI-based diagnosis and the criteria for the therapeutics. Further evidence is needed to solely rely on CAD in colonoscopy to determine an appropriate endpoint[15]. Some regulatory coordination may be needed to use the combination of an AI-assisted device and CAD software[15]. The differences

in levels of AI performance would be considered and adjusted for application in clinical situations[14]. More high-quality datasets are needed to establish deep learning algorithms[14].

CONCLUSION

The area for AI application is rapidly expanding in the diagnosis and therapeutics of GI diseases. AI utilization in image recognition is currently being used to diagnose diseases and assist with personalized therapy. Future studies on disease-phenotype association are needed to maximize the capacity and performance of AI to aide in practical situations.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the colleagues for their support.

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Artificial Intelligence in Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

Artif Intell Gastroenterol 2021 June 28; 2(3): 77-84

DOI: 10.35712/aig.v2.i3.77

ISSN 2644-3236 (online)

MINIREVIEWS

Biophysics inspired artificial intelligence for colorectal cancer characterization

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Author contributions: Hardy NP, Dalli J, Mac Aonghusa P, Neary PM and Cahill RA were all involved in the research, planning and construction of this piece.

Conflict-of-interest statement: Cahill RA receives speakers fees from Stryker Corp, Johnson and Johnson/Ethicon and Olympus, consultancy fees from Touch Surgery and DistalMotion and research funding from Intuitive Surgery and holds research funding from the Irish Government in collaboration with IBM Research in Ireland and Deciphex and from EU Horizon 2020 with Palliare. Hardy NP and Dalli J are employed as researchers in this collaboration.

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Abstract

Over the last ten years artificial intelligence (AI) methods have begun to pervade even the most common everyday tasks such as email filtering and mobile banking. While the necessary quality and safety standards may have understandably slowed the introduction of AI to healthcare when compared with other industries, we are now beginning to see AI methods becoming more available to the clinician in select settings. In this paper we discuss current AI methods as they pertain to gastrointestinal procedures including both gastroenterology and gastrointestinal surgery. The current state of the art for polyp detection in gastroenterology is explored with a particular focus on deep leaning, its strengths, as well as some of the factors that may limit its application to the field of surgery. The use of biophysics (utilizing physics to study and explain biological phenomena) in combination with more traditional machine learning is also discussed and proposed as an alternative approach that may solve some of the challenges associated with deep learning. Past and present uses of biophysics inspired AI methods, such as the use of fluorescence guided surgery to aid in the characterization of colorectal lesions, are used to illustrate the role biophysics-inspired AI can play in the exciting future of the gastrointestinal proceduralist.

Key Words: Gastroenterology; Artificial intelligence; Gastrointestinal surgery; Deep learning; Biophysics; Machine learning

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Ireland

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 28, 2021
Peer-review started: January 29, 2021
First decision: May 2, 2021
Revised: May 21, 2021
Accepted: June 18, 2021
Article in press: June 18, 2021
Published online: June 28, 2021

P-Reviewer: Ding L, Panteris V
S-Editor: Gao CC
L-Editor: A
P-Editor: Li JH

Core Tip: In this piece we provide an overview of current state of the art in gastroenterology and gastrointestinal surgery. We discuss current deep learning artificial intelligence methods for colorectal lesion detection and characterization as well as exploring biophysics inspired artificial intelligence methods and the potential role they can play in the future of gastroenterological practice.

Citation: Hardy NP, Dalli J, Mac Aonghusa P, Neary PM, Cahill RA. Biophysics inspired artificial intelligence for colorectal cancer characterization. *Artif Intell Gastroenterol* 2021; 2(3): 77-84
URL: https://www.wjgnet.com/2644-3236/full/v2/i3/77.htm
DOI: https://dx.doi.org/10.35712/aig.v2.i3.77

INTRODUCTION

One of the most fulfilling yet challenging aspects of medical practice revolves around the art of correct decision-making. Current training models within medicine address this through experiential learning and graded autonomy over time along with sub specialization in order for an individual to reach competency and, ideally, mastery within their chosen field. Despite now widespread use of decision support systems in areas such a manufacturing and business, automated decision support for the modern clinician in clinical practice remains in its infancy. The last ten years have seen all medical specialties introduce artificial intelligence (AI) methods as a topic for research and increasingly it is beginning to impact clinical practice as supportive data accrues. Success rates have however varied with areas such as radiology (chest X-ray and mammogram interpretation) and ophthalmology (retinal disease progression) emerging as early beneficiaries[1-3]. Increasingly interest is developing regarding the application of these principles to gastrointestinal disease and its interventions.

GASTROINTESTINAL INTERVENTION

The practice of gastroenterological endoscopy has also seen promising developments regarding in situ determination of colonic lesions through AI methods culminating in the recent launch of commercially approved, AI software (GI-Genius, Medtronic, MN, United States) to aid in the detection of colorectal polyps at colonoscopy[4]. Commencing in 2003, initial endeavour in this domain involved early computer-aided detection software performing post hoc analysis on static images ("The Colorectal Lesion Detector System" by Maroulis *et al*[5] and Karkanis *et al*[6]). The state-of-the art thereafter quickly progressed to post-hoc video, and subsequently real-time video, analysis. Recently published trials have shown significantly improved polyp detection rates with these technologies along with indicators of a potential ability to characterise lesions (hyperplastic *vs* adenoma) in some cases[7,8]. The aforementioned studies all employ deep learning (DL), a subset of machine learning within AI that emerged in the mid-2010s, as their modus operandi[9]. DL capitalizes upon recent advances in computing capabilities to implement learning algorithms consisting of many networked layers of interconnected processing units known as neurons, arranged as neural networks. For colonoscopy, DL architectures best suited to image recognition such as convolutional neural networks are most applicable.

The GI Genius currently represents the "state of the art" accessible to the practicing clinician today. This "intelligent endoscopy module" acts as an adjunct to the gastroenterologist during a colonoscopy to highlight regions with visual characteristics consistent with different types of mucosal abnormalities and so stops short of being an autonomous polyp detection tool and provides no characterization. Powered by closed, selective datasets which may not be representative of general practice (*e.g.*, in terms of bowel prep, withdrawal times, *etc.*) the module neither records nor reports its findings but instead presents areas of the screen for the endoscopist to interpret their significance including whether to biopsy, resect or disregard. Surface feature detection learned from these datasets has yet to prove its performance in real world practice in particular regarding accuracy (a typical colonoscopy comprises 50000 frames so even a tiny false positive frame rate could generate significant distraction), explainability

("telling you the settings used in the machine") and interpretability ("why should I believe it?"). While pertinent to Food and Drug Administration approval, these considerations are particularly import when expanding into the concept of lesion characterization and, even more so, true decision support. Like all DL, system performance depends on the assumption that all possible future polyps are represented by previously encountered polyps upon which the system learned. Nevertheless, this system is truly groundbreaking in its existence as a commercial product and opens up the possibilities for AI integration at scale, including articulation of the value proposition of digital assistance as the norm.

Gastrointestinal surgery, an allied field, is also comprised of sequential steps each requiring numerous operator-led decisions but has unique decision-support challenges and unique barriers to AI implementation (although it too is increasingly delivered *via* image-driven minimally invasive approaches, whether by standard or robotic-assisted laparoscopy). DL as an AI method, while highly efficient at tasks such as image recognition, does not as readily lend itself surgical video where the landscape is more complex with less hallmarks available to exploit during structure differentiation (for example ureter and vascular identification during dissection *vs* lesion detection on plain film X-ray). Current AI methods within surgical practice are limited to tasks such as instrument detection or segmentation of procedures into their procedural phases with little AI assistance currently available in the more intricate components of surgery such as tissue identification or classification progressively during dissection[10,11]. In general, surgical procedures are not as easily represented by individual static images like the other specialties mentioned thus far and while video provides a deeper situational understanding for the experienced operator, it makes artificially intelligent interpretation much more challenging. Combined with this increased complexity, the datasets required to train current DL systems for surgery (*i.e.*, many thousands of recorded surgical cases) do not currently exist in volumes comparable to endoscopic polyp images, retinal photographs, or mammograms.

BIOPHYSICS

Biophysics-inspired approaches to AI in surgery may present an alternative, or perhaps even better, a complimentary/synergistic approach to the current DL strategies in both gastrointestinal endoscopy and surgery. The term "biophysics" was first proposed by Karl Pearson in 1892 as an all-encompassing term to describe the application of physics principals to describe biological phenomena[12]. It would not be until the 1950s however, following significant advancements in physical measurement techniques, that the potential contributions of biophysics within the field of medicine could be realized. Initial endeavours sought to understand and describe biological phenomena such as haemoglobin dissociation and cell-cell interactions and structure [13,14]. The field then progressed to more complex tasks such as computerized simulation of blood flow and tissue perfusion using biological compartment models contingent on vascular parameters such as vascular density, perfusion rate and permeability[15]. More recent still, the combining of AI methods with biophysics principles has resulted in paradigm shifts in areas such as the study of protein folding and structure and promises to modify drug research processes[16,17]. It is now possible to study and predict protein-protein interactions by combining existing knowledge of protein structural biology and biophysics with machine learning in order to make predictions about the behaviour of previously undocumented proteins [18]. This technology has many potential uses including advancing understanding of inflammatory signaling processes, the search for cancer driving mutations and in new drug discovery. Currently, mechanisms of drug development include processes such as "target deconvolution" whereby the potential new agent, once identified, must be screened against all the known proteins in the human body. This laborious and resource intensive task aims to identify potential drug benefits and importantly to identify any potential off-target effects that may be undesirable. Harnessing the power of AI in conjunction with biophysics, researchers are now able to use computational modelling to simulate the physical interactions between molecules and potential target proteins[17]. Furthermore, comprehensive databanks of human proteins (the proteome) now exist with which to evaluate any new drugs. This permits in silico creation of a full pharmacological profile of any given drug molecule.

While biophysics inspired approaches such as those mentioned have numerous benefits, it is worth noting however that such methodology can only be employed in

cases where an in-depth mechanistic understanding of all involved elements has been achieved. Therefore, utilization is limited to fields with a strong human understanding of relevant biological and physio-chemical components and furthermore efforts may be derailed where incorrect perceptions of what is true exist.

NEARINFRARED ENDOLAPAROSCOPY

In contemporary, gastrointestinal surgical practice, the advent of nearinfrared (NIR) endolaparoscopy (combining conventional endoscopic and/or minimally invasive laparoscopic techniques with NIR imaging) provides great scope for development of such AI algorithms. This technology utilizes an extended electromagnetic illumination wavelength (up to 800 nm) to detect exogenous agents capable of fluorescence (there is no background biological fluorescence at these wavelengths)[19]. Such agents can be profiled dynamically as well as absolutely (presence/absence) to garner information regarding the biological features of the tissue, including disease. This has already proven useful clinically in visual determination of intestinal perfusion during surgery where the NIR imagery is presented alongside the white light appearances, but interpretation remains qualitative by the surgeon. Via AI methods however, the added information provided by NIR tissue assessment over standard white light viewing can be combined with our existing understanding of tissue biology to enhance the proceduralist's understanding of the field in front of them and to assist them in their task. To date indocyanine green (ICG) represents the most successful NIR agent upon which AI recommending systems have been based (and indeed it remains the only currently approved NIR fluorophore although others are in development) and it is likely that development of such decision support systems will in turn enable broader AI development across more standard surgical imagery[20]. However, for now, ICG in combination with NIR provides an excellent test-case to describe the application of biophysics-inspired AI for gastrointestinal interventions (both endoscopy and image-guided surgery).

NIR-ICG TISSUE PERFUSION

ICG is a fluorescent dye used extensively within the now established field of fluorescent guided surgery[21]. When given intravenously it remains within the vasculature with a half-life of 2.5-3 min and can be seen using a near infra-red camera [22]. It is currently used as a subjective decision-making adjunct in tasks such as anatomical delineation (biliary anatomy) and tissue physiology assessment (colorectal anastomosis formation and gastric conduit formation post oesophagectomy)[23-25]. It has also been used to assist in the identification of solid organ tumours however the non-selective nature of the dye leaves this staining method vulnerable to false negatives secondary to accumulation in other areas of pathology such as inflammation [26,27].

Intra-operative ICG perfusion angiograms to assist operator decision making during colon transection and anastomosis represents the most successful utilization of ICG in gastrointestinal surgery to date. Trials assessing subjective surgeon interpretation of these angiograms have been equivocal in their conclusions with respect to reducing complication rates and overall patient benefit however[28-30]. Numerous groups have set about quantifying these perfusion angiograms using time-fluorescence curves with the aim of reducing subjectivity of interpretation and ideally automating it entirely through computer vision and AI[31-35]. Son *et al*[36], in their landmark paper demonstrated the perfusion patterns seen during quantitative tracking of ICG colonic angiograms and subsequently analyzed these curves. They concluded that measurable parameters within these time-fluorescence curves such as the fluorescence slope, time from first fluorescence increase to half maximum value ($T_{1/2\,Max}$) and time ratio ($T_{1/2max}$ /T_{max}) could be used to detect areas of insufficient perfusion and reduce anastomotic complications[36]. Building on this work, Park *et al*[34], recently described an AI based real-time microcirculation analysis system (AIRAM) capable of generating more accurate and consistent perfusion assessment results when compared to the original parameter-based method described above. Using a corpus of 50 training videos the authors developed an unsupervised learning algorithm that identified 25 distinct colonic perfusion patterns during ICG inflow and outflow. Each perfusion pattern was then assigned a "risk level" or "assessment of adequacy of perfusion" (safe, intermediate, and dangerous) based on each pattern's performance using a simulator

of colonic circulation. Subsequent testing on 15 unseen videos demonstrated comparable results between the original parameter-based methodology and the AI algorithm with a computer processing time of less than 50 s.

Capitalizing on the well described biophysical differences in perfusion characteristics between malignant and benign tissues (abnormal angiogenesis such as capillary sprouting and increased interstitial pressures) and demonstrating these differences in colorectal lesions using ICG to create unique signatures, we have recently shown too that these signatures can be used to discriminate tissue accurately using traditional machine learning techniques without the need for large volumes of data and DL[37,38]. Blood flow, as well as the active and passive uptake of substances, are altered in malignant tissues. While these differences in fluorescence appearance can at times be appreciable to the human eye on screen, they are subtle, occur at different rates across the full field of view and transpire over several minutes. This complexity, along with the known variability between individuals to interpret intra-operative fluorescence footage, certainly requires the need for computer vision to interpret these differences [39].

To develop this biophysics inspired AI recommender, a commercially available Pinpoint Endoscopic Fluorescence Imaging System (Stryker Corp, Kalamazoo, MI, United States) was used to interrogate lesions within the distal colon transanally following intravenous administration of ICG. A bespoke fluorescence intensity tracker was then used to map intensity changes (representing blood inflow and outflow through tissue) on the multi-spectral intra-operative videos obtained. Tissues in these training videos with known pathology (healthy tissue, benign tissue, malignant tissue) were chosen as "regions of interest" and the fluorescent intensity changes tracked within these tissues to create "perfusion signatures" for each tissue type. The data created from these training videos were then taken and fitted to a parametric curve derived from a biophysical model of *in vivo* perfusion. A supervised machine learning based classification model was designed using these training perfusion signatures and then applied to tissue signatures of previously unseen videos in real time. Using this method the algorithm was able to successfully discriminate between healthy, cancerous and benign tissue in a pilot study of 20 patients with 95% accuracy[37,38]. Such systems employed clinically, providing objective feedback to the endoscopic operator, would permit either immediate local resection in the case of early disease or prompt appropriate, expedited referral for definitive surgical management in the case of more advanced disease. We are currently exploring the validity of this approach in non-colonic tumours with early results demonstrating generalizability of principle across tissue types and also in applying this working prototype to flexible endoscopic systems for more proximal colonic lesions.

CONCLUSION

Biophysics-inspired AI has numerous strengths over DL approaches when it comes to healthcare (Table 1). The transmutability of biophysics inspired AI is not seen in DL methods where for example, data sets collected to train colon cancer identification algorithms likely will not translate to other cancer types. In addition to solving the issue of training data volumes, biophysics inspired principles also provide answers to the "black box" concerns of DL use in medicine. Using DL methods, conclusions drawn by the system, while potentially accurate, are not "explainable" (the ability of the parameters used to justify the result) given the complexity of the algorithms used. This raises ethical dilemmas and accountability concerns where AI is used to direct patient treatment such as the decision to remove tissue or leave in-situ. Along with increased explainability, biophysics inspired modelling facilitates better system interpretability (the ability to associate a cause to an effect). The interrogation of tissue, through fluorescence guided surgery, allows artificially intelligent analysis of the fundamental properties of the tissue itself over pattern recognition within segmented images[40]. Furthermore, the detection and interpretation of these discrete tissue signals is likely less prone to the bias seen with other AI methods where deficiencies in the trainings data used, such as under-representation of particular conditions or people, negatively impacts the pattern detection capabilities of the AI method[41].

For these reasons, biophysics represents a core, although as yet underutilized, element of the next AI move in gastroenterology. This may be as a means to compensate for the apparent lack of video data that exists to train DL models or to augment DL methods by unlocking another realm of tissue specific information that is imparted by analysis of ICG behaviour within tissues. The extra information gleaned

Table 1 Artificial intelligence methods in healthcare: A comparison of biophysics inspired machine learning and deep learning methods

Criteria	Biophysics inspired machine learning	Deep learning
Principle	Identification of discriminating features within data set prior to system training based on already proven biophysical properties	Discriminating features/patterns in data discovered through analysis of large databanks
Training corpus for system to accurately assess unseen cases	Small to moderate data cohorts	Large training data corpuses required
Explainability	Settings, *e.g.*, parameter description and number, used in algorithms are easily described	Complex algorithms utilizing numerous parameters and hyperparameters to control the learning process mean such algorithms often poorly understood
Interpretability	Conclusions reached are easily appreciated and can be explained logically by an appropriately trained individual	Human comprehension of sophisticated algorithm predictions/results may be difficult (including for experts in the field)
Generalizability	Accurate extrapolation of results to unseen cases as well as adaptation of such systems to other similar uses	High degree of specialization within DL systems makes adaptation to other similar uses difficult
Bias	Well described, transparent and biophysics-based features help reduce or identify bias within such systems	Bias within training datasets may be perpetuated by DL systems through subtle mechanisms that may even be imperceptible to humans

DL: Deep learning.

from the tissues' biology, combined with AI methods, lay the blueprint for the creation of full field of view topographic maps that are biologically representative of each individual lesion and potentially even facilitate automation of procedures using fluorescent signal guidance.

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Artificial Intelligence in Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

Artif Intell Gastroenterol 2021 June 28; 2(3): 85-93

DOI: 10.35712/aig.v2.i3.85

ISSN 2644-3236 (online)

MINIREVIEWS

Implications of artificial intelligence in inflammatory bowel disease: Diagnosis, prognosis and treatment follow up

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Author contributions: Almomani A, Hitawala A, Abureesh M, Qapaja T, Alshaikh D, and Zmaili M formulated the initial draft; Saleh MA, and Alkhayyat M critically revised the manuscript.

Conflict-of-interest statement: No conflicts of interest.

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Abstract

Driven by the tremendous availability of data, artificial intelligence (AI) using deep learning has emerged as a breakthrough computer technology in the last few decades and has recently been acknowledged by the Task Force on AI as a golden opportunity for research. With its ability to understand, learn from and build on non-linear relationships, AI aims to individualize medical care in an attempt to save time, cost, effort and improve patient's safety. AI has been applied in multiple medical fields with substantial progress made in gastroenterology mainly to facilitate accurate detection of pathology in different disease processes, among which inflammatory bowel disease (IBD) seems to drag significant attention, specifically by interpreting imaging studies, endoscopic images and videos and -to a lesser extent- disease genomics. Moreover, models have been built to predict IBD occurrence, flare ups, persistence of histological inflammation, disease-related structural abnormalities as well as disease remission. In this article, we will review the applications of AI in IBD in the present medical literature at multiple points of IBD timeline, starting from disease prediction *via* genomic assessment, diagnostic phase *via* interpretation of radiological studies and AI-assisted endoscopy, and the role of AI in the evaluation of therapy response and prognosis of IBD patients.

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: United States

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: April 25, 2021
Peer-review started: April 25, 2021
First decision: May 7, 2021
Revised: May 18, 2021
Accepted: June 28, 2021
Article in press: June 28, 2021
Published online: June 28, 2021

P-Reviewer: Chen Q, Knudsen T
S-Editor: Fan JR
L-Editor: A
P-Editor: Li JH

Key Words: Artificial intelligence; Machine learning; Inflammatory bowel disease

Core Tip: There has been a substantial progress made in artificial intelligence in gastroenterology including inflammatory bowel disease. Machine learning would play a major role in predicting disease flare up, response to treatment and overall patient' prognosis.

Citation: Almomani A, Hitawala A, Abureesh M, Qapaja T, Alshaikh D, Zmaili M, Saleh MA, Alkhayyat M. Implications of artificial intelligence in inflammatory bowel disease: Diagnosis, prognosis and treatment follow up. *Artif Intell Gastroenterol* 2021; 2(3): 85-93
URL: https://www.wjgnet.com/2644-3236/full/v2/i3/85.htm
DOI: https://dx.doi.org/10.35712/aig.v2.i3.85

INTRODUCTION

Artificial intelligence (AI) refers to any technique by which the machine performs complex cognitive tasks similar to those of the human brain such as problem solving or learning. Machine learning (ML) is a subdivision of AI in which the machine automatically learns and improves without being explicitly programmed. Machine learning includes multiple techniques such as deep learning (DL), Bayesian inferences, support vector machines (SVM), artificial neural networks (ANNs), convolutional neural network (CNN) and others[1].

The intelligence of computing machinery was first described in the 1950[2], yet stayed dormant for few decades until the accumulation of large digital and clinical data and the evolution of computer systems which steered the wheel towards a more efficient utilization of available resources. At present, AI has been applied in multiple medical fields, including radiology, neurology, orthopedics, pathology, ophthalmology, in addition to the numerous applications in the field of gastroenterology including neoplastic and non-neoplastic disease processes such as infection, inflammation, and hemorrhage[3-6]. Yet it is not enough for the computer to only learn from the big dataset, this has to translate into meaningful clinical implications that will have positive outcomes in the way patients are being handled. Despite the novelty of this field, multiple applications stand there pointing to this clinical utility of AI. Taking inflammatory bowel disease (IBD) patients as an example, some of the algorithms that will be discussed later in this review had shown the potential ability of the computer to predict the histology by direct visualization of the mucosa. In an ideal world, this would mean that the AI algorithm can diagnose the patient while on the endoscopy table without the need for the invasive biopsy, and that physicians can immediately and more confidently start with treatment and any needed application for insurance companies rather than waiting for the biopsy result for days. In this example, AI demonstrates how can these algorithms save the patient and the clinician time to reach the diagnosis, improve patient's safety by omitting the need for biopsy, and improve the efficiency and workflow. To emphasize more on this point, the American Society for Gastrointestinal Endoscopy (ASGE) assembled the Task Force on AI that aims to direct research efforts toward AI implications that are expected to have more meaningful outcomes[7].

IBD, which is the main interest of this article, is a multifactorial disease of the gastrointestinal tract that results from complex interactions between various genetic, immune system, environment and microbiome-related factors. The non-linear relationships and interactions between the aforementioned factors-as with most living organism's phenomena-made the prediction of the disease onset, accurate diagnostic means, and customization of IBD treatment challenging tasks to achieve, presenting the application of the AI with its non-linear algorithms as a perfectly matching solution[8]. Furthermore, AI, and particularly DL, allows for maximum patient's stratification and optimal individualization of both diagnostic and therapeutic choices in addition to a tailored prognostic view, which positively affect the cost, health and safety.

Among other non-neoplastic processes, the application of AI in IBD seems to have dragged a significant attention especially in the last decade. The aim of this article is to review the applications of AI in the timeline of IBD; starting from the prediction of the disease onset, to diagnostic, therapeutic and finally follow up options.

AI AND IMAGES ANALYSIS

The diagnosis of IBD is a multistep process that matches disease's inherent complexity and multifactorial nature surrounded by a large number of confounding factors[8]. In clinical practice, IBD is diagnosed in an affected subject who is expressing compatible symptoms of either ulcerative colitis (UC) or Crohn's Disease (CD) in addition to a radiological, endoscopic and/or histological evidence of the corresponding inflammatory pattern. Despite the use of multiple scoring systems in an attempt to standardize the diagnostic efforts, the interpretation of any of these tests–and hence the final score- is still susceptible to a significant inter- and intra-observer variability, which only adds fog to the diagnostic horizon[9]. AI offers a great resource for human-independent interpretation and standardization, and has been increasingly recognized in the literature as a promising alternative for biopsy-guided diagnosis, severity determination, identification of remission and prediction of relapses. Multiple models have been developed and applied in different studies to explore this field mainly guided by the ability of the AI to interpret various radiological and laboratory data.

AI-guided interpretation of radiography

The current gold reference standard for diagnosing IBD is colonoscopy, which carries the risk of bowel perforation and procedure-related discomfort. Thus, looking for a different less invasive methods for diagnosis is justifiable and so is the application of AI. Computed tomography (CT) and magnetic resonance imaging (MRI) play a vital role in indicating the presence and extent of the disease, however; this comes at a time cost and more importantly-great subjectivity in the radiological interpretation. Despite the scarce literature in this field, the implementation of AI has shown its ability to standardize the interpretation process to better assess the extent of bowel involvement in a timely fashion with good results when compared to the manual interpretation (Table 1).

The presence of a structural bowel damage in IBD patients is a common cause for medical therapy failure, and early identification of such an entity is of a great value [10]. For this reason, Stidham *et al*[11] developed and validated a semi-automated model to identify strictures in CD patients. To validate the model, two expert radiologists retrospectively reviewed 138 CT-enterography scans for the presence of structural bowel abnormalities in previously known CD patients. The same scans then underwent semi-automated measurement analysis (maximum bowel thickness, maximum bowel dilatation minimum lumen diameter, and presence of stricture). The researchers found that the structural bowel damage measurements collected by the two expert radiologist were similarly comparable to those collected by the model, with no statistically significant difference between the average mean absolute measurements scored by the model compared to that between the two radiologists. The accuracy of radiologist-defined intestinal strictures using automated acquired measurements had an accuracy of 87.6%.

While the ultrasound and the CT use are generally limited by the gas interference and the exposure to the ionizing radiations, respectively; MRI has the ability to overcome both of these issues and the utilizations of AI-aided interpretation makes perfect sense. However, in contrast to the CT images which yield reproducible values, MRI images are greatly influenced by many other factors (ex: Signal fluctuations, heterogeneities in tissue) which complicate the processing of the data and limit the application of the automated techniques, and not surprisingly, further add to the inter-observer disagreement[12]. Training such AI models requires lots of human effort to make the labeled training data that should include all disease spectrum of severity available. Because of these technical and logistic issues, developing a semi-automated model (rather than fully-automated) is a reasonable alternative. Mahapatra *et al*[13,14] successfully developed their own semi-automated classification model to segment the affected bowel regions in CD patients using MRI data and achieved excellent results, required less training time, fewer labeled training samples and less expert effort when compared to their own fully-automated model.

Table 1 Artificial intelligence implications in the interpretation of radiography in inflammatory bowel disease patients

Ref.	Purpose	AI/DL model	Design	Result
Stidham *et al* [11], 2020	To identify structural bowel damage in IBD patients using AI-guided CT image analysis	semi-automated	Retrospective	Structural bowel damage measurements collected by semi-automated approaches are comparable to those of experienced radiologists
Mahapatra *et al*[13], 2016	To evaluate and compare semi-automated to fully automated models in identifying affected bowel segments in MRI of IBD patients	Semi-automated	Retrospective	Semi-automated model outperformed the fully automated model in the ability to segment the affected bowel regions in CD patients using MRI data with less required training time, training samples and expert effort

IBD: Inflammatory bowel disease; AI: Artificial intelligence; DL: Deep learning; CD: Crohn's Disease; CT: Computed tomography; MRI: Magnetic resonance imaging.

AI-guided interpretation of endoscopic images and capsule systems

The interpretation of endoscopic image analysis is of a great interest to the research community and is a main focus and a top priority for the AI ASGE Task Force[7], and is probably the fastest growing. Within the last 10 years, AI-guided endoscopic image analysis (images or videos) has been assessed in different scenarios (Table 2). For example, in 2015, Peng *et al*[15] developed an ANN to study the seasonal variation effect on the onset, relapse and severity of IBD patients. Assigning IBD (UC and CD) patient from 2003 to 2010 as a training cohort, the researchers utilized several meteorological data as an input layer {maximum temperature, minimum temperature, maximum air pressure, minimum air pressure, and humidity} and validated their model on a cohort of IBD patients from the year 2011. This ANN was able to predict the frequency of relapse with a great accuracy (Mean square error = 0.009, Mean absolute percentage error = 17.1%). However, this model had limited ability to predict the onset and severity of IBD.

Later in 2019, Maeda *et al*[16] developed a SVM model to predict the persistence of histologic inflammation in UC patients using endoscopic images. In this retrospective study, the researchers collected data from 187 patients with UC who had endoscopic observation followed by biopsy. Data and images from 87 patients were used to train the model and the remaining 100 patients were assigned for validation. This model achieved an impressive sensitivity, specificity, and accuracy of 74% [95% confidence interval (CI): 65%-81%], 97% (95%CI: 95%-99%), and 91% (95%CI: 83%-95%), respectively, with a great reproducibility.

The importance of the gastrointestinal tract evaluation (ex: *via* endoscopy) largely stems from its ability to predict the clinical outcome and response[17]. However, CD is usually evaluated *via* colonic and terminal ileum visualization and biopsy without a pan-enteric evaluation in spite of the high prevalence of proximal small bowel involvement in more than 50% of patients and its weight on the prognosis[18]. In an attempt to address this defect, a panenteric capsule system (Pillcam Crohns Capsule, Medtronic, Dublin, Ireland) has been recently developed, approved and integrated into the clinical practice[19], however; as with endoscopic means this system was also subject to the inter-observer variability of the human being during image analysis.

In response to these challenges, Gottlieb *et al*[20] conducted an interesting prospective multinational clinical trial using a DL algorithm in 2020 to score the severity of UC from full-length endoscopy videos. In this trial, researchers prospectively collected panenteric videos from a phase 2 clinical trial evaluating mirikizumab use in UC patients from 14 countries. In the first stage, a CNN was used to grade single frames, and in the second stage a recurrent neural network was used to aggregate the grading throughout the entire film. 795 full-length endoscopy videos were obtained from 249 patients, with 19.5 million image frames being assessed. Model's scores were compared to one endoscopic Mayo score (eMS) and one UC Endoscopic Index of Severity (UCEIS) scored by expert human subjects. The inter-rater agreement between either side predictions was compared using quadratic weighted kappa (QWK) metric and showed outstanding results, with a QWK of 0.844 for eMS (95%CI: 0.787–0.901) and 0.855 for UCEIS (95%CI: 0.80–0.91). Interestingly, this study also showed a good performance at the area of large inter-observer variability. For example, for eMS scores of 1 and 2 where the inter-observer variability is substantial, the model showed a specificity of 92% and 76.92% respectively; and a sensitivity of 64.71% and 60%, respectively.

Table 2 Artificial intelligence implications in the interpretation of endoscopic and capsule images of inflammatory bowel disease patients

Ref.	Purpose	AI/DL model	Design	Result
Peng *et al* [15], 2015	To predict the seasonal variation effect on the onset, relapse and severity of IBD patients	ANN	Retrospective	Great accuracy in predicting the frequency of relapse (Mean square error = 0.009, Mean absolute percentage error = 17.1%)
Maeda *et al* [16], 2019	To predict the persistence of histologic inflammation in ulcerative colitis patients using endoscopy images	SVM	Retrospective	Sensitivity, specificity, and accuracy of 74%, 97%, and 91%, respectively
Gottlieb *et al* [20], 2020	Determine the severity of UC from full-length endoscopy videos	CNN	Prospective	Inter-rater agreement factor (QWK) of 0.844 for eMS and 0.855 for UCEIS
Takenaka *et al*[21], 2020	To identify histological remission using colonoscopy images	Deep Neural Network	Prospective	Histologic remission identified with 92.9% accuracy
Stidham *et al* [22], 2019	To identify remission from disease group using colonoscopy images	CNN	Retrospective	Successfully identified the remission from the moderate-to-severe disease group with an AUROC of 0.966, a sensitivity of 83.0%, a specificity of 96.0%, PPV of 0.87, and a NPV of 0.94

AI: Artificial intelligence; DL: Deep learning; ANN: Artificial neural networks; SVM: Support vector machines; AUROC: Area under the receiver operating characteristic curves; NPV: Negative predictive value; PPV: Positive predictive value; CNN: Convolutional neural network.

One of Gottlieb *et al*[20]'s novelty was that their model was trained using videos rather than images and therefore allowed for a full model autonomy of prediction. However, image analysis itself has been previously implemented in other models. The two main models of endoscopic image analysis using AI algorithms were constructed by Takenaka *et al*[21] and Stidham *et al*[22] separately in the same year. In their model, Takenaka *et al*[21] trained their algorithm (the deep neural network for evaluation of UC, or DNUC) using retrospectively-obtained endoscopic images from UC patients who also underwent histological evaluation (biopsy) from 2014 to 2018. The DNUC algorithm was then prospectively validated using a real-time image analysis from a second cohort of UC who underwent endoscopic evaluation with biopsy from 2018 to 2019. The DNUC was able to correctly identify histologic remission with 92.9% accuracy, denoting the potential future ability of AI to identify endoscopic and histological remission without the need for mucosal biopsy.

Similarly, Stidham *et al*[22] constructed a multi-layer CNN model to categorize the images into a remission group (defined by Mayo subscore 0-1) and a moderate-to-severe disease group (defined by Mayo subscore 2-3). These images were also graded by two expert reviewers, and weighted κ agreement was used to measure model-reviewer agreement. The model was trained using retrospectively-obtained images from 3082 UC patients. The researchers used 90% of the cohort to train the model and 10% for validation. In the last step, the model underwent external validation using 30 full-motion colonoscopy videos to simulate real-life scenario. This CNN showed a great ability to distinguish between the remission and the moderate-to-severe disease groups with an area under the receiver operating characteristic curves (AUROC) of 0.966, a sensitivity of 83.0%, a specificity of 96.0%, a positive predictive value of 0.87, and a negative predictive value of 0.94. The agreement between the CNN-scored images and the human-scored images was also fairly good (κ = 0.84; 95%CI: 0.83-0.86) and very close to the agreement in between the two human experts (κ = 0.86; 95%CI: 0.85-0.87).

AI-GUIDED INTERPRETATION OF GENOMICS

The use of AI in the interpretation of gene expression has also been infrequently described (Table 3). Several biomarkers like micro-RNAs, single nucleotide polymorphisms, or microbiota have been indicated to have discriminating potential for the differential diagnosis of IBD[23].

For example, Khorasani *et al*[24] has recently utilized the 240 IBD-risk loci identified by the Genome-wide association studies (GWAS)[25] to develop their own model in 2020. In this model, the researchers used a recently developed feature selection algorithm combined with SVM classifier to differentiate UC patients from healthy subjects based on the values of expression for 32 genes obtained from colon samples.

Table 3 Artificial intelligence implications in the interpretation genomic of inflammatory bowel disease patients

Ref.	Purpose	AI/DL model	Design	Result
Khorasani *et al* [24], 2020	To differentiate UC patients from healthy subjects using colon samples	SVM-DRPT	Retrospective	Predicted all active cases of UC with an average precision of 0.62 in the inactive cases
Wei *et al*[27], 2013	To predict the risk of IBD using genomic data of risk loci	Advanced ML techniques	Retrospective	Successfully predicted IBD with an unprecedented predictive power with AUCs of 0.86 for CD and 0.83 for UC

IBD: Inflammatory bowel disease; AI: Artificial intelligence; DL: Deep learning; CD: Crohn's Disease; UC: Ulcerative colitis; ML: Machine learning; SVM-DRPT: Support vector machines-developed feature selection algorithm.

This model was able to successfully predict all active cases of UC, with an average precision of 0.62 in the inactive cases. Despite the limitation of the training datasets (only two), this model outperformed BioDiscML[26] on the basis of average precision. Wei *et al*[27] had also previously utilized this large multinational GWAS data in synthesizing and validating their own IBD-risk predicting model by identifying the disease loci, and achieved an unprecedented predictive power with areas under the curve (AUCs) of 0.86 for CD and 0.83 for UC. Despite these interesting results, it is worth emphasizing that the use of genomic-based models is still in a very early stage of research and is not yet well-adapted in clinical practice.

AI AND IBD: TREATMENT AND FOLLOW UP

The most useful clinical application of AI might be in its potential ability to assess treatment effectivity and response to medications, and numerous studies have been published in this field (Table 4). Waljee *et al*[28-32] published few studies where they assessed treatment response using AI. In one study[28], they developed their algorithm using phase-3 clinical trial data on Vedolizumab for CD from GEMINI I and II assessing corticosteroid-free remission at week 6 and week 52. Patients predicted to be in corticosteroid-free remission by the algorithm achieved the endpoint 35.8% of the time at week 52, but only 6.7% of the time at week 6. This algorithm was able to predict with reasonable accuracy as to which patients were unlikely to achieve remission at week 6. In a similar design, Waljee *et al*[29] developed a machine algorithm to predict durable response to Ustekinumab in patients with CD[29]. They analyzed data from three phase-3 randomized clinical trials (UNITI-1, UNITI-2, and IM-UNITI) and built 2 models, the first using only baseline data and the second using data till week 8. The week-8 model had an AUROC of 0.78 (95%CI: 0.69-0.87). In the testing data set, about 49% patients classified as likely to achieve clinical success did actually achieve it after week 42, while only about 11% achieved remission in those classified as likely to have treatment failure.

Another study by Waljee *et al*[30] aimed to assess an algorithm to predict thiopurine non-responders, nonadherence and shunters[30]. In this study, the researchers used laboratory and age data for algorithm training and compared it to thiopurine metabolite measurement in predicting the outcomes. The algorithm was able to differentiate clinical responders from non-responders with AUROC curve of 0.856, while the thiopurine metabolite had AUROC curve of 0.594 ($P < 0.001$), and hence this ML model demonstrated a clean superiority in outcome prediction compared to the laboratory measurement. This algorithm was further externally validated on the SONIC clinical trial data set[31]. This method is clinically quite relevant, as the data used by the algorithm are readily available and very cost effective.

A similar study by Waljee *et al*[32] developed an algorithm using laboratory values and age to identify IBD patients in objective remission on thiopurines and to assess if the algorithm was able to predict fewer clinical events as compared to measurement of thiopurine metabolites[32]. The clinical events were defined as new steroid prescriptions *per* year, hospitalizations *per* year and surgeries *per* year. For objective remission, the algorithm was superior to thiopurine metabolite measurement and statistically significant, with AUROC of 0.79 (95%CI: 0.78–0.81) *vs* 0.49 (95%CI: 0.44–0.54), respectively, and P value of $< 2.2 \times 10^{-16}$. In patients with sustained algorithm-predicted remission, statistically significant reduction in steroid prescriptions/year and hospitalizations *per* year were seen, proving the superiority of the machine-learning algorithm to thiopurine metabolite measurement.

Table 4 Artificial intelligence implications in the treatment and prognosis of inflammatory bowel disease patients

Ref.	Purpose	AI/DL model	Design	Result
Waljee *et al* [28], 2018	To predict corticosteroid-free biologic remission	Random Forest modeling	Retrospective	At week 52, patients predicted to fail succeeded 6.7% of the time
Waljee *et al* [29], 2019	To predict long-term response to ustekinumab	Random Forest modeling	Retrospective	*Per* week-8 model, only 11% predicted to fail achieved remission
Waljee *et al* [30], 2010	To predict response to thiopurines	Random Forest modeling	Retrospective	The model was superior to metabolite measurement in predicting non-responders.
Waljee *et al* [31], 2018	To externally validate previously developed thiopurine algorithm	Random Forest modeling	Retrospective	The algorithm accurately predicted objective remission with AUROC 0.76
Waljee *et al* [32], 2017	To identify patients in objective remission on thiopurines and analyze if these patients had fewer clinical events *per* year	Random Forest modeling	Retrospective	AUROC for algorithm-predicted remission was 0.79 *vs* 0.49 for thiopurine metabolite proving model superiority

AUROC: Area under the receiver operating characteristic curves; AI: Artificial intelligence; DL: Deep learning.

AI AND IBD: PROGNOSIS AS DETERMINED BY THE MACHINE

Similar to studies on treatment response, AI has also been shown to have a significant potential in the prognostication of IBD patients (Table 3). Waljee *et al*[33] developed two machine learning models using clinical parameters to predict hospitalization and outpatient corticosteroid use for IBD within 6 mo[33]. The AUROC for the random forest longitudinal model using previous hospitalization or steroid use was 0.87 (95%CI: 0.87–0.88). The accuracy of the model was significant, which would allow for a personalized management of high-risk patients. Genome wide association studies and microbiome data have also been used in some studies in addition to the referred earlier. For example, a study by Cushing *et al*[34] used RNA extraction and human transcriptome microarray from mucosal biopsies of uninflamed tissue from operative specimens after ileocolic resection in CD patients. Their study showed that anti-tumor necrosis factor -naïve and -exposed patients have unique expression profiles at the time of surgery, which may be utilized to assess the risk of non-recurrence.

Morilla *et al*[35] conducted a study on patients with acute severe UC to predict the response to steroids, infliximab and cyclosporine. They used microarray analysis of microRNA expression profiles from colon biopsy specimens. Their deep neural network-based classifier was able to identify 9 microRNAs plus 5 clinical factors associated with response to treatment. Their panel discriminated between steroid responders and non-responders with 93% accuracy (AUC = 0.91). Based on microRNA levels, they developed three algorithms that distinguished responders to infliximab from non-responders with 84% accuracy (AUC = 0.82), and responders to cyclosporine from non-responders with 80% accuracy (AUC = 0.79).

CONCLUSION

AI has been widely applied in multiple medical sciences[3-6]. Among its numerous applications in the field of gastroenterology, AI implications in IBD seems to be the fastest growing and the most promising (Tables 1-4). This has been largely driven by the tremendous availability of data which necessitates finding a path to efficiently utilize it in a safe and cost-effective manner. The ultimate goal of AI is to provide a human-independent interpretation of the data to allow for a standardized diagnostic process and minimize the inter- and intra-rater variability. The patient-tailored management is an extra-privilege that AI can also provide using its complex neural algorithm's ability to understand the non-linear interactions between the factors contributing to IBD, build on it and predict the result. Given the tremendous availability of the data, AI is expected to save time, effort and money. However, training a model and validating it would –at least initially- require all three of these, which makes the AI industry very challenging. Most of the current models were validated retrospectively which limits the external validation. More prospectively-validated models are needed for the medical community to familiarize with AI if it's to be adopted by physicians and integrated into their clinical practice.

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Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
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ISSN 2644-3236 (online)

Artificial Intelligence in *Gastroenterology*

Artif Intell Gastroenterol 2021 August 28; 2(4): 94-123

Published by Baishideng Publishing Group Inc

A I G
Artificial Intelligence in Gastroenterology

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Bimonthly Volume 2 Number 4 August 28, 2021

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Artificial Intelligence in Gastroenterology

Bimonthly Volume 2 Number 4 August 28, 2021

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

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INDEXING/ABSTRACTING

There is currently no indexing.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Jia-Hui Li*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jin-Lei Wang*.

NAME OF JOURNAL
Artificial Intelligence in Gastroenterology

ISSN
ISSN 2644-3236 (online)

LAUNCH DATE
July 28, 2020

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Rajvinder Singh, Ferruccio Bonino

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2644-3236/editorialboard.htm

PUBLICATION DATE
August 28, 2021

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Artif Intell Gastroenterol 2021 August 28; 2(4): 94-104

DOI: 10.35712/aig.v2.i4.94

ISSN 2644-3236 (online)

MINIREVIEWS

Clinical use of augmented reality, mixed reality, three-dimensional-navigation and artificial intelligence in liver surgery

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Author contributions: Wahba R and Stippel DL designed the research study, performed the research; analyzed the data and wrote the manuscript; have read and approved the final manuscript; Thomas MN performed the research, wrote the manuscript; have read and approved the final manuscript; Bunck AC analyzed the data and wrote the manuscript; have read and approved the final manuscript; Bruns CJ designed the research study, has read and approved the final manuscript.

Conflict-of-interest statement: There is no conflict of interest.

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Abstract

A precise knowledge of intra-parenchymal vascular and biliary architecture and the location of lesions in relation to the complex anatomy is indispensable to perform liver surgery. Therefore, virtual three-dimensional (3D)-reconstruction models from computed tomography/magnetic resonance imaging scans of the liver might be helpful for visualization. Augmented reality, mixed reality and 3D-navigation could transfer such 3D-image data directly into the operation theater to support the surgeon. This review examines the literature about the clinical and intraoperative use of these image guidance techniques in liver surgery and provides the reader with the opportunity to learn about these techniques. Augmented reality and mixed reality have been shown to be feasible for the use in open and minimally invasive liver surgery. 3D-navigation facilitated targeting of intraparenchymal lesions. The existing data is limited to small cohorts and description about technical details *e.g.*, accordance between the virtual 3D-model and the real liver anatomy. Randomized controlled trials regarding clinical data or oncological outcome are not available. Up to now there is no intraoperative application of artificial intelligence in liver surgery. The usability of all these sophisticated image guidance tools has still not reached the grade of immersion which would be necessary for a widespread use in the daily surgical routine. Although there are many challenges, augmented reality, mixed reality, 3D-navigation and artificial intelligence are emerging fields in hepato-biliary surgery.

Key Words: Augmented reality; Mixed reality; 3D; Navigation; Artificial intelligence; Liver surgery; Liver resection; Image guided surgery

Manuscript source: Invited manuscript

Specialty type: Surgery

Country/Territory of origin: Germany

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: April 9, 2021
Peer-review started: April 9, 2021
First decision: July 3, 2021
Revised: July 10, 2021
Accepted: August 27, 2021
Article in press: August 27, 2021
Published online: August 28, 2021

P-Reviewer: Mutter D
S-Editor: Liu M
L-Editor: A
P-Editor: Li JH

Core Tip: Virtual three-dimensional (3D)-reconstruction models from computed tomography/magnetic resonance imaging scans of the liver might be helpful for visualization during liver surgery. Augmented reality, mixed reality and 3D-navigation could transfer such 3D-image data directly into the operation theater. Augmented reality and mixed reality have been shown to be feasible for the use in open and in minimally invasive liver surgery. 3D-navigation facilitated targeting of intraparenchymal lesions. Randomized controlled trials regarding clinical data or oncological outcome are not available. Up to now there is no intraoperative application of artificial intelligence in liver surgery. The usability of all these sophisticated image guidance tools has still not reached the grade of immersion which would be necessary for a widespread use in the daily surgical routine.

Citation: Wahba R, Thomas MN, Bunck AC, Bruns CJ, Stippel DL. Clinical use of augmented reality, mixed reality, three-dimensional-navigation and artificial intelligence in liver surgery. *Artif Intell Gastroenterol* 2021; 2(4): 94-104
URL: https://www.wjgnet.com/2644-3236/full/v2/i4/94.htm
DOI: https://dx.doi.org/10.35712/aig.v2.i4.94

INTRODUCTION

The surgical liver anatomy is defined not only by external landmarks but more important by its three-dimensional (3D) intra-parenchymal vascular and biliary architecture. It shows a high-grade of variation in each individual, making liver anatomy even more complex. In addition, liver lesions are often located intraparenchymally, which makes them invisible for the surgeon. Therefore, a high grade of anatomical knowledge before and during hepato-biliary surgery is directly related to the post-operative success and outcome for the patients[1]. Especially spatial, 3D-orientation is of utmost importance in the liver: (1) For pre-surgical localization of intrahepatic lesion; (2) For exact planning of the resection line; and (3) For intraoperative identification of the lesions and orientation during the parenchyma dissection. Hence hepato-biliary surgeons have been ambitious to use computer and image guidance techniques to facilitate preoperative planning and intraoperative procedures. Computer-assisted 3D-segmentation and -reconstruction techniques have helped to transfer 2-dimensional (2D) images, slices, of the liver from a computed tomography (CT)- or magnetic resonance imaging (MRI) -scan back to a 3D structure familiar to the surgeon's perception of the real anatomy. First applications of segmentation and virtual 3D-reconstruction of the liver dated from the early 90s of the last century[2,3]. Summarized under the term "virtual hepatectomy" this 3D-preoperative liver segmentation technique has improved outcome after major liver resection and living liver donation. It has become a standard procedure at specialized liver centers[4,5]. The next step was to transfer the preoperative reconstructed 3D-images into the operative theater- followed by early applications of intraoperative navigation with stereotactic systems[6]. The additional 3D-image information was presented on a secondary screen and the surgeon has to mentally merge the real live situation and the virtual 3D reconstruction of the liver. In the 1990s years the challenges became even greater[7] with the introduction of laparoscopic liver surgery. "Virtuality" has emerged to liver surgery: Performing the laparoscopic operation only according to a displayed 2D image. Years later passive-polarizing 3D display techniques reintroduced spatial orientation into minimally invasive surgery and has shown to improve the surgical performance[8,9].

"Augmented reality" (AR) or "mixed reality" (MR) is created by superimposing the virtual 3D model of the liver on the laparoscopic screen or directly on the liver. At this point the fusion between image data and real-world anatomy took place - which was performed up to that point in the surgeon's mind. AR/MR should facilitate this procedure and so the surgical process. A key factor to achieve this is calibration and registration, which means to match the 3D liver model and the real liver to create AR/MR. This is still a major source of error[10]. Artificial intelligence (AI) might be the next step in liver surgery. It has the potential to help the surgeon to identify

anatomical structures. One novel way to integrate AI in liver surgery could be achieved by automatic tissue recognition according to the laparoscopic image and image fusion with the virtual 3D model.

Aim of this review is to evaluate the clinical usage of AR and MR, 3D-navigation and AI in liver surgery.

For the comprehensive literature review utilizing MEDLINE (PubMed) was performed using the search terms "mixed reality liver", "augmented reality liver", "navigation liver", "artificial intelligence surgery" and "artificial intelligence liver" (publication date from January 1991 until January 2021). Only articles in English language were considered. Review articles were excluded. The query retrieved in total 450 publications. Duplicates were identified by Endnote leaving 433 citations for review. The headlines and abstracts of those citation were reviewed manually. Finally, 44 citations were considered relevant to the topic.

TECHNIQUES TO CREATE AR AND MR IN OPEN LIVER SURGERY

While using AR/MR the first step is to perform the segmentation and reconstruction of a virtual 3D liver model out of the 2D-CT/MRI scan. After that this 3D model must be superimposed intraoperatively onto the liver. Therefore, a registration and calibration process must be performed: Anatomical landmarks of the liver must be identified and then matched to the corresponding points on the virtual 3D model. The accuracy between 3D model and the real-life anatomical structures is determined by the precision of this registration process. Anatomical landmarks on the surface of the liver and/or vascular structures defined by intraoperative ultrasound can be obtained [10] for the registration process.

In open liver surgery AR and MR could be realized using different techniques: (1) The virtual 3D model is projected on the surface of the liver or the abdominal wall; (2) The liver is visualized through a scope and displayed on a secondary screen ("open laparoscopy"). On that screen the virtual 3D model is superimposed on the image of the real liver. Using this technique, the surgeon has to look away from the operative field to use the AR/MR model; (3) the 3D model is superimposed on a semi-transparent display, which is placed between the surgeon and the operative space. The surgeon has to look through this semi-transparent display to see the real liver and to perform the surgery; (4) The liver is visualized through the camera of a tablet pc and the virtual 3D-model was then superimposed onto the liver image on the tablet's screen; and (5) A so called "hologram" was created on head-mounted semitransparent display. In this setting the surgeon could see the real liver through the semitransparent display (which is worn like glasses) and the "hologram" was superimposed on the semitransparent display using it as a projection screen.

AR AND MR IN OPEN LIVER SURGERY

Visualizing the liver through a scope was a first step of AR/MR in open liver surgery. Onda *et al*[11] described two cases of liver resection (right hepatectomy and partial hepatectomy), where this technique has been successfully used. However the technique was time consuming: 10 hr for preoperative planning and 3D-model reconstruction, one hour for the intraoperative setup and 1-2 min for the registration process. Data on clinical outcome were not available[11]. Okamoto *et al*[12] used to create AR/MR with the open scope technique and *via* a so-called see-through display, which is mounted directly between the surgeon and the operative space[12]. Two hepato-biliary procedures were reported with this technique (bile duct resection, right hepatectomy). Operation time and blood loss were 245 min/242 mL and 530 min/1329 mL respectively. The scope technique to create AR/MR was also used to identify disappeared colorectal liver metastasis after chemotherapy. In three patient this AR/MR technique was used to find and finally resect the tissue of the disappeared metastasis[13]. Using a tablet pc is an easy, state-of-the-art video-based variation of the scope see-through AR/MR technique in open liver surgery. One case is described using this AR technique to perform a left hepatectomy and hepatico-jejunostomy with complex biliary reconstruction for hilar cholangio-carcinoma[14]. Yasuda *et al*[15] used a comparable technique with a tablet pc as display "in" the operative field combined with the open-scope technique. In a series of eight patients they described an accuracy/registration error between the 3D virtual model and the real liver of 1 mm to 11 mm. Data regarding clinical outcome parameters were not available. Still an

unsolved problem using AR/MR and 3D-navigation is the high grade of deformation of the liver during open surgery. The superimposed images could not follow this deformation and the error between the 3D model and real anatomy increases during the process of parenchyma dissection. Golse *et al*[16] have recently described an AR technique during open liver surgery using a marker less non-rigid registration system. They showed in four patients that registration was possible and the 3D model could be superimposed on the liver following some deformation.

Lately head-mounted semitransparent displays (*e.g.*, Hololens) have been introduced to open liver surgery. With this technique the surgeon can see a so called "hologram" superimposed on the real world and handle it *via* gesture recognition without the need of an input device (*e.g.*, touchpad or touch screen). It is right now not possible with this technique to match the hologram directly on the real liver - in fact the hologram is projected somewhere in the visual field of the user. A first study evaluated the use of the hololens regarding anatomical identification of liver lesions. Pelani *et al*[17] could show in an out-of-the-operation-room study including 28 surgeons, that the correct identification of a simulated liver lesion could be performed in 6 s with the Hololens compared to 24 s using the 2D-CT scan of the liver. Saito *et al*[18] described the intraoperative use of the hologram technique. Here the hologram was superimposed above the operative field. In the first patient with more than 20 colorectal liver metastasis the 3D hologram of the liver was used to identify the liver lesions and to visualize the parenchyma dissection line. In the second case the hologram was used to facilitate the identification of a complex hilar anatomy in order to perform the glisonnean pedicel approach in a patient with an HCC. In this case multiple contributors of the surgical procedures have worn the hololens at the same time (Table 1).

AR AND MR IN LAPAROSCOPIC LIVER SURGERY

In laparoscopic surgery the real-world 3D appearance is transferred into a virtual 2D image on a screen. This leads to a loss of spatial orientation, which is a major challenge. Therefore, anatomical orientation is aggravated. With the use of 3D laparoscopic systems spatial orientation was reintroduced to minimally invasive surgery. This accelerated complex laparoscopic procedures and facilitated them[8,9]. AR and MR could provide precious additional information about the liver anatomy and localization of intrahepatic lesions on the virtual image. Image projection on the abdominal surface for trocar positioning and anatomical orientation was the first level of AR in laparoscopic liver surgery[19]. Volonté *et al*[19] described in a study with four patients the use of the projection technique: The 3D-modell was projected on the abdominal wall. This early version of AR was used to visualize the anatomy and to place the trocar ports for laparoscopic approaches. In a clinical study on 24 patients this AR image projection technique on the abdominal wall resulted in less deviation between the planned trocar position and the real trocar positions[20]. The next step of AR in minimally invasive surgery was similar to the use in open liver surgery: To place additional image information on the display. The surgeon could see the laparoscopic image and the reconstructed virtual 3D model at the same time on the same screen - but without image fusion[21]. This was followed by image fusion of the virtual 3D model and the laparoscopic image of the liver. The registration and matching process of both to create AR is crucial. As in open surgery this relied on a manual registration by the surgeon. In a feasibility study Schneider *et al*[22] could show that semi-automatic registration of a superimposed 3D model was feasible in 16 out of 18 patients. This facilitated and speeded the process up, but with lower precision compared to the standard manual registration algorithm. Kang *et al*[23] described an AR system in an in-vivo porcine model, which could superimpose the intraoperative laparoscopic ultrasound image on the real liver. Therefore they used a stereotactic navigation system and 3D laparoscopic imaging system. In 2015 one case of a transthoracic minimally invasive liver resection guided by AR was described. Here the registration process and fusion of the virtual 3D model and the liver anatomy was performed by a specialized computer scientist to ensure accuracy by using visible landmarks on the liver surface corresponding to the virtual 3D model[24].

Robotic platforms for surgery have the potential to integrate multiple additional information into the operation field in the view of the surgeon. Right now, the integration of ultrasound and indocyanine green (ICG) imaging are standard features of robotic surgical platforms. *Pessaux et al*[25] described in 2015 three cases of a liver segmentectomy supported by superimposed 3D models of the liver. The registration

Table 1 Augmented and mixed reality in open liver surgery

Ref.	No of procedures	Technique	Key outcomes
Onda *et al*[11], 2013	2 liver resections	Open stereo-scope, AR created on a passive - polarizing 3D display	Open scope technique feasible, 10 hr pre-op image preparation, 1 h intraoperative setup, 1-2 min for registration process
Okamoto *et al* [12], 2013	2 HPB procedures	Video see-through display	Position of virtual 3D model and organ image closely corresponded, registration error 5 mm
Ntourakis *et al* [13], 2016	3 patients with 4 disappeared CRLM	Open stereo-scope, AR created on video screen, registration performed by an additional computer technician	AR helped to detect disappeared all metastases, R0, planned security margin 1 cm, registration time within 6 min
Tang *et al*, 2017 [14]	1 patient	AR created on a tablet pc as see-trough display	Feasible, improved vision compared to video based AR system
Yasuda *et al* [15], 2018	7 patients including minor and major liver resections	Open scope technique combined with AR created on a tablet pc with infrared sensor	Tablet pc method feasible, registration error 1-11 mm
Saito *et al*[18], 2020	2 HPB procedures	3D hologram on head mounted display	Feasible, orientation improved, multiple surgeons used the technique at the same time, hologram reduced task load

CRLM: Colorectal liver metastasis; HPB: Hepato-biliary; AR: Augmented reality; 3D: Three-dimensional; R0: R0 Resection.

and image fusion were again manually performed by a computer scientist with the help of an additional video mixer[15,25]. Automatic compensation of the laparoscopic motion during AR is another new feature: The location of the 3D model was adapted to the changed perspective of the laparoscope during the resection. In a series of 10 patients this led to an accuracy of 5 mm between the virtual 3D model and the real anatomic position of the liver[26] (Table 2).

AR AND MR FOR 3D NAVIGATION

Preoperative use of a virtual 3D models for planning followed by intraoperative use *via* AR for orientation leads to the next level of image-guided liver surgery: Intraoperative navigation. A navigation systems should not only visualize the anatomy but also guide the surgeon through the resection and show correlated to the used surgical instruments the location of important anatomical structures, at best before they were visible.

Early versions of navigation systems from the 2000s years often based on intraoperative ultrasound. They were able to guide a needle for thermal ablation into liver lesions[27]. The combination of the ultrasound technique with 3D virtual reconstruction of the liver and stereotactic navigation systems, already known from neurosurgery, followed after that[28]. Beller *et al*[29] described the clinical use of a navigation system for open liver surgery. The system was based on optical electromagnetic tracking: Marker shields must be placed on the instruments, which were scanned by a camera system placed above the operative space The system used 3D virtual image reconstruction of the liver, matched the 3D image with intraoperative ultrasound and could show the position of the used instruments during liver parenchyma transaction on the virtual 3D image and the ultrasound image[29]. In this early study 32 navigated liver resection were compared to 32 conventional liver resections. The authors could show that in the navigation group the planned dissection line could be maintained with an accuracy of 5 mm. Also, the rate of R1-resection was significantly reduced in the navigation group[29]. The navigation technique was optimized during the following years[30]. Peterhans *et al*[10] developed a stereotactic navigation system for open liver surgery. This system superimposes the position of the instruments and the ultrasound image on the virtual 3D liver model on a secondary screen. The first clinical evaluation of this system was performed on 9 patients undergoing oncologic liver resection. The optimized workflow of the system resulted in short landmark definition and acquisition times of just one minute, which has made the navigation system ready to use in the operation theatre[10]. The largest cohort of patients that underwent liver resection supported by a 3D navigation system was published by the group from Bern/Switzerland with 65 patients over a period of four years. They combined 3D-navigated liver resection and 3D-navigated thermal ablation

Table 2 Augmented and mixed reality in minimally invasive liver surgery

Ref.	No of procedures	Technique	Key outcomes
Volonté *et al* [19], 2011	4 procedures	Projection of the virtual 3D model on the body surface	Anatomical orientation and trocar placement improved
López-Mir *et al* [20], 2013	12 procedures	Projection of the virtual 3D model on the body surface	lower deviation between planned and actual trocar positions using AR
Pessaux *et al* [25], 2015	2 robotic liver resections	Virtual 3D model superimposed on console display, registration performed manually by a computer scientist	AR and registration process feasible, time to create AR 8 min
Schneider *et al* [22], 2020	18 laparoscopic liver resections	Passive polarizing 3D laparoscope, optical tracking of the laparoscope, semi-automatic registration	semiautomatic registration an image fusion achieved in 16/18 manual registration *vs* semiautomatic accuracy 11 mm *vs* 14 mm

AR: Augmented reality, 3D: Three-dimensional.

in order to perform parenchyma sparing treatment instead of formal major anatomical liver resections. The technical accuracy, matching the virtual 3D model and the real liver, could be optimized to 4.5 mm deviation. They also described a new technique of landmark acquisition and registration: The landmarks on the liver surface were combined with intrahepatic vascular structures acquired by ultrasound[31].

In the following years the electro-magnetic navigation technique was transferred to minimally invasive liver surgery[28,32] and later also combined with AR. On the laparoscopic image of the real liver the 3D virtual model was superimposed and the surgical instruments were tracked and could be navigated in this AR environment [33]. Thenceforth AR, MR and navigation techniques tread a parallel development path[13].

Spatial orientation is especially important in laparoscopic thermal ablation of liver lesions. Tinguely *et al*[34] showed in a cohort of 54 patients, which were treated with pure laparoscopic 3D navigated microwave ablations a registration accuracy of 8.1mm. Yet, the early local recurrence rate in this cohort was high with 32%. Thomas *et al*[35] described an optimized system for laparoscopic ultrasound navigated microwave ablation lately. With this navigation tool novices could achieve an accuracy and a speed in targeting defined liver lesion comparable to expert surgeons. In a cohort of 27 patients Aoki *et al*[36] described the use of a laparoscopic navigation system with instrument tracking. This system displays the position of the instrument on the reconstructed 2D-CT image. As a result of the use of the navigation system a low median tumor margin (R0-Resection) of 9 mm could be achieved. The latest development combining AR and stereotactic 3D navigation in laparoscopic liver surgery was described by Prevost *et al*[26]. Their navigation system could create an AR overlay of the intrahepatic structures directly around the stereotactic tracked dissection instrument. Ten patients could be successfully operated with the system, showing a calibration time of 9 min for the navigation system with a registration error of 9.2 mm (Figures 1 and 2)[26]. Organ deformation may reduce the precision of the registration and navigation process during the surgical procedure. Updating the navigation information by intraoperative real-time CT image acquisition, using injected fiducials could further minimize the registration error and increase precision in a pre-clinical setting[37] (Table 3).

FLUORESCENCE GUIDED NAVIGATION TECHNOLOGY AND ROBOTIC PLATFORMS

During the last 10 years the use of real time-fluorescence technique with ICG has been established in open and laparoscopic liver surgery. By easy-to-see intraoperative green fluorescence it could facilitate evaluating the liver anatomy[38], visualize tumor lesions[39] and optimize segmental and subsegmental anatomical resections as well parenchyma dissection in major liver surgery[40,41]. Compared to the above mentioned navigation systems, ICG is more an intraoperative staining technique. It visualizes liver parenchyma or lesions directly through an optical system and "navigates" the surgeon during the operation. Fusion of real time-fluorescence imaging with pre-operative CT-or MRI-data combined with the intraoperative view to

Table 3 Augmented and mixed reality for 3D Navigation

Ref.	Number of procedures	Technique	Key outcomes
Beller *et al* [29], 2007	33 open liver resections	Stereotactic optical navigation system, combined with a virtual 3D model and ultrasound, dissection device tracked and navigated on ultrasound image	Navigation successful in 32/33 cases, difference between projected and actual vascular dissection lever 6mm, R0 resection in 30 cases
Peterhans *et al*[10], 2011	9 open liver resections	Stereotactic navigation system, combined with a virtual 3D model and ultrasound, landmark acquisition on the liver surface, dissection device tracked and navigated on the virtual 3D model	Navigation successful in all cases, median accuracy 6.3 mm
Banz *et al* [32], 2016	65 open liver resections	Stereotactic optical navigation system, combined with a virtual 3D model and ultrasound, dissection device tracked and navigated on the virtual 3D model, landmark acquisition with ultrasound possible	Combination of 3 d navigated resection and thermal ablation in 16 patients, accuracy optimized to 4.5 ± 3.6 mm
Tinguely *et al* [35], 2017	54 laparoscopic image guided microwave ablation	Laparoscopic stereotactic navigation system, combined with a virtual 3D model, landmark acquisition on the liver surface, ablation device tracked and navigated on the virtual 3D model, standard 2D laparoscopic display	Registration time 4:38 min, accuracy 8.1 ± 2.8 mm, early local recurrence rate 32%
Aoki *et al* [37], 2021	27 laparoscopic liver lesions	virtual real-time CT-guided volume navigation, electromagnetic tracking of the surgical instruments displayedon the preoperatively acquired CT images	Registration time < 2 min, registration error 12 mm, histologic resection margin 9 mm
Prevost *et al* [26], 2020	10 laparoscopic liver resections	stereotactic augmented reality navigation, virtual 3D liver model superimposed on the real liver with a 3D laparoscopic system, instruments tracked	Registration time 8:50 min, registration error 9.2 mm, facilitates to find disappeared liver lesions

AR: Augmented reality; 3D: Three-dimensional.

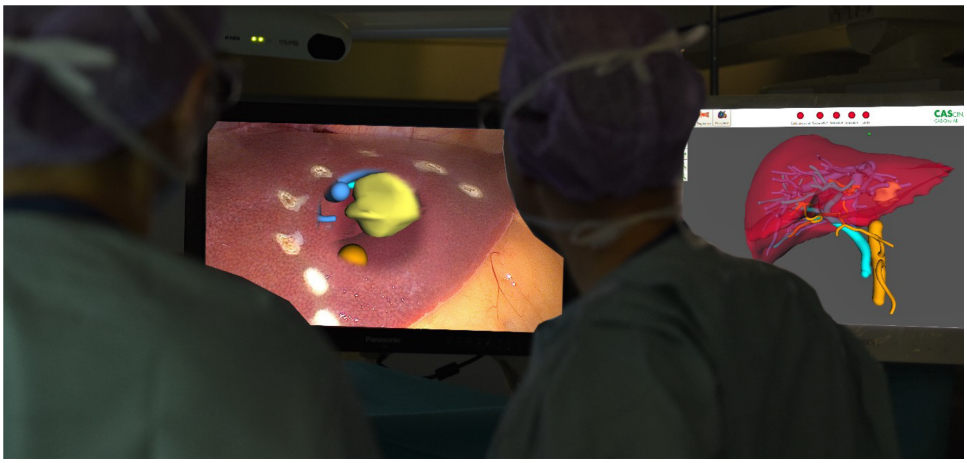

Figure 1 shows the use of augmented reality during laparoscopic liver resection using a 3D passive polarizing display technique. The complete virtual three-dimensional model of the liver is visible on a second screen (right picture). On the main screen augmented reality is created (left picture). Citation: Prevost GA, Eigl B, Paolucci I, Rudolph T, Peterhans M, Weber S, Beldi G, Candinas D, Lachenmayer A, Efficiency, Accuracy and Clinical Applicability of a New Image-Guided Surgery System in 3D Laparoscopic Liver Surgery. *J Gastrointest Surg* 2020; 24(10): 2251-2258, Copyright © The Author(s) 2020, Published by Springer Nature[26].

create AR would be a further step in navigation technique. Here robotic surgical platforms may become a game-changer, because they create a 3D minimally invasive surgical environment with real-time fluorescence and ultrasound imaging in one display. Adding a virtual 3D model of the liver from preoperative image data, intraoperative navigation could lead to the next level of immersion.

AI

Deformation of the liver tissue is still a major issue for precise registration and the substantial use of navigation and image superimposition during surgery. Convolutional neural networks are able to learn soft tissue behavior, which could be

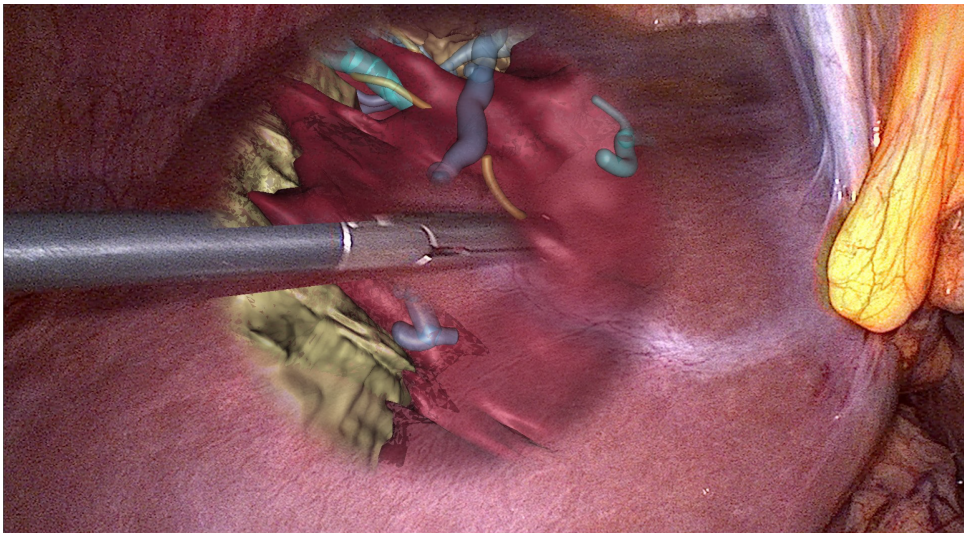

Figure 2 Directly on the laparoscopic three-dimensional image of the liver there is only that part of the virtual three-dimensional model superimposed on an area, which is relevant for the parenchyma dissection during that phase of the operation. At the area, where the lesion is located and the parenchyma dissection will be performed, the virtual three-dimensional model is matched around the tracked/navigated dissection tool. Citation: Prevost GA, Eigl B, Paolucci I, Rudolph T, Peterhans M, Weber S, Beldi G, Candinas D, Lachenmayer A, Efficiency, Accuracy and Clinical Applicability of a New Image-Guided Surgery System in 3D Laparoscopic Liver Surgery. *J Gastrointest Surg* 2020, 24(10), 2251-2258, Copyright © The Author(s) 2020, Published by Springer Nature[26].

transferred to surgical navigation[42]. Elastic surface based-matching registration algorithms may reduce registration errors[43]. Unfortunately up to now there is no clinical intraoperative use of AI in liver surgery. Aspects of machine learning are integrated in the AR/MR and navigation systems. But automated registration and recognition of anatomical structures of the liver is not available for clinical use up to now.

DISCUSSION

Due to the invisibility of intrahepatic vascular anatomy during surgery and the high variability, preoperative analyzes of the anatomy and planning of the resection is essential in liver surgery. Therefore, there is a high need for image guidance in hepato-biliary surgery. The use of preoperative 3D virtual reconstruction image techniques have evidence-based optimized the outcome after major liver surgery[1]. The next step of using image guidance was to transfer the 3D image of the liver into the operation theater. The feasibility of AR, MR and intraoperative 3D-navigation has been proven up to now, but the majority of the systems are still in an experimental status. The scenario for clinical use-cases in hepato-biliary surgery is not clearly defined up to now. It is still not clear under which circumstances the use of intraoperative AR and MR or navigation leads to a benefit - for the surgeon to facilitate the operative procedure or for the patient to optimize his outcome?

Minimized safety margins, increased R0-rates, increased number of potential treatable lesion, minimized blood loss, shorter operation time, "visualization" of disappeared liver metastasis, precise sub-segmental anatomical resections, flattened learning curve of complex procedures could be theoretically optimized by the usage of intraoperative AR, MR and 3D navigation in hepato-biliary surgery.

These factors should be evaluated systematically and addressed clearly with high-quality studies, which have not been conducted up to now.

Another important issue is the usability of the virtual 3D technique. The intraoperative use of AR/MR and 3D-navigation changes the workflow during liver resection. It is important that the surgeon feels comfortable with the system and is not limited by the technique, so a high grade of usability is mandatory. This is still a major drawback of the available systems: Additional secondary screens are needed (displays, tablet pc or head-mounted display), secondary cameras above the operative field, marker shields have to be placed on the instruments, registration and calibration must be performed manually and the technique in general is often limited to certain anatomic areas of the liver. Systematic data about the usability is still missing in scientific

literature. The low grade of usability and the high cost of image guidance systems (200000 euro to 600000 euro for infrastructure plus additional running costs) limit the further development right now. Thinking about navigation the image of driving a car comes into our mind: A navigation system should tell us where to go, show us the shortest and easiest way to our goal - and where and when the driver should be careful. AR/MR and 3D-navigation in liver surgery have not reached this level of immersion right now. If this is really necessary during surgical procedures could be discussed. It could be enough to support the surgeon with some additional information during cardinal steps of a procedure. AI support is up to now not available in hepato-biliary surgery in the operating theater. Many procedures while using AR and 3D-navigation could be facilitated with AI in the future. Especially the problem of soft tissue deformation, which is omnipresent in liver surgery, could be approached by AI techniques.

CONCLUSION

Although there are still many challenges, AR, MR, 3D-navigation and AI are emerging fields in hepato-biliary surgery. The benefit of these sophisticated computerized image guidance techniques should be measured by its impact on clinically relevant outcome parameters in the future. As shown by the huge effort that was made by hepato-biliary surgeons in the past in this field, these techniques will be further developed over the next years.

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Artificial Intelligence in Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

Artif Intell Gastroenterol 2021 August 28; 2(4): 105-110

DOI: 10.35712/aig.v2.i4.105

ISSN 2644-3236 (online)

MINIREVIEWS

Application of artificial intelligence in microbiome study promotes precision medicine for gastric cancer

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Author contributions: Li ZM conceptualized the paper; Li ZM and Zhuang X wrote the paper; all authors read and approved the final manuscript.

Supported by Health Commission of Hubei Province Scientific Research Project, No. WJ2021Q023.

Conflict-of-interest statement: The authors declare that they have no competing interests to disclose.

Manuscript source: Invited manuscript

Specialty type: Gastroenterology

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Abstract

The microbiome has been identified as a causing factor for many cancers. *Helicobacter pylori* contributes to the development of gastric cancer (GC) and impacts disease treatments. The rapid development of sequencing technology is increasingly producing large-scale and complex big data. However, there are many obstacles in the analysis of these data by humans, which limit clinicians from making rapid decisions. Recently, the emergence of artificial intelligence (AI), including machine learning and deep learning, has greatly assisted clinicians in processing and interpreting large microbiome data. This paper reviews the application of AI in the study of the microbiome and discusses its potential in the diagnosis and therapy of GC. We also exemplify strategies for implementing microbiome-based precision medicines for patients with GC.

Key Words: Artificial intelligence; Sequencing; Microbiome; Gastric cancer

Core Tip: Artificial intelligence (AI) helps us understand the role of the microbiome in gastric cancer (GC) and further promote the development precision medicine. AI can be applied in the following three aspects: (1) AI improves the diagnostic accuracy for GC based on big data and gastric microbiome; (2) AI aids pathologists to diagnose gastric biopsies rapidly by sensitively detecting low abundance microbes; and (3) AI regulates individual's dietary intake by giving new insight into host-microbiome

and hepatology

Country/Territory of origin: China

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 16, 2021
Peer-review started: March 16, 2021
First decision: April 15, 2021
Revised: April 22, 2021
Accepted: July 9, 2021
Article in press: July 9, 2021
Published online: August 28, 2021

P-Reviewer: Abreu de Melo MI, Kinami S, Moradi L, Sharma J
S-Editor: Fan JR
L-Editor: Wang TQ
P-Editor: Li JH

interactions.

Citation: Li ZM, Zhuang X. Application of artificial intelligence in microbiome study promotes precision medicine for gastric cancer. *Artif Intell Gastroenterol* 2021; 2(4): 105-110
URL: https://www.wjgnet.com/2644-3236/full/v2/i4/105.htm
DOI: https://dx.doi.org/10.35712/aig.v2.i4.105

INTRODUCTION

Gastric cancer (GC, also known as stomach cancer) is the second leading cause of cancer-related mortality globally, with over 70000 new cases diagnosed every year[1]. The 5-year survival rate of GC is lower than 15%, even in the United States[2]. According to Lauren's criteria, GC can be classified into two main types: Diffuse and intestinal. The diffuse type usually appears in younger patients and tends to be more aggressive, whereas the intestinal type is usually found in older patients and is caused by chronic infection with *Helicobacter pylori* (*H. pylori*)[3]. The microbiota in the stomach is extremely rich and complex[4]. DNA sequencing and computational methods are making astounding advances in the identification of conserved ribosomal RNA (rRNA) genes for pathogenic microorganisms. More than 100 phylotypes have been uncovered in humans, and the majority of gastric microbiota falls within five phyla, including *Bacteroidetes, Firmicutes, Proteobacteria, Actinobacteria*, and *Fusobacteria*. *H. pylori* belongs to *Proteobacteria*. *H. pylori* infection triggers multistep progression from chronic gastritis, atrophic gastritis, and intestinal metaplasia to carcinoma finally. However, the issue of how the gastric microbiota interplays with *H. pylori* (namely, does the gastric microbiota lead to a more virulent *H. pylori* or, *vice versa*, does *H. pylori* facilitate the carcinogenesis of the microbiota?) is still not clear. This might have implications for clinical management.

Artificial intelligence (AI) is the simulation of human intelligence processes by computers and has been applied in various fields, such as image processing and natural language processing. AI is playing an increasingly important role in healthcare. It has been demonstrated that AI algorithms can support humans in simplifying the multidimensional, complex metagenomic data of gene profiling and elucidating the peculiar signatures of beneficial microbes in the gastrointestinal tract [5]. As a core branch of AI, machine learning (ML) focuses on building mathematical models that help machines make predictions or decisions without being explicitly programmed. In the field of ML, deep learning (DL) has become the dominant approach for ongoing work with big data. DL, a subset of ML, is inspired by the information processing system discovered in the human brain. DL uses numerous layers of algorithms (artificial neural networks) to extract higher-level features from raw input. Briefly, ML is a core branch of AI, and DL is performed to implement ML. ML and DL have been successfully used to predict the risk of GC[6].

AI MAKES ACCURATE PREDICTIONS WITH BIG DATA AND THE GASTRIC MICROBIOME

Gastroenterology is a field where AI can make a significant difference. Traditional diagnostic methods have insufficient resolution ability to estimate the invasion depth of early GC in the clinic. Thus, over one-third of advanced GC cases with lesions around the cardia are not easily detected by image-based methods[7]. However, AI-assisted image analysis using endoscopic detection can make more accurate assessments and provide more details than conventional analysis[8]. There are still two main limitations in AI-assisted image analysis. First, there are relatively few data serving as learning and testing materials for building DL models. Second, the diagnostic accuracy is greatly affected when low-resolution images, which endoscopists usually encounter in clinical practice, are input. The above two points may cause certain defects in medical decisions based on image analysis. Remarkably, the combination of AI and the microbiome shows great potential in precision medicine for GC.

High-throughput sequencing is becoming a common technology for typing microbial isolates, especially in clinical samples. Many gene mutations, transcriptional differences, translational differences, epigenetic variations, and metabolic changes have been identified as being associated with the heterogeneity and stage of GC. High-throughput sequencing generates massive microbial data. A deep understanding of microbial data is helpful to explain the relationship between microbes and diseases[9]. Virulence among *H. pylori* strains and host genetic polymorphisms contribute to GC susceptibility. AI algorithms effectively improve our understanding of the gastric microbiota due to two major advantages. First, AI methods can be applied to extract microbial genomic DNA from sequencing samples. Second, AI methods can simultaneously examine all genes in all organisms contained in a sample. Combined with other parameters, such as food habits, duration of infection, and physical activity, AI algorithms can provide better health advice to GC patients. A recent study has started to explore the ability of DL to treat diseases related to gut dysbiosis based on the individual's microbiome pattern[10]. In the future, researchers can develop AI algorithms to regulate the individual's dietary intake and plan their meals when we fully understand the microbiome differences between people with and without disease (Figure 1).

AI IDENTIFIES LOW ABUNDANCE MICROBES USING SEQUENCING DATA

Studying the microbiome composition of primary samples provides a chance to understand the role of pathogenic microorganisms in disease development. In the late 2000s, two large-scale international human microbiome projects (HMPs), Metagenomics of the Human Intestinal Tract[11] and the HMP[12], were initiated to study microorganisms in the human body and to develop computational methods that analyze sequenced metagenomes. However, it seems challenging due to the low number of microbial DNA relative to the host DNA. Accurate identification of the microbiome requires the removal of all possible sequencing reads that originate from human DNA. Bacterial identification was commonly completed by characterization of uniform genomic coverage[13]. For example, the sequence identity of 16S rRNA gene fragments greater than 97% can be classified into separate operational taxonomic units (OTUs), which means the phylogenetic boundaries of different bacterial species[14]. Bacterial identification can also be completed based on coverage along a narrow region of their genomes. For example, analysis of amplicon sequence variants improves the sensitivity and specificity and decreases the problem of inflated microbiota datasets due to falsely identified OTUs originating from misclustered sequences[15]. Recently, Lupolova *et al*[16] found that ML algorithms made a good attribution of the host sources of *S. enterica* serovar Typhimurium isolates[16]. The combination of 16S rRNA gene sequencing data and AI algorithms may reveal the essential role of low-abundance bacteria in the alteration of the gut microbiota composition.

It is challenging to quantify and characterize microbiome profiling in samples where the bacterial content is relatively low. The microbial community in the stomach is typically restricted by the lower luminal pH, which selects for acid-resistant bacterial populations and usually limits the colonization densities to < 1000 colony-forming units per gram (CFU/g)[17]. The current approach for detecting the bacteria of fecal or environmental samples cannot be directly used to analyze the microbiome from the upper gastrointestinal tract, such as the stomach. This is partly because the high amount of human DNA in the samples confounds microbial identification. Klein *et al*[18] designed a DL algorithm that can be used to detect *H. pylori* on regular whole slide images of gastric biopsies, achieving a sensitivity of 100%[18]. Detecting the low abundance bacteria without sample processing facilitates the establishment of a rapid diagnostic method. Recently, we designed magnetic nanoparticles with a broad range of capture potentials *via* electrostatic attractions[19]. This system can rapidly and efficiently capture bacteria at a low concentration of 10 CFU/mL within 1 h. The capture efficiency was more than 90%. It can be used to evaluate the microbiome profile of gastric biopsies in future studies.

AI UNCOVERS HOST-MICROBIOME INTERACTIONS

A comparative study of GC and chronic gastritis using an approach targeting the 16S

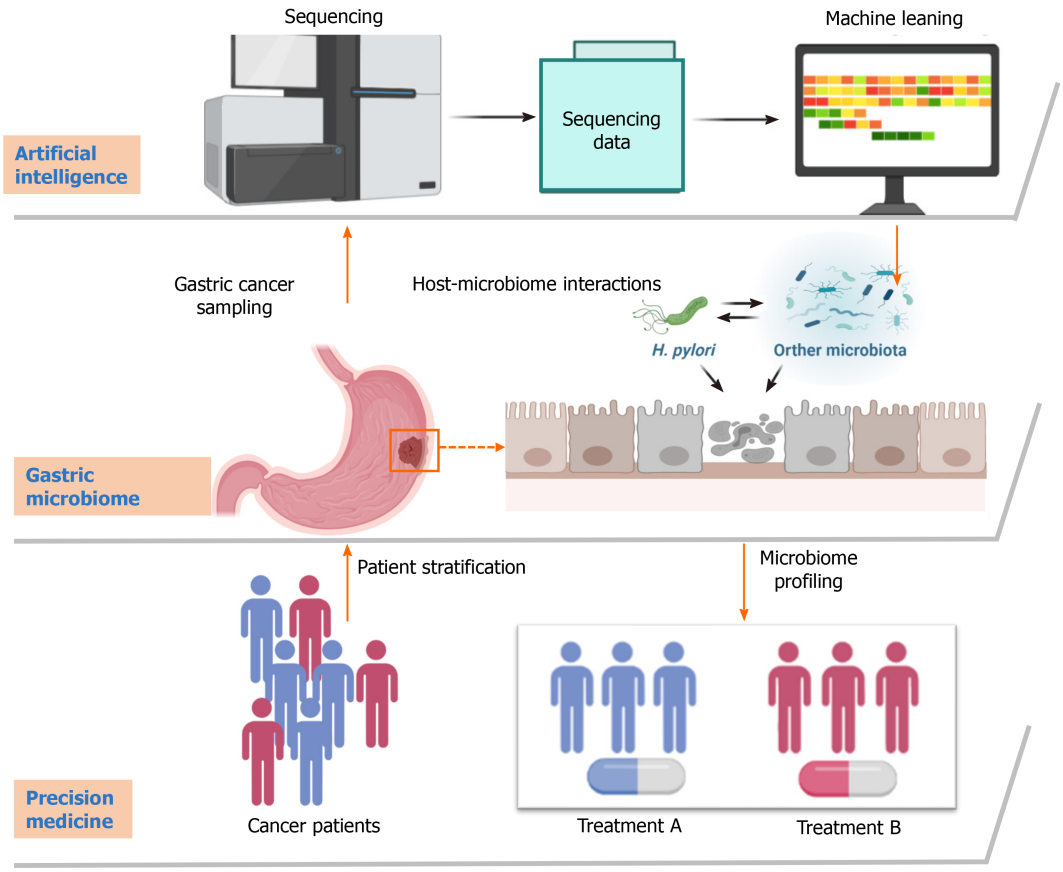

Figure 1 Introducing artificial intelligence and microbiome study to precision medicine for gastric cancer. The sequencing profiles of individual patient microbiomes are analyzed by artificial intelligence (AI), which helps patients to be classified into sub-groups. At the molecular level, AI reveals the molecular mechanisms of microbe-host interactions. At the individual level, AI allows gastric cancer patients to be treated with effective drugs, such as supplementing commensal bacteria, engineered bacteria, and microbiome-targeted drugs.

rRNA gene of mucosal biopsies showed that bacterial diversity was decreased in GC patients[20]. Patients with GC had a large number of non-*Helicobacter* Proteobacteria. Colonization with bacteria other than *H. pylori* breaks the balance between the resident gastric microbiota and the host, which may increase the risk for *H. pylori*-related cancer. Another study evaluated the microbiota composition in normal, peritumoral, and tumoral tissues by 16S rRNA gene profiling and found that microbial diversity was significantly reduced in peritumoral and tumoral microhabitats[21]. *H. pylori*, *Prevotella copri*, and *Bacteroides uniformis* were relatively less abundant in the tumoral microhabitat, whereas *Prevotella melaninogenica*, *Streptococcus anginosus*, and *Propionibacterium acnes* were more abundant. The authors proposed the hypothesis that chronic atrophic gastritis with atrophy (the acidity of the microenvironment of the stomach is reduced) was attributed to *H. pylori* substitution by a cancer-prone microbiota[22]. Additionally, the same research team found a close relationship between the subtype of immune cells (regulatory T cells and plasmacytoid dendritic cells) and gastric microbiota dysbiosis within the tumor microenvironment. It is already known that *H. pylori* infection functions in the development of precancerous lesions, such as chronic gastritis. Nevertheless, the dramatic changes in the composition of the stomach microbiome play a more direct role in the later stages of cancer. Moreover, the microbiome affects the therapeutic response of GC patients, and the treatment also impacts microbial composition. Distal gastrectomy impacts postoperative gut microbiota composition, leading to higher abundances of *Escherichia, Shigella*, *Veillonella*, and *Clostridium XVIII* and a lower abundance of *Bacteroides*[23]. Immune checkpoint inhibitors targeting programmed cell death 1 (PD-1)/programmed cell death ligand 1 were recently added to the therapeutic arsenal for GC. The microbiome composition interferes with the response to these inhibitors. A recent study reported that nonresponders to PD-1 blockade immunotherapy can be distinguished from responders according to the ratio of putatively favorable to unfavorable bacteria[24]. Thus, the role of the microbiome in cancer-immune interactions is gaining much attention. When we learn more about host-microbiome interactions, nonresponders to

checkpoint inhibitors are easier to select and treat by personalized immunotherapy.

Due to the practical limitations of analysis methods, there are still large gaps on how the microbiome mechanically affects host function at the system and community levels. Notably, the past few decades has seen significant work on AI in filling these existing gaps. AI algorithms can co-analyze heterogeneous datasets and capture changes at the microbial and host levels. These methods can be classified into four types: Interfering protein-protein interactions, interfering RNA-mediated interactions, interfering microbe-host metabolic networks, and integrating multiple interspecies and intraspecies networks and omic datasets[25]. The powerful multiomics tools and rapidly developed AI algorithms can greatly enhance or perhaps revolutionize microbiome research. This collaboration provides hopeful expectations to improve our current understanding of GC mechanisms, as well as better detection and treatment.

CONCLUSION

We live in a world surrounded by data and microbes. The gastric microbiome occupies an important position in maintaining the individual's health. A large quantity of complex sequencing data are generated by high-throughput technologies. However, inherent challenges still exist in data processing, including confounding variables from abundant organisms, the integration of different omics data, and the relationships between microbes and their hosts. Currently, big data are easier than ever to analyze due to the assistance of AI technologies. AI is evolving as an important tool for the proposal of new biological hypotheses and the discovery of biomarkers from the available data. In the future, the renewal of the stomach of dysbiosis patients may be achieved by synthetic biology and food engineering based on our understanding of the microbiome and the performance of AI.

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Artificial Intelligence in Gastroenterology

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Artif Intell Gastroenterol 2021 August 28; 2(4): 111-123

DOI: 10.35712/aig.v2.i4.111

ISSN 2644-3236 (online)

MINIREVIEWS

Phase angle through electrical bioimpedance as a predictor of cellularity in inflammatory bowel disease

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Author contributions: All authors contributed to the writing of the article and review of the scientific article; Fernandes SA organized the structure of the article regarding the order of the subheadings covered; Fernandes SA and Pinto LP wrote the introduction; Fernandes SA wrote the conclusion.

Conflict-of-interest statement: All authors declare no conflicts-of-interest related to this article.

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Abstract

It is estimated in Western industrialized countries that inflammatory bowel disease (IBD) has a prevalence of 1 for every 200 inhabitants. In the past, the fat mass disproportionate increase in relation to the fat-free mass was considered uncommon in patients with IBD, due to the observation of the disease being more common with weight loss and malnutrition. However, more in-depth investigations demonstrate that the fat/lean mass disproportion stands out both in prevalence in patients with new diagnoses of ulcerative colitis or Crohn's disease as well as a factor of poor prognosis to the natural evolution of the disease or to the therapeutic response. Another important aspect associated with obesity in IBD is the increased risk of drug clearance [including anti-tumor necrosis factor (TNF) and anti-integrin agents], resulting in short half-life and low trough drug concentrations, since the levels of TNF secreted by adipocytes sequester anti-TNF agents,

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Brazil

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: May 28, 2021
Peer-review started: May 28, 2021
First decision: June 16, 2021
Revised: June 19, 2021
Accepted: July 26, 2021
Article in press: July 26, 2021
Published online: August 28, 2021

P-Reviewer: Wen XL
S-Editor: Liu M
L-Editor: Filipodia
P-Editor: Liu JH

which could result in suboptimal response to biologics. In view of these characteristic aspects of the inflammatory process of IBD, the identification of cellular functioning is necessary, which can be associated with the staging of the underlying disease, biochemical parameters, and body composition, helping as an indicator for a more accurate clinical and nutritional conduct.

Key Words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Phase angle; Cellularity; Bioelectrical impedance

Core Tip: Inflammatory bowel disease (IBD) patients have a severe inflammatory process that negatively reflects their absorption of vitamins and minerals, resulting in poor nutritional status. Even though it has already been described that these patients need a greater supply of calories and proteins, how will we know if the cells of this patient will be able to metabolize and absorb these nutrients to avoid worsening their nutritional status by overfeeding? Having a tool that serves as a guide for cellular functionality and integrity, such as the phase angle through electrical bioimpedance, is of great relevance in the clinical and nutritional management of patients with IBD.

Citation: Fernandes SA, Rossoni C, Koch VW, Imbrizi M, Evangelista-Poderoso R, Pinto LP, Magro DO. Phase angle through electrical bioimpedance as a predictor of cellularity in inflammatory bowel disease. *Artif Intell Gastroenterol* 2021; 2(4): 111-123
URL: https://www.wjgnet.com/2644-3236/full/v2/i4/111.htm
DOI: https://dx.doi.org/10.35712/aig.v2.i4.111

INTRODUCTION

Inflammatory bowel diseases (IBD) are systemic diseases that affect the gastrointestinal tract and can be subdivided into ulcerative colitis (UC) and Crohn's disease (CD)[1,2]. UC is characterized by an inflammatory process of the mucosa, which originates in the rectum and can progress continuously to the other segments of the colon, and CD can directly affect the gastrointestinal tract in all its extension, continuous or discontinuous form (more prevalent), presenting a transmural inflammatory process and being characterized by abscesses or fistula formations between bowel loops or between intestines and other organs[1]. This persistent inflammatory process contributes significantly to the impairment of the patient nutritional status and consequently the clinical condition of malnutrition. What draws a lot of attention is that malnutrition in patients with IBD is in patients with IBD is more prevalent when compared with patients without IBD[3]. The volume loss and/or muscle functionality and/or physical performance is a key marker of malnutrition and/or sarcopenia, in addition the disproportionate relationship between fat mass and lean mass is considered a factor of poor prognosis of the disease or for the therapeutic response[4].

Important tools recommended for assessing nutritional status are software-based anthropometric analyzes, such as bioelectrical impedance analysis (BIA), computed tomography (CT), and dual X-ray absorptiometry (DEXA)[5]. However, the easiest method and access to clinical practice ends up being bioimpedance, but it is not indicated in cases of changes in body composition (BC), such as changes in body fluids. On the other hand, the BIA not only provides the composition distribution within the classic model of compartmentalization of the human body, that is, fat mass and lean mass, but also provides a parameter called phase angle (PA), which through a mathematical formula, using the values of resistance and reactance, being these parameters of evaluation of the vitality and the integrality of the cell. Values above 6 indicate preserved cellular activity[6], in addition to being currently considered an important predictor of morbidity and mortality, taking into account inflammatory processes and nutritional status[4,7-9].

RELATED ASPECTS OF IBD WITH PA

IBD

These diseases had their first phase of acceleration of incidence in the middle of the 19th century, a period in line with a change in life habits brought about by the Industrial Revolution. Subsequently, a new period of increased incidence occurred in the new industrialized countries, in the mid-20th century. Since the 2000s, it has been estimated that in Western industrialized countries, IBDs have a prevalence of 1 for every 200 inhabitants[10,11].

CD can directly affect the gastrointestinal tract in all its extension, and it is traditionally subdivided into phenotypes considering: (1) Non-penetrating, non-stenosing inflammatory involvement; (2) Stenosing involvement, resulting from fibrosis; and (3) Penetrating disease, characterized by abscesses or fistula formations between bowel loops or intestines and other organs. The disease occurs in cycles of inflammatory outbreaks and may cause the progression of its structural data[1].

UC occurs through the inflammatory affection of the mucosa, starting in the rectum, being able to progress continuously to the other segments of the colon. As in CD, the exact pathogenesis of the disease is not completely clarified, but four factors are related: Genetic susceptibility, intestinal microbial flora, uncontrolled immune response, and external environmental factors[2].

There are several environmental factors related both to the genesis of the disease and to the exacerbation of the inflammatory condition, among them smoking, low consumption of vitamin D, use of non-steroidal anti-inflammatory drugs, use of antibiotics, depression and psychosocial stress, low dietary fiber consumption, and high dietary consumption of fats and proteins[1,10].

Eating habits have been changing over time and may have been a crucial factor in the higher prevalence of IBD in Europe and North America. The dynamic changes in the diet of industrialized countries may be related to the increased incidence of IBD in these countries. It is worth remembering that when highlighting the diet in the pathogenesis of these diseases, the interaction between diet, microbiome, and mucosal barrier integrity must be emphasized, which are interconnected factors. The breakdown of hemostasis between such components can increase the chances of developing the disease or controlling the disease in those patients already diagnosed [12].

In 1988, Sonnenberg[13] published his pioneering study associating increased consumption of sugar and margarine with the highest incidence of CD in Europe. Since then, several other studies have corroborated that the high-fat diet is a risk factor for the development of IBD as well as for the disease control. It is important to highlight the differences between the types of fat and their impact on disease: The pro-inflammatory potential of ω-6 polyunsaturated essential fatty acids, the association between long-chain triglycerides, and the stimulation of the proliferation of intestinal lymphocytes as well as the pro-inflammatory mediators and the action of the high-fat diet capable of reducing intestinal permeability and increasing serum levels of endotoxins[14].

In the past, the disproportionate increase in fat mass in relation to the fat-free mass (FFM) was considered uncommon in patients with IBD, due to the observation of the disease being more common with weight loss and malnutrition. However, more in-depth investigations demonstrate that the fat/lean mass disproportion stands out both in prevalence in patients with new diagnoses of UC or CD, as well as a factor of poor prognosis to the natural evolution of the disease or to the therapeutic response[15].

It is important to highlight the pathogenic mechanism of IBD, as its aggression process significantly compromises the proper cellular functioning and, consequently, the individual's homeostasis.

The pathogenesis of IBD-CD and UC-remains unclear. We know that intestinal inflammation results from a dysregulation of the immune system in response to changes in the commensal intestinal microbiota (non-pathogenic). Genetic studies have shown that interactions between microbiota and host have a prominent role in the pathogenesis of IBD and involve genomic regions that regulate defense against microorganisms and intestinal inflammation[16].

Among the genetic findings, some of the most cited are involving nucleotide oligomerization domain 2, autophagy genes, and components of the interleukin route 23 - helper T cell 17 (IL23/Th17), which regulate intestinal immune mechanisms[17].

The gut microbiota, in its role of modulating the intestinal inflammatory response, when altered by environmental factors such as diet, obesity, exposure to helminths, and the use of antibiotics, can lead to an increased risk of developing IBD. In patients with IBD, changes in the diversity and density of bacteria (and even viruses and

fungi), and in the functions of the bacteria present (oxidative stress, nutritional regulation) have been described[18-20]. It is still unclear what exactly are the microorganisms involved, but recent studies show the importance of the phyla Firmicutes and Proteobacteria in the pathogenesis of IBD[19].

Other environmental factors such as geography (higher incidence in industrialized countries), diet high in fat and sugar and poor in fruits and vegetables, smoking, psychological stress, appendectomy, and medications also alter the risk for IBD[21].

Immune dysregulation in IBDs is characterized by epithelial damage (abnormal mucus production and inadequate cell repair), inflammatory increase *via* microbiota, and cell infiltration in the lamina propria, including T cells, B cells, macrophages, dendritic cells, and neutrophils, causing a failure immune regulation in the face of the inflammatory process. The cells activated in the lamina propria produce high levels of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1-β, interferon-gamma, and IL23/Th17[21].

The immune system is divided into innate immunity and adaptive immunity. Innate immunity includes the function of the epithelial barrier of the intestinal mucosa, antibacterial proteins, pH of the stomach limiting microbial growth, innate immunity cells such as neutrophils, macrophages, dendritic cells, and natural killer T cells, in addition to cytokines and innate molecules (IL-1, TNF, denfensins). Adaptive immunity is pathogen-specific and usually initiated in circumstances in which innate immunity is not effective in isolation from the pathogen's aggression. After exposure to the pathogen, it usually takes several days to activate finally the adaptive immune response, including T and B cells. The microbiome's immune response is regulated in response to the aggressor's action, and it is this regulation that determines the immune protection of the microbiota or exacerbated inflammatory response with significant cellular damage. This regulatory compromise of immune action causes IBD[21].

By understanding the inflammatory routes involved in IBD, we can analyze some of the most used drugs for its treatment. The first to be used were corticosteroids, which manage to induce remission in most cases but have important adverse effects in the long term[22], not being indicated for the period of maintenance and control of the disease. Drugs such as azathioprine and methotrexate are also indicated for their immunosuppressive effects, including in combination with anti-TNF drugs[23-26]. Anti-TNF (infliximab, adalimumab, certolizumab), anti-interleukin 12/23 (ustekinumab), and anti-integrin (vedolizumab) present more complex actions on immunological routes according to their degree of cell selectivity, which is directly related to the profile medication safety[26-29].

As previously stated, the inflammatory process of IBD and the effective immune response to this inflammation have a direct connection with the patient's food intake as well as his nutritional status[21].

Nutritional status in IBD

Patients with UC and CD may be affected by malnutrition (6% and 22%)[3,30,31], but the prevalence is greater in CD, given its capacity to affect one or more parts of the gastrointestinal tract, reducing the absorption of macro and micronutrients[4]. Lack of treatment response, fistulizing and stenotic phenotypes, and previous bowel resections in CD are typical aspects of patients with higher risk of malnutrition[30].

Malnutrition in IBD is five times higher when compared with non-IBD patients[3]. According to the European Crohn's and Colitis Organization, IBD subjects should be routinely screened for malnutrition. Body mass index (BMI) and involuntary weight change should be assessed[30].

There are significant differences in nutritional status in IBD. CD patients remain malnourished for longer periods, with higher protein-energy malnutrition[5] and impaired absorption of micronutrients. On the other hand, UC patients have more protein-energy malnutrition during disease activity or hospitalization[30,32-34].

Symptoms that cause weight loss with depletion of body fat deposit, muscle mass, and fluid loss are diarrhea, high-output fistulas, decreased appetite, and restrictive diets often imposed in structuring disease during a flare[3,4,30,34]. Patients with active disease commonly have nausea, vomiting, abdominal pain, anorexia due to inflammation, and medication[6]. Inflammatory response mediated by pro-inflammatory cytokines such as TNF and IL-1 and 6, increasing energy expenditure, and anorexigenic hormones contribute to undernutrition[7]. Active inflammation leads to chronic anemia and protein loss within the intestinal lumen[34].

Chronic bowel inflammation or intestinal surgery may accelerate the intestinal transit resulting in increased stool volume and diarrhea, as well as the loss of epithelial integrity and small intestine bacterial overgrowth. Increased motility can cause malabsorption, altered BC, and micronutrient deficiencies[6,9]. CD patients with ileal

involvement frequently have reduced nutrient absorption, mainly vitamins C, B12, D, K, folate, and magnesium[30,33].

Micronutrient deficiency in IBD is often associated with disease complications[2,4] as well as the use of certain medications. Glucocorticoids can reduce calcium, zinc, vitamin D, and phosphorus contributing to osteoporosis. Methotrexate and sulfasalazine therapies, used for long periods, might impair the absorption of folic acid causing anemia[32,34].

Malnutrition in patients with IBD should be treated adequately because it worsens prognosis, increases complication rates and mortality, and decreases quality of life[4]. Micronutrient deficiency should be corrected and is best achieved by a multidisciplinary team[2]. There is low staff awareness on the role of nutrition in patient care, and this can be the main barrier for nutrition recognition and optimization[30,35].

While in Europe and Asia CD patients usually gave have a lower BMI ≤ 18.5 kg/m^2, in the United States, obesity (BMI ≥ 30.0 kg/m^2) is more common in IBD patients, probably associated with local dietary habits[30]. The prevalence of obesity in IBD is 15%-40%, and an additional 20%-40% are overweight[31,36]. An important feature in obese patients with CD is the loss of lean mass[4] and sarcopenia (low muscle strength combined with low muscle mass or quality)[30,33,34].

Disproportional accumulation of visceral fat (VF) can be observed in CD patients[34, 37,38] regardless of nutritional status and may be associated with the maintenance of disease activity due to an overexpression of pro-inflammatory adipokines[31] and increased levels of lipopolysaccharides (LPS). Serum levels of LPS were correlated with the severity of the disease and were observed an increase 6-fold and 2-fold in activity CD and remission CD, respectively, when compared to controls[39].

The ratio of VF/BMI (expressed in grams of fat per BMI) was increased both in malnourished and obese CD patients when compared to controls, indicating the possible presence of an adiposopathy by a higher VF tissue volume[30]. The degree of VF may be caused by several factors, including corticosteroid use, prior abdominal surgery, structuring disease or penetrating complications, and CD activity[40].

Another important aspect associated with obesity in IBD is the increased risk of drug clearance (including anti-TNF and anti-integrin agents), resulting in short half-life and low trough drug concentrations since the levels of TNF secreted by adipocytes sequester anti-TNF agents, which could result in suboptimal response to biologics[7, 36].

The risk of complications, hospitalizations, and infections might be increased in obese patients with IBD, and nutritional therapy for obesity could be a potential adjunct therapeutic target in patients with IBD[36,37].

The type and distribution of abdominal fat were associated with complicated disease in patients with IBD[41]. The use of corticosteroids increases body fat and decreases lean mass. Loss of muscle mass can occur during IBD and has been associated with increased morbidity and risk of infectious complications[42].

A systematic review demonstrated that approximately one-third of CD patients have altered BC, with reduced BMI, FFM, and fatty mass when compared with controls, despite only 5% being underweight by BMI criteria[7]. Taken alone, BMI is inaccurate for assessing BC[8]. CD patients have lower lean mass when compared to UC. Body fat decreases with increasing disease severity and FFM decreases with longer duration of the disease in both CD and UC[43].

Muscle loss is a key marker of malnutrition or sarcopenia, although the ability to monitor accurately lean tissue in clinical is limited[7]. Important recommended tools to evaluate the nutritional status are software-based analysis anthropometries such as BIA, CT, and DEXA[5].

ELECTRICAL BIA

The compartmentalization of the human body, not only in the classic model usually used in clinical practice, in which it is evaluated only the BC in fat mass and FFM, but also the cellular analysis as proposed by Ellis[44], has been applied studied.

BIA provides us with data on the evaluated substrate in relation to its physical dimensions or changes in its conductive properties, where these properties may change due to changes in electrochemical processes, temperature, pH, hydration status, and viscosity of the fluid or biological tissue analyzed. With this information, it is feasible to monitor possible physiological changes in different living beings[45].

In different disease situations, the evaluation of the composition of the cellular structure and whether it has functioned has shown very important indexes in the

patient's prognosis, becoming an independent factor of mortality[46,47]

Compared to other methods of assessing BC with independent measurement by the observer, the BIA method is characterized by making a quick, non-invasive, low-cost, and portable measurement without presenting any risk to the patient[48]. Its electrical current is imperceptible, as it has a low amplitude (800 μA) and a high frequency (50 kHz), enough to generate resistance to non-energy-conducting tissues and at the same time evaluate cell viability. In this body evaluation, there are two parameters of great importance: Body resistance (R) and reactance (Xc). R is the opposition offered by the body to the passage of electrical current, being inversely related to water and electrolytes contained in body tissues. Xc is the capacitance (viability) of the cell membrane properties, which may vary due to its integrity, function, and composition [49].

Tissues of increased fluid and electrolytic composition such as cerebrospinal fluid, blood, muscles, are high electrical conductors. Fatty tissues, bones, and the air that fills some spaces in the body, such as the lungs, are highly resistant to electric current[50]. The conductivity of biological tissues is practically ionic, that is, the electrical charges are transferred by the ionization of salts, bases, and acids dissolved in the body fluid [51]. Therefore, biological conductivity is directly proportional to the amount of body fluid volume. For this reason, in the patient who is in a state of hyperhydration, the value of lean mass is overestimated, with changes in the result of the body evaluation being one of the limitations of this method[50]

Bearing in mind that BIA is based on the theory of body symmetry, where the level of hydration and the percentage of fat are constant, when we are faced with different realities, with age group, ethnic group, body shape, or different clinical conditions, we do not have "universal" equations used in all situations, requiring another parameter as a reference point[52].

In view of these diversities, the clinically established bioimpedance parameter is the PA. The PA is calculated from the mathematical formula PA = tangent arc (Xc/R) x 180, which considers R and Xc. In addition, the relationship of these components of the current results in a geometric graph, where the relationship of R and Xc will result in an angle then defined as PA (Figure 1)[53,54].

PA has gained popularity in recent years as it is a fast method, applicable in the clinic and that reflects cell vitality and integrality, where the higher values indicate preserved cell activity[6,53,55,56]. In healthy individuals, PA can vary between 6° and 7°[53].

Because it is considered an important predictor of health status including inflammation, malnutrition, and disease, low PA values are associated with apoptosis or alteration in the selective permeability of membranes, compromising their integrity and metabolic functions[4,7-9]. High PA indicates intact cell membranes and high body cell mass, showing a good relationship also with the skeletal muscle structure preserved in its volume and/or functionality. Thus, PA can be one of the markers for monitoring nutritional status[9].

There are still few published studies regarding the use of PA and assessment of nutritional status in IBD[3,8].

Emerenziani *et al*[34] evaluated the nutritional status and PA in CD patients who received conventional therapy and anti-TNF therapy and concluded that mean values of PA and FFM were significantly lower in patients under conventional therapy when compared with controls and patients with infliximab therapy. Mean PA value increased from 4.6 ± 0.3 to 6.2 ± 0.4 ($P < 0.05$), after the induction therapy with infliximab (12 ± 2 wk)[7]. Conversely, another study that also assessed the impact of biological therapy on BC of patients with CD did not observed difference between the PA values after 6 mo of infliximab therapy (6.2 *vs* 6.8; $P = 0.94$)[42].

Back *et al*[57] compared BC in patients with CD and UC and found that patients with CD have more impaired nutritional status when compared to patients with UC (PA 6.46 ± 0.76 and 6.83 ± 0.080; $P = 0.006$)[3]. In another UC study, with 59 patients in clinical remission (94.9%), the PA had a negative correlation with inflammatory markers, C-reactive protein (CRP) ($r = 0.59$; $P < 0.001$), and erythrocyte sedimentation rate ($r = 0.46$; $P < 0.001$) and positive correlation with lean mass[58].

Mentella *et al*[38] investigated the association of disease activity, BMI, and PA with vitamin D deficiency in patients with IBD and reported a negative association between BMI and vitamin D serum levels in both CD and UC patients ($P < 0.01$), and PA was associated to hypovitaminosis D in both groups (CD: Odds ratio = 0.64, $P < 0.05$; UC: Odds ratio = 0.49, $P < 0.01$).

Recently, Cioffi *et al*[8] showed that BIA-derived PA is a valid indicator of nutritional status in CD patients, the values decrease with increasing disease activity, and PA was slightly better in patients receiving biologic therapy (infliximab).

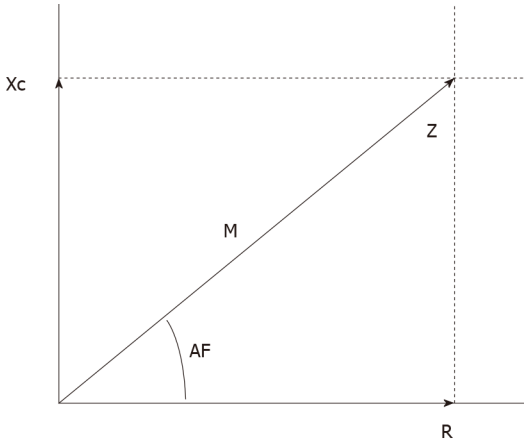

Figure 1 The relation of body resistance and reactance that results in a geometric graph indicating the angulation of the electric current according to the cellular structure. Adapted Kyle *et al*[50]. R: Body resistance; Xc: Reactance.

PA might be considered a valid tool to assess nutritional status in IBD patients, as supported by nutritional biomarker evaluation[8] or as a complement of the other nutrition assessment methods. Its measurement in isolation may not be sensitive enough to capture all factors that can influence nutritional status[9].

It is possible to associate laboratory parameters with PA so that their values show greater reliability to the actual clinical condition of the patient with IBD. When analyzing the association between PA and biochemical parameters, previous studies have shown that hemoglobin was lower in patients with CD with active disease, compared to those in remission. Albumin, CRP, and total protein did not differ between groups with active and remission CD and, interestingly, all serum protein parameters, such as albumin, pre-albumin, and total protein, were directly correlated to PA. However, fibrinogen and CRP were inversely associated[8].

The cellular nutrition for its preservation of functionality and structure is very important for a good response to treatment of IBD, including the surgical approach in the pre, peri, and post-operative period[4,8,42].

IBD, nutrition in surgery

The clinical intractability of IBDs is one of the main factors for surgical indication (Figure 2)[59,30]. People with CD may need at least one surgery throughout their lives, that is about 80% to 90%, of which 50% will need the second surgery and 25% a third surgery. Patients with CD and UC will undergo one or more surgical procedures during their lifetime, 47% and 16%, respectively[61-64].

In CD, the location of the disease (ileal, colonic, ileocolic), the severity of symptoms (disease activity), the history of previous surgeries, the presence of very complex diseases, and the nutritional status are conditioning factors in the definition of the surgical procedure (colectomy total proctocolectomy, total recto colectomy). A weight loss of ≥ 15% in 3 mo and hypoalbuminemia (< 2.5 g/dL) are risk factors for surgical complications, which can be increased in patients who received biological therapy preoperatively[30,64-66].

Some data related to nutritional aspects are noteworthy when considering surgical intervention. At an outpatient level, the nutritional deficit of patients with CD is between 50% and 60% and in UC between 50% and 60%[64]. This malnutrition condition increases, when hospitalized, that is, about 80% to 90% and 60% to 70% of CD and UC, respectively. Considering this scenario, nutritional screening for the identification of patients at risk should be performed routinely, since it is an indication of the need for early nutritional intervention. The following tools are recommended: Perioperative nutrition screen score or nutritional risk screening 2002[30], associated with the analysis of the percentage of weight loss, biochemistry, food intake, and BC, since these changes are directly related to postoperative[30,67,68] complications, due to nutritional deficit and immunological[68].

With the advances of studies that seek to evaluate changes in BC and their impact on IBD, the presence of sarcopenia stands out. Ryan *et al*[69] demonstrated that 52% of patients with CD and 37% with UC had sarcopenia. The impact of changes in BC in IBD promotes undesirable consequences such as bone demineralization (osteopenia and osteoporosis), inadequate response to therapy, impaired surgical response, and

Ulcerative retocolitis	Crohn's disease
Clinical intractability	Clinical intractability
Growth retardation / child	Growth retardation / child
Extraintestinal manifestations (pyoderma gangrenosum)	Extraintestinal manifestations
Presence of high-grade dysplasia or adenocarcinoma in the colorectal segment	High-grade dysplasia
	Presence of adenocarcinoma
Emergency surgery: Hemorrhage, intestinal obstruction, toxic megacolon and intestinal perforation	Bowel obstruction
	Refractory intestinal subocclusion
	Internal and external fistulas
	Palpable abdominal mass
	Perianal disease

Figure 2 Factors of indication for surgery in inflammatory bowel diseases. Adapted from Rubin *et al*[59].

poor quality of life[69-71]. In addition to these, Erős *et al*[72], identified sarcopenia, through meta-analysis, as an independent predictor of surgical complications. These showed reduced fat and reduced body fat mass, according to the increase in the severity and duration of IBD, respectively.

Fiorindi *et al*[73] conducted an intervention study with 61 IBD patients (45 CD and 16 UC) that sought to analyze the effect of long-term nutritional pre-rehabilitation on the postoperative result in elective surgery for IBD. In the initial assessment, muscle mass reduction was present in 28% of the cases and significantly associated with the presence of ileostomy and a previously performed IBD surgery. During the preoperative, intervention phase, there was an improvement in body weight, BMI, fat free mass, fat free mass index, and the PA[43].

Despite this, PA derived from electrical bioimpedance is a valid indicator of nutritional status in patients with CD, since its values decrease with the increase in disease activity, a clinical condition that is decisive in the decision of the surgical procedure in IBD. Thus, the assessment of BC should be recommended in clinical practice for the screening, monitoring, and determination of nutritional intervention, even in the preoperative period of patients with IBD[4,8,42,74].

This nutritional intervention when performed early, with the objective of nutritional rehabilitation in the preoperative of elective surgeries, ERAS Principles, demonstrates positive responses in the modulation of the BC of individuals with IBD. And so, it represents an important strategy to mitigate the response to surgical stress in lean tissue, even more evident in patients who are at high nutritional risk. Likewise, the use of early nutritional therapy in the postoperative period will provide a significantly reduced hospital stay and a faster recovery of intestinal function[8,30,63].

Still within the context of artificial intelligence and the improvement in the assessment of BC, proposals for the use of raw BIA measures can be an interesting alternative for populations where the use of regression formulas does not apply. In addition to using the isolated PA as a prognostic marker, R and Xc have been used graphically in a method called the electrical bioimpedance vector (BIVA)[75].

This method consists of the direct analysis of the R and Xc vectors, where their clinical applicability depends on a healthy reference population for comparison. The measurements must be adjusted by the height (H) of each individual and recorded in a Cartesian plane where the horizontal axis represents the standardized resistance for the height (R/H) and the vertical axis represents the reactance standardized by the height (Xc/H). Ellipses of tolerance of 50%, 75%, and 95% (or Z score), of the reference population, are drawn from a centralized mean vector[76,77].

The vector of the studied population will be compared with that of the reference population, determining within which Z score range it is for hydration information, cell body mass, and cell integrity[77].

From validation studies with different populations and diseases, the position of the vector on the graph brought clinical significance to the method. Not only as a classification of a single measure, the method also allows the monitoring and change of BC status[78].

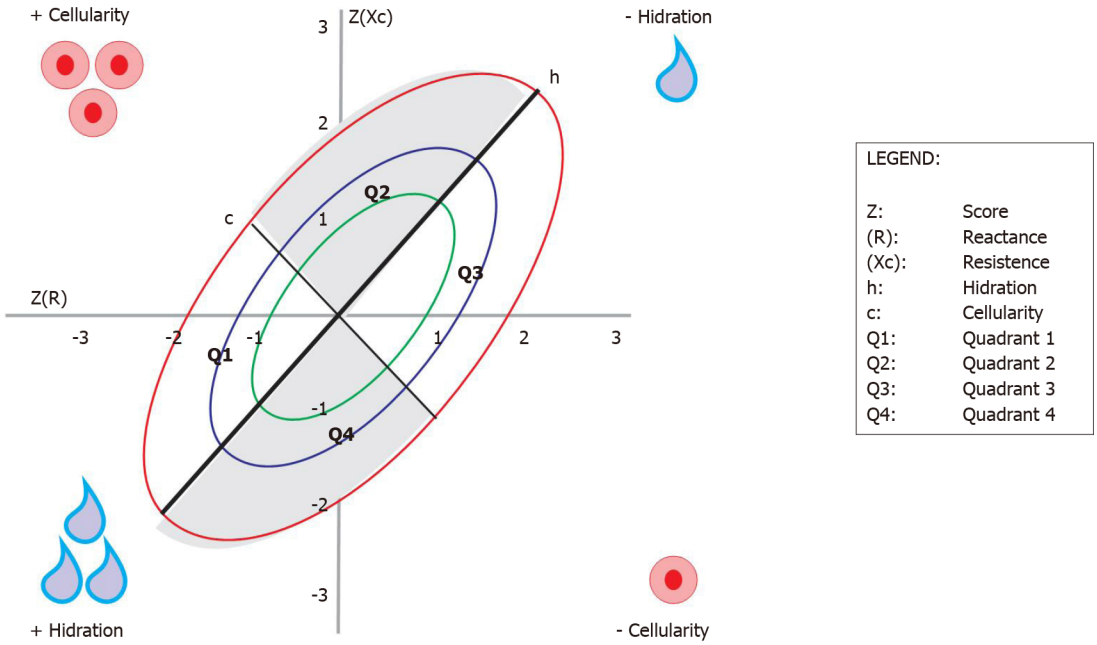

Figure 3 Graphic representation of electrical bioimpedance vector by quadrants and ellipses, according to body conditions[79]. Fernandes SA, Leonhardt LR, da Silva DM, Alves FD, Marroni CA. Bioelectrical impedance vector analysis evaluates cellularity and hydration in cirrhotic patients. *World J Hepatol* 2020; 12: 1276-1288. Copyright ©The Author(s) 2020. Published by Baishideng Publishing Group Inc.

The upward or downward displacement of vectors parallel to the largest axis of the ellipse indicates a progressive change in tissue hydration (dehydration towards the upper pole; hyperhydration with apparent edema towards the lower pole). Vectors migrating parallel to the smallest axis, above on the left, indicate more cell mass and, below on the right, indicate less body cell mass (Figure 3)[79].

When changes in nutritional status and hydration occur simultaneously, the vectors migrate in the two main directions. In the context of IBD, to date, there are no studies using the BIVA to study the degrees of hydration and cellularity of these pediatric or adult patients.

CONCLUSION

Assessing the individual's cellular condition has shown to be a watershed in the therapeutic planning of patients, whether in the clinical and/or nutritional approach. Given this knowledge, the PA is shown to be a very important parameter in this context of cellularity, because in addition to informing the integrality and cellular functionality, it is a method independent of the observer. In different populations, the PA is an independent marker of mortality and is indicated as a parameter for monitoring clinical and nutritional prognosis. We show in this bibliographic review that there are some studies on IBD and PA and their importance in the management of these patients, making the therapeutic approach more accurate and expanding a long-term vision for the result of sustained remission of the disease. It should be noted that there are still few studies that address the PA and IBD and none using the BIVA method in this population, which indicates an area of research to be explored.

ACKNOWLEDGEMENTS

Our consideration to the GEDIIB - Study group on inflammatory bowel disease in Brazil.

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Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
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ISSN 2644-3236 (online)

Artificial Intelligence in *Gastroenterology*

Artif Intell Gastroenterol 2021 October 28; 2(5): 124-140

Published by Baishideng Publishing Group Inc

A I G

Artificial Intelligence in Gastroenterology

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Artificial Intelligence in Gastroenterology

Bimonthly Volume 2 Number 5 October 28, 2021

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AIMS AND SCOPE

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

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

INDEXING/ABSTRACTING

There is currently no indexing.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Jia-Hui Li*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jin-Lei Wang*.

NAME OF JOURNAL
Artificial Intelligence in Gastroenterology

ISSN
ISSN 2644-3236 (online)

LAUNCH DATE
July 28, 2020

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Rajvinder Singh, Ferruccio Bonino

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2644-3236/editorialboard.htm

PUBLICATION DATE
October 28, 2021

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Artif Intell Gastroenterol 2021 October 28; 2(5): 124-132

DOI: 10.35712/aig.v2.i5.124

ISSN 2644-3236 (online)

MINIREVIEWS

Artificial intelligence for cancer detection in upper gastrointestinal endoscopy, current status, and future aspirations

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Author contributions: El-Nakeep S formulated the research question and done the literature search and provided the medical background of the topic; El-Nakeep M provided the technical and engineering and computational background of the topic and the intellectual explanation of the methods of artificial intelligence; Both authors wrote and approved the final submitted draft.

Conflict-of-interest statement: The authors declare they have no conflict of interest.

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Abstract

This minireview discusses the benefits and pitfalls of machine learning, and artificial intelligence in upper gastrointestinal endoscopy for the detection and characterization of neoplasms. We have reviewed the literature for relevant publications on the topic using PubMed, IEEE, Science Direct, and Google Scholar databases. We discussed the phases of machine learning and the importance of advanced imaging techniques in upper gastrointestinal endoscopy and its association with artificial intelligence.

Key Words: Artificial intelligence; Upper gastrointestinal endoscopy; Esophageal cancer, Gastric cancer, Barrett's esophagus

Core Tip: This minireview aims to explore an important topic; the role of artificial intelligence in upper gastrointestinal (GI) endoscopy detection of cancer. We tried to delineate the most common obstacles encountered when trying to implement artificial intelligence in upper GI endoscopy for cancer detection and characterization. Moreover, we tried to outline the future prospects of this technique, along with its benefits, and uncertainties. This topic summarizes the wide scope for integration of

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Egypt

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: June 6, 2021
Peer-review started: June 6, 2021
First decision: June 23, 2021
Revised: June 26, 2021
Accepted: September 1, 2021
Article in press: September 1, 2021
Published online: October 28, 2021

P-Reviewer: Wang G, Yasuda T, Yu H
S-Editor: Liu M
L-Editor: A
P-Editor: Li JH

artificial intelligence, between the practicing physicians and the computational engineers and how their collaboration could provide a better healthcare services.

Citation: El-Nakeep S, El-Nakeep M. Artificial intelligence for cancer detection in upper gastrointestinal endoscopy, current status, and future aspirations. *Artif Intell Gastroenterol* 2021; 2(5): 124-132
URL: https://www.wjgnet.com/2644-3236/full/v2/i5/124.htm
DOI: https://dx.doi.org/10.35712/aig.v2.i5.124

INTRODUCTION

Upper gastrointestinal (GI) cancers affecting the esophagus and stomach are responsible for more than one and half million annual deaths worldwide. Both are considered aggressive cancers, discovered mostly at an advanced stage, when curative measures are no longer applicable[1].

The current standard method for diagnosis of upper GI cancers is upper GI endoscopy and biopsy, using a white light endoscopy. The most common upper GI cancers encountered are esophageal adenocarcinoma, Barrett's esophagus (BE) and gastric cancer[2]. Artificial intelligence (AI) could add more accuracy to early cancerous and precancerous lesion detection in the upper GI during endoscopic evaluation[3].

Regardless of the great progress of AI in colonoscopy examinations, the integration of AI in upper GI endoscopy is still a new area of research with only a few pilot studies available, mostly due to unavailability of large datasets annotating upper GI cancers[2].

A recent meta-analysis examined the effect of AI in detecting *Helicobacter pylori* (*H. pylori*) infection during upper GI endoscopy, and found eight studies with pooled sensitivity of 87%, and specificity of 86%[4]. Moreover, another study combined the effect of neoplasm detection and *H. pylori* infection status, and found twenty-three studies with high pooled diagnostic accuracy in upper GI neoplasms; 96 in gastric cancer, 96% in BE, 88% in squamous esophagus and 92% in *H. pylori* detection[5].

IMPORTANCE OF USING AI IN UPPER GI ENDOSCOPY

The miss rate of detecting upper GI cancers reaches 11.3% according to a meta-analysis by Menon and Trudgill[6], and even higher rates could be observed in superficial neoplasms, reaching 75% (*i.e.*, gastric superficial neoplasia)[7]. According to a recent meta-analysis by Arribas *et al*[3], using AI integrated upper GI endoscopy yielded pooled sensitivity of 90%, and specificity of 89% for detection of neoplastic lesions, independent of the type of neoplasia (whether esophageal adenocarcinoma, BE, or gastric adenocarcinoma).

Expert sensitivity and specificity criteria in detecting the upper GI tumors differ from the detection and characterization of colorectal polyps for a few reasons. First, due to over-specialization of certain types of upper GI cancers according to the geographical prevalence of the cancer, for example, in the gastroenterologist's practice, resulting in limited training for the detection of non-prevalent types of cancers. AI integrated systems don't suffer the same geographical bias, thus offering better detection independent of the prevalence of GI cancer types[3]. Colon cancer prevalence is higher, enabling more data storage and more training.

The second reason, lesions that are minimal (in size or in depth) or hard to visualize by the inexperienced endoscopist, could be easily detected using the AI assistance[2]. Furthermore, gastric cancer lesions can be masked after eradication of *H. pylori*, this masking is due to regression of the mucosal elevation (decrease in its height) caused by the regression of chronic inflammatory process of *H. pylori* infection, or due to the coverage of the neoplastic area with atypical mucosa or even healthy columnar mucosa[8,9]. Advanced imaging techniques[10], when associated with AI, might help in detection of these masked neoplastic lesions.

Third reason being that training is not adequate in postgraduate courses, either because of insufficient interest (due to different cancer prevalence), or insufficient resources (especially for the computer simulation programs)[11]. However, an AI cumulative sensitivity of 91% for early-stage neoplasia proves that AI integrated systems will increase the efficacy of diagnostic upper GI endoscopy immensely. Thus, there is an urgent need for AI implementation in the clinical setting, even more urgent than the lower GI colonoscopy. Diagnostic settings have the issue of less experienced endoscopists compared to intervention intended settings, so early cancerous lesions tend to be easily overlooked (undetected)[3]. This of course will not eliminate the need for experienced endoscopists; however, integration with AI will have the best yield [12], considering that most of the upper GI lesions are non-polypoid which require higher level of skills for detection than colorectal cancer.

AI IN UPPER GI ENDOSCOPY

Machine learning (ML) must pass through multiple phases for validation in both training and testing (as shown in Figure 1). The AI used in endoscopy is ML, the most prevalent type of ML is deep learning (DL).

The first wave of AI was logic based handcrafted knowledge. In this logic-based handcrafted algorithms were developed separately for each task. This allowed the reasoning behind decisions of the first wave to be quite high, because every step of decision was handcrafted. However, the machine was unable to learn. The second wave of AI (the current wave) is the statistical ML in which the machines can learn from data, with an easily implemented learning algorithm, to generate a model used to carry out decisions. This eliminates the difficult part of designing and implementing a task-specific algorithm. While this raised the level of ML, it also caused a huge decline in the reasoning for the decisions. This means that the reasoning behind a wrong decision becomes hard to identify, rendering the algorithm a black box. The best way to avoid highly wrong decision rates is for provide a large amount of variable data to the machine to learn from[13].

ML passes through many phases. First phase is the training phase; where an annotated dataset is used to train the ML system, and then validated by determining the number of images it correctly identified. Second is the testing phase where a non-annotated dataset is given to the ML system to examine its diagnostic capabilities in comparison to experts in the field, and then using this ML system in a clinical setting, either in real time or in prospective trials to evaluate its performance in a real-world clinical setting.

There are two types of gastric lesion examinations identified during upper GI endoscopy using AI: (as shown in Figure 2): (1) Lesion detection (to know whether it is present or absent) and localization (to know its exact location in the GI tract); and (2) Lesion characterization (to assess its histological prediction).

The first type uses images with low or moderate quality, but the second type uses advanced optical diagnostic tools including: Narrow band imaging (NBI), chromoendoscopy, endocytoscopy, optical magnification, among others[14,15]. All types use semi-automatic identification, where the endoscopist delineates the affected area and centers the polyp near the endoscope lens for better visualization[14]. Invasion depth has been successfully predicted (with 89% diagnostic accuracy) through coding systems that are not very complicated, a proposed implementation of automated DL models in gastric cancers. Furthermore, another proposed implementation of a modified version by the same author is faster by 13 min in the test stage on unknown data, but has a slightly lower accuracy of 82%, with similar performance to experts and higher than trainees[16].

CURRENT STATUS, WHAT IS ACHIEVED AND WHAT IS NOT

If feasibility and usefulness of non-real time can be proved, then technical feasibility of real time is achievable, with an increased degree of sophistication of implementation and cost. Improvement of this real time feasibility could be accomplished through software programming of graphic processing unit (GPU) and central processing unit (CPU), along with implementation of specialized hardware systems.

Most implementations in AI use DL algorithms such as convolutional neural network (CNN). Wu *et al*[17] did the only randomized controlled trial (RCT) available on the topic. The team examined the diagnostic accuracy of their AI system using a

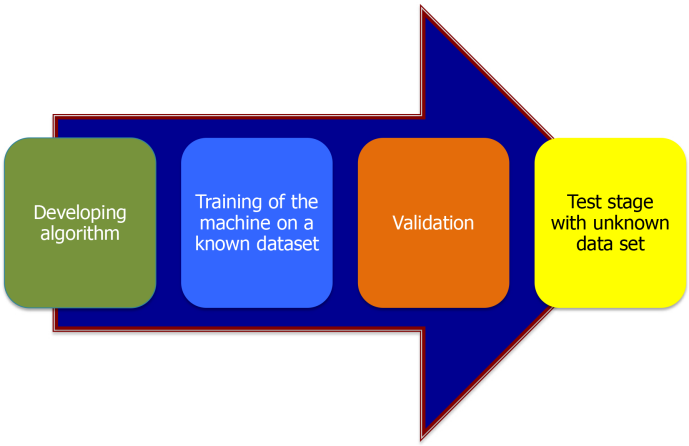

Figure 1 Showing the phases of machine learning.

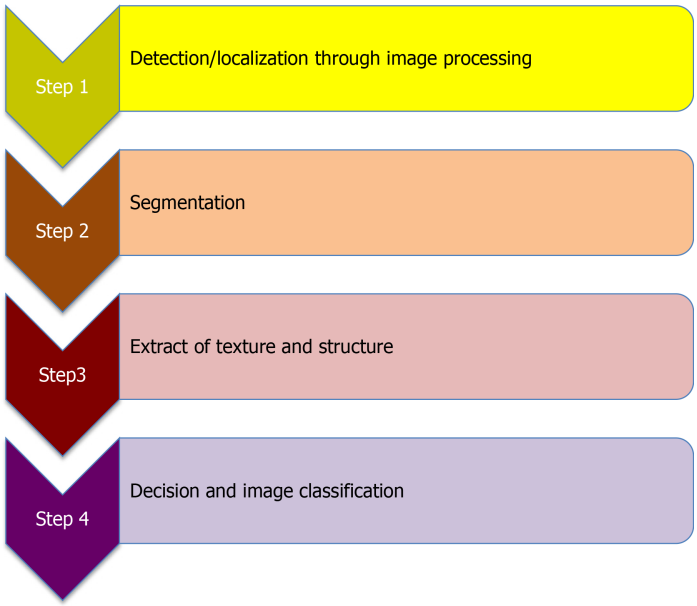

Figure 2 Showing the Step manner approach from detection to characterization.

deep convolution neural network. The system aimed to decrease the blind spots during upper GI endoscopy[17]. Unfortunately, they only examined images of benign and malignant lesions, not during a real time endoscopy performance.

Comparing white light alone *vs* linked color imaging showed that endoscopists had a lower miss rate with linked color imaging (30.7% *vs* 64.9%) in detecting early gastric cancers post-*H. pylori* eradication[18]. Linked color imaging is a technique that enhances the color range and brightness of images, developed by Fujifilm, Tokyo, Japan[19].

White light for detection of upper GI neoplasms is the most common and the standard technique. Other methods using advanced high-quality imaging are becoming increasingly available in most endoscopy centers. These advanced imaging techniques increase the sensitivity and specificity of diagnostic accuracy, especially in BE. There is a noticed "synergy" between AI integrated systems and advanced imaging techniques. On the other hand, the bias in having good quality images is apparent when identifying artifacts and lighting errors as cancerous lesions, or as called "spectrum bias" (this is a systematic error, where the data used do not represent the patients in question). This is equal in AI and humans[20,21].

While, dye-based imaging enhanced endoscopy (IEE) uses a dye to enhance detection of neoplastic lesions, this might not be helpful for examining a wide tract for lesions, nor for spraying the whole GI tract with dye. However, equipment enhanced IEE (eIEE) solves these problems. eIEE was originally classified into lightening-only

techniques along with blue laser imaging (BLI), BLI-bright and NBI (Olympus), autofluorescence imaging (Olympus), and post-processing-only techniques such as: Flexible spectral image color enhancement - (Fujifilm) and iSCAN - (Pentax), all from Tokyo, Japan[22,23].

LCI merges the two techniques by low frequency intensity light, red color extraction, and variation enhancement in a red-green-blue color space digital image post-processing. The post-processing system has three modes of color enhancement (A, B and C) with varying grades. This yields enhancement of hemoglobin-related information and neoplastic lesion in C2 and C3 modes or enhancement of neoplastic structures in B7 and B8[10].

The visualization using a NBI was mostly used to detect the histological features in the research studies. NBI is an advanced imaging technology that uses digital optical methods to visualize more enhanced images than the standard white light[24]. NBI helps to examine the vascularity and abnormal histological features on site during colposcopy, thus adding AI to narrow band could improve the detection of the exact histology of polyps and saves time and effort waiting for histopathological assessment that may delay the intervention[25]. In addition, the NBI technique is easier than other more sophisticated techniques as chromoendoscopy[26].

Shin *et al*[27] used high resolution microendoscopy to detect esophageal cancer using AI integration, showing sensitivity of 93% and specificity of 92% in the training set and similar results, albeit slightly lower, in the test and independent sets.

Moreover, in other techniques like, capsule endoscopy, images taken couldn't be adjusted in position lightening or quality as they are dependent mainly on gut motility, plus their role in upper GI tract evaluation is still limited[28,29].

Online processing causes limitation on the acceptable latency requiring it to be low, so real time application mostly uses parallelization of the machine process. Current high-end GPU offer higher parallelization than current high-end CPUs, due to larger number of cores. An example for this issue appears when Nvidia Tensor RT, a software development kit SDK for highly parallel machine learning, marketed to reach up to 40 × performance speed than CPU only applications. Tensor RT runs only on CUDA (compute unified device architecture), which runs only on Nvidia graphic card. Furthermore, other libraries, as "Caffe", can be used either by CPU or GPU, through switching a flag in the source code[30,31].

Localized data sets and implementations, limited to specific institutions, will cause bias in methodological validation. Thus, public records of images and datasets are preferable to decrease this bias. On the other hand, implementation doesn't suffer the same urgency for public recording[32].

While latency in offline detection could reach days, this is not acceptable in online real time detection, as the latency during endoscopy procedures will cause missing of the lesions in vivo, but improvement is more beneficial, as the ideal scenario is no latency.

While some studies showed promising results in vitro, there is still work to do offline in order to get a real time implementation which can detect neoplasia during the endoscopy conduction in vivo[33]. However, of 36 included studies in a recent meta-analysis exploring the AI integration in all types of upper GI cancers[3], only three studies were in a clinical setting and one was RCT, but even the RCT was on images not real time, and the rest of studies were on stored images offline. Furthermore, very few studies included videos or live *in vivo* validation.

The first real time study for detection of gastric cancer was performed using an online AI system with Raman spectroscopy integrated to GI endoscopy in vivo. Total computation time ranged from 100-130 milliseconds for analysis, with diagnostic accuracy of 80%[34].

Ohmori *et al*[35] introduced a new AI system that could process 36 images per second, making it adequate for RT integration in upper GI endoscopy. One concern of the authors is that limiting their processing to high quality images could impair the RT usage at the time being.

A recent meta-analysis by Arribas *et al*[3], concluded that we need to focus more on real time AI systems in upper GI endoscopy, because due to small number of studies (only two were retrieved in this metaanalysis[36,37], we are still uncertain of the feasibility of integration of AI with the endoscopists in RT situations.

In Ebigbo *et al*[37], they used a live-stream camera, examining the classification and segmentation of 14 BE patients, with diagnostic accuracy of 89.9%. AI prediction takes 1.19 s with "ensembling" and 0.13 s without "ensembling".

Luo *et al*[36] performed the first aided AI RT implementation study in upper GI endoscopy. During a case-control study in six different hospitals in China, they developed a new AI system for RT examination named Gastrointestinal Artificial

Intelligence Diagnosis System (GRAIDS), with latency of only 40 ms, and high diagnostic accuracy irrespective of the level of training of the endoscopists.

Imaging techniques, such as volumetric laser endomicroscopy, are used in BE to characterize different layers of the mucosa[38]. Characterization ideally includes the location, type and stage of neoplasia in the GI tract. A future prospect is the prognosis of this type.

"AI system is watching" is a statement that shows how endoscopists are more keen on clear videos and imaging when they know that an AI system will use those datasets [3,39].

The "blackbox" nature of CNN learning algorithms, means that we don't know how the AI system reached its diagnosis, thus no human learning could be benefited from AI neoplasia recognition[40]. This is accompanied by the lack of training and lack of learning interest in postgraduates, mostly due to the cancer prevalence problems mentioned before. The story is different in colonoscopy, where in most studies, experts in the field usually beat the AI systems or show equal diagnostic efficacy, also where experts beat beginners or junior physicians[41-44].

Another solution presented by the AI implementation, is that only one system could be used in all types of upper GI endoscopy. In a multicenter study done by Luo *et al* [36], they used a new system called GRAIDS. This system allowed for the examination of all types of upper GI neoplasms including both esophageal and gastric in a single system. In addition, the system showed similar diagnostic accuracy when compared to experts[36].

AI implementation in upper GI endoscopy proceeds first from detection (the lesion is present or not), to segmentation (the lesion is differentiated from the surrounding normal tissue), and then to characterization (the lesion is histologically predicted). A quality assessment tool for diagnostic accuracy studies called QUDAS score and its modified version are used for quality assessment of these diagnostic accuracy trials [45].

FUTURE ASPIRATIONS

One of the most promising findings was the early detection of precancerous lesions with chronic inflammatory background (chronic atrophic gastritis) with high specificity of all grades (mild, moderate and severe)[46]. This research might offer a solution to the hypothetical problem of background inflammatory state confusion with cancer. However, future validation is needed to reach our goal.

Accumulation of datasets, with the help of experts in annotating the pictures and videos of lesions in the upper GI endoscopy and linking them to the histopathological findings is mandatory for the progress of the AI in upper GI endoscopy. And public datasets will allow researchers to conduct their algorithm freely, without limitation to geographical regions or expert specialization in certain types of cancers.

Using a single system for detection of pan GI neoplasms with acceptable diagnostic accuracy for all GI regions is the ultimate goal, in addition to resolving the real time delay for image processing, which is still only scarcely examined in upper GI endoscopy.

CONCLUSION

Using AI integration with upper GI endoscopy could benefit trainees and general practitioners. Building a dataset library that is accessible to the researchers, with upper GI lesions apparent irrespective of the geographical area could be of great benefit to even experts in the fields with limited knowledge of the non-prevalent cancers in their area of practice.

ACKNOWLEDGEMENTS

Dr. Anup Kasi [Assistant Professor of Oncology in University of Kansas School of Medicine, Kansas City, KS (Medical Oncology), Unites States of America] edited the final version of the manuscript for English language flow and grammar.

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Artificial Intelligence in Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

Artif Intell Gastroenterol 2021 October 28; 2(5): 133-140

DOI: 10.35712/aig.v2.i5.133

ISSN 2644-3236 (online)

MINIREVIEWS

Application of artificial intelligence in liver diseases: From diagnosis to treatment

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Author contributions: Li Q collected and screened references, wrote original draft; Mao XR and Li JF supervised, reviewed, edited the manuscript and made the funding acquisition; All authors have read and approve the final manuscript.

Supported by National Natural Science Foundation, No. 81800528; the Natural Science Foundation of Gansu Province, No. 20JR5RA364; Key Research and Development Project of Gansu Province, No. 20YF2FA011; and the Health Industry Research Project in Gansu Province, No. GSWSKY2018–24.

Conflict-of-interest statement: Authors declare that they have no conflicts of interest.

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Abstract

Infectious or noninfectious liver disease has inexorably risen as one of the leading causes of global death and disease burden. There were an estimated 2.14 million liver-related deaths in 2017, representing an 11.4% increase since 2012. Traditional diagnosis and treatment methods have various dilemmas in different causes of liver disease. As a hot research topic in recent years, the application of artificial intelligence (AI) in different fields has attracted extensive attention, and new technologies have brought more ideas for the diagnosis and treatment of some liver diseases. Machine learning (ML) is the core of AI and the basic way to make a computer intelligent. ML technology has many potential uses in hepatology, ranging from exploring new noninvasive means to predict or diagnose different liver diseases to automated image analysis. The application of ML in liver diseases can help clinical staff to diagnose and treat different liver diseases quickly, accurately and scientifically, which is of importance for reducing the incidence and mortality of liver diseases, reducing medical errors, and promoting the development of medicine. This paper reviews the application and prospects of AI in liver diseases, and aims to improve clinicians' awareness of the importance of AI in the diagnosis and treatment of liver diseases.

Key Words: Artificial intelligence; Machine learning; Liver disease; Diagnosis; Treatment; Prognosis

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

Received: June 30, 2021
Peer-review started: June 30, 2021
First decision: July 28, 2021
Revised: August 9, 2021
Accepted: August 31, 2021
Article in press: August 31, 2021
Published online: October 28, 2021

P-Reviewer: Hanada E
S-Editor: Liu M
L-Editor: Kerr C
P-Editor: Li JH

Core tip: Liver disease has inexorably risen as one of the leading causes of global death and disease burden. As a hot research topic in recent years, the application of artificial intelligence (AI) in medical fields has attracted extensive attention. The application of machine learning in the liver diseases can help clinical staff to diagnose and treat different liver diseases quickly, accurately and scientifically, which is of importance for reducing the incidence and mortality of liver diseases, reducing medical errors, and promoting the development of medicine. This paper reviews the application and prospects of AI in liver diseases.

Citation: Li Q, Li JF, Mao XR. Application of artificial intelligence in liver diseases: From diagnosis to treatment. *Artif Intell Gastroenterol* 2021; 2(5): 133-140
URL: https://www.wjgnet.com/2644-3236/full/v2/i5/133.htm
DOI: https://dx.doi.org/10.35712/aig.v2.i5.133

INTRODUCTION

Infectious or noninfectious liver diseases cause a significant disease burden. There were an estimated 2.14 million liver-related deaths in 2017, representing an 11.4% increase since 2012[1]. Traditional diagnosis and treatment methods have various dilemmas in different causes of liver disease. With the development of artificial intelligence (AI) technology, new technologies have brought more ideas for the diagnosis and treatment of some liver diseases.

AI is an algorithm-based application field that simulates human mental processes and intellectual activities, enabling machines to solve problems with knowledge. In the information age, AI is widely used in the medical field and can provide accurate diagnosis and treatment for complex diseases, reduce medical errors, and promote the development of medicine[2]. For example, using deep learning architecture visual pattern analysis to detect basal cell carcinoma and distinguish malignant and benign lesions, the diagnosis accuracy rate is > 90% compared with experts[3]. There are two common types of AI. The first type is expert systems and the second is machine learning (ML), which is the core of AI and the basic way to make a computer intelligent (Figure 1). ML requires many data to train, which systematically improves computer performance in the process. By doing so, computers are able to shed light on previously unascertainable relationships that traditional statistical methods could not detect. ML is also capable of analyzing data types that were previously unavailable for advanced computer analysis, such as image and text data.

The area offering the most exciting new applications in healthcare is ML. Many studies in recent years have suggested that ML technology has many potential uses in hepatology, ranging from exploring new noninvasive means to predict or diagnose different liver diseases to automated image analysis. From the identification of liver areas at risk of radiation toxicity to the use of drug structures to predict the risk of liver injury, the accuracy of diagnosis and the effectiveness of treatment can be improved, and the efficiency can also be improved through automation. Although promising data from preclinical studies are now available, the application of AI in liver disease is far from being applied in clinical practice, so the application of AI in liver disease and other diseases remains challenging and deserves further study.

NEW ROUTES OF LIVER DISEASE DIAGNOSIS

Liver disease is not an independent disease. Because the specific types of lesions are different, the diagnostic methods differ. Different examination methods can be selected according to the specific types of liver diseases to be examined. For example, at present, the common diagnostic method for nonalcoholic fatty liver disease (NAFLD) is liver ultrasound (US)[4,5]; the common diagnostic method for liver fibrosis is liver biopsy[4]; the diagnosis of liver cancer (LC) mainly uses imaging images and biomarkers, and the staging mainly uses the Barcelona staging system. However, due to subjective and invasive factors, the current examination methods have certain limitations in the diagnosis of some liver diseases. The sensitivity and

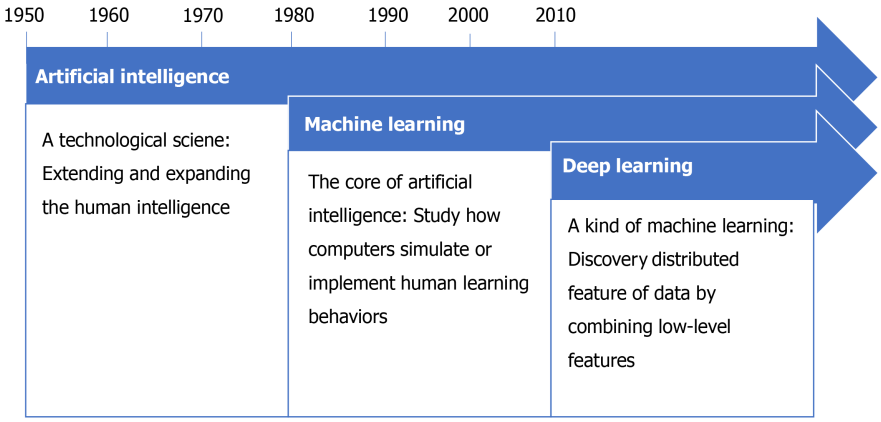

Figure 1 Timeline of the main concepts of artificial intelligence.

specificity of liver US decrease with increasing body mass index because US is subjective. As a solid tumor, hepatocellular carcinoma (HCC) has significant temporal and spatial heterogeneity, which can predict the treatment response and prognosis of HCC[6]. The Barcelona staging system does not include the histological and molecular characteristics of tumors. The application of AI has filled the gaps in these respects. By designing noninvasive examination means to intelligently analyze images and pictures, AI has improved the diagnostic efficiency and accuracy of clinicians.

Design noninvasive examination

The prevalence of NAFLD is currently increasing, and there are currently no accurate diagnostic means or targeted medicines. The application of AI can realize the early diagnosis of NAFLD, which is expected to reduce the further deterioration of the disease. Current research has developed automatic liver segmentation based on deep learning tools used for quantitative abdominal computed tomography (CT) of liver fat. This fully automated CT tool provides rapid and objective assessment that can be used in a large retrospective cohort for future studies. If hepatic steatosis proves to be an independent risk factor for future adverse events, the automated tool can also be used for opportunistic NAFLD screening with any nonenhanced CT, including liver (abdomen or chest) scan, regardless of the clinical indications of imaging[7]. In addition, a technique that combines noninvasive markers with the ML approach is suitable for optimal identification of NAFLD risk assessment and can also be extended to predict other types of disease caused by metabolic syndrome[8]. The use of ML algorithms to establish a prediction model of NAFLD based on laboratory parameters is also a current research direction. A prediction model named the NAFLD ridge score, which can be easily calculated and obtain a high negative predictive value, is recommended as the simplest and most predictive ML model to exclude NAFLD[9].

Liver fibrosis, regardless of the etiology, is believed to be key to the progression of any form of chronic liver disease (CLD), and persistent fibrosis is widely believed to be a major driver of the eventual development of cirrhosis and liver failure[10,11]. Liver biopsy is considered to be the gold standard for staging liver fibrosis; however, it is invasive and is limited by sample error, interobserver variability and various potential complications[12]. Radiological and serum markers of fibrosis are also used to assess liver fibrosis[13], and it is not reliable to accurately distinguish the stages of fibrosis in these patterns. There is a clear need for safe, effective and reliable noninvasive assessment modalities. A study that aimed to develop and validate a deep learning system (DLS) for staging liver fibrosis by using portal venous phase CT images demonstrated that a DLS trained by using a large amount of CT data allowed for highly accurate staging of liver fibrosis. In this study, DLS was superior to radiologists and serum fibrosis tests in diagnosing significant fibrosis, advanced fibrosis and cirrhosis[14]. In addition, an existing model called deep learning radiomics of elastography has shown the best overall performance in predicting liver fibrosis stage, which has certain value and practical value for the accurate noninvasive diagnosis of liver fibrosis stage in hepatitis-B-virus-infected patients[15].

Dig deeper into the medical images

HCC is the most common primary liver cancer and has significant temporal and spatial heterogeneity. AI-based imaging, i.e., imaging omics, can quantitatively

analyze tumor imaging to reveal the imaging manifestations of these heterogeneous characteristics. The concept of imaging omics was first proposed by Lambin *et al*[16] in 2012. It mainly extracts a large number of influential features from high-throughput radiological images and then uses statistics and AI algorithms to select the most valuable imaging omics to construct tumor predictive models. In essence, the significance of imaging omics is to dig deeper into the information of traditional medical images to compensate for the deficiency of the human eye.

Similarly, there is a need for better clinical classification of indeterminate liver nodules; however, the use of a single biomarker to predict the presence of cancer is difficult due to its multifactorial nature[17]. An AI-based predictive model of HCC reduced the misclassification rate by approximately half compared with that of a single tumor marker[18]. In addition, radiomics ML can be trained to diagnose hepatic nodules using the European Association for the Study of the Liver (EASL) guidelines in patients with HCC disease classified as uncertain cirrhosis[19]. According to EASL, indeterminate nodules include all nodules that do not provide arterial enhancement and washout [two major Liver Imaging Reporting and Data System (LI-RADS) features] and require biopsy regardless of LI-RADS; however, biopsies of cirrhosis carry life-threatening risks, including bleeding and tumor spread[20]. A study demonstrated that ML-based radiometric features using arterial and portal phase quantitative CT feature changes can enable the noninvasive diagnosis of HCC in patients with indeterminate nodules of cirrhosis. This feature will help to identify patients at high risk of HCC who should be prioritized for treatment to achieve significant clinical benefits[19].

AN ALTERNATIVE TREATMENT OPTION FOR LIVER DISEASES

Worldwide, CLD is a leading cause of morbidity and mortality[21]. There are a few therapeutic approaches for liver dysfunction, such as direct antiviral drugs (DAAs) for hepatitis C virus (HCV) and transarterial chemoembolization (TACE) for HCC[22]. Because some patients are resistant to DAAs and do not respond well to antiviral therapy and individualized responses to primary TACE vary among patients, AI seems to be an alternative option. AI has attracted attention for treatment of liver diseases in recent years, especially hepatitis C and LC[23]. AI can go beyond human reasoning to build drug-resistance predictive models from many complex combinations and overcome the limitations of traditional techniques, which may be effective in avoiding the emergence of a resistant virus, reducing medical costs and providing precise and personalized treatment advice for doctors and patients.

Build predictive models

With the popularization of DAAs and the application of new detection technologies and service models, global progress has been made in the detection and treatment of HCV. However, some patients with HCV are resistant to DAAs and do not respond well to antiviral therapy, and the current lack of means to screen these patients may delay disease treatment. AI algorithms can go beyond human reasoning to build predictive models from many complex combinations. A current study identified all variants of HCV whole-genome sequences that could be evaluated, and a support vector machine (SVM) based on a machine algorithm was the best prediction model. Similar models can be used to determine the best treatment for other viral infections and cancers[24].

Coinfection with human immunodeficiency virus 1 and HCV is common in some populations today; however, treating coinfections is a challenge. A previous study demonstrated that a multiple quantitative structure–activity relationship model showed high performance in predicting multitarget inhibitors with anti-HIV and -HCV activity[25]. The application of ML methods enables us to identify variables associated with reduced HCV treatment intake. The most recent variable, people who inject drugs (PWIDs), was identified as a major limiting factor associated with therapeutic intake deficit, even when priority criteria were met. PWIDs refers to people who have been injected at some point but are not currently using oral contraceptives or abusing drugs. In fact, intelligent network interruption analysis has been used as a targeted strategy to effectively interrupt HCV transmission between PWIDs [26]. Its application in clinical decision-making of infectious diseases should be expanded to optimize treatment and prevention strategies.

Provide personalized treatment advice

Due to the well-known limitations of TACE, AI seems to be an alternative treatment option for HCC. Some studies have reported the use of fusion imaging (FI) techniques to overcome the limitations of traditional techniques. FI is an AI-based technology that allows the fusion of two different imaging modes[27]. A prospective randomized study conducted by Huang *et al*[28] showed that the technical response rate of FI in ablation for hepatic nodules < 5 cm was close to 100% and reported the special usefulness of FI in tumors at less obvious and dangerous sites, not only to accurately delineate the target lesion and critical organs, the structures that may be close to the target area of ablation can also be accurately delineated.

The clinical decision support system (CDSS) is the software that is designed to be a direct aid to clinical decision-making, in which the characteristics of an individual patient are matched to a computerized clinical knowledge base and patient-specific assessments or recommendations are then presented to the clinician or the patient for a decision[29]. One study applied AI technology to clinical realworld data of patients with primary HCC, explored the precise treatment of disease and built up the AIbased CDSS, HCC CDSS. In the internal use verification process of HCC CDSS in West China Hospital, the matching accuracy rate between HCC CDSS and the multidisciplinary team treatment scheme reached 95.10%. This scheme is conducive to optimizing the clinical treatment decision of LC and can provide precise and personalized treatment advice for doctors and patients[30].

AI-DRIVEN PREDICTION FOR LIVER INJURY

Drug-induced liver injury (DILI) is a serious problem in clinical treatment and a common cause of drug development failure or withdrawal from the market[31]. Therefore, compound hepatotoxicity is important to determine.

Accurate estimation of the prognosis of patients with liver disease can help clinicians make appropriate treatment plans for different individuals; however, due to the complex process of CLD, the extensive impact on the systemic system and organs, and the lack of an adequate understanding of the nature of the development of liver disease, the understanding of the prognosis of different liver diseases is still limited. In recent years, HCV infection among LC patients and the mortality rate of HCV have been on the rise. Therefore, prediction of the prognosis of HCV patients has also attracted attention. Cirrhosis is a common, high-risk disease with slow clinical progression, and readmission and death in patients with cirrhosis are common and unpredictable. None of the clinically available predictive scores for cirrhosis can account for the broad range of clinical and psychosocial factors that may be associated with cirrhosis mortality. Individualized responses to primary TACE vary among patients with HCC. In addition, identifying a robust survival subgroup for HCC would also significantly improve patient care. The application of the prediction model of disease prognosis based on AI can improve the understanding of the prognosis of some liver diseases to a certain extent and provide an auxiliary reference for doctors' decision-making.

Analyze drug structure

AI is a low-cost, fast method to collect information on potential toxicity, and great efforts have been made in hepatotoxicity prediction in recent years. A study proposed that the integration of the Top-5 model could significantly improve the performance of hepatotoxicity prediction. The integrated Top-5 model consists of five base classifiers: Random Forest (RF) using Substructure Count, SVM using Chemistry Development Kit Extended, SVM using Chemistry Development Kit, SVM using PubChem, and RF using Klekota–Roth Count[32]. The deep learning model is also a stable and highly accurate predictive model of DILI, which can provide very useful safety information for early drug discovery and rational clinical drug use[33].

Predict risk of deterioration and mortality

The prediction of the prognosis of HCV patients has attracted attention in recent years. One study showed that the recurrent neural network model was superior to the logistic regression (LR) model in predicting HCC risk in patients with HCV-associated cirrhosis, including patients with supraventricular tachycardia following antiviral therapy; thus, it can be used to identify patients at high risk for HCV-associated cirrhosis to develop HCC and to inform risk-based HCC expansion and surveillance strategies[34].

None of the clinically available predictive scores for cirrhosis can account for the broad range of clinical and psychosocial factors that may be associated with cirrhosis mortality. ML techniques have been used to help fill these gaps in cirrhosis but are not yet widely available. In one study, three AI models were established, including LR, kernel SVM and RF classifier, and showed that these models had difficulty predicting readmissions and deaths in cirrhosis at 30 and 90 d. The accuracy of the AI model is comparable to that generated using the model for the end-stage liver disease-NA (MELD-NA) score alone, requiring additional biomarkers to improve the predictive power[35].

Another study developed and validated a cirrhosis mortality model (CIMM) using variables selected from ML algorithms. The results showed that ML can help select important variables for more transparent risk scoring while maintaining high accuracy. The synthetic hybrid CIMM performed better than the widely used model for MELD-NA score[36].

Speculate personalized response

For patients with LC, individualized responses to primary TACE vary. An AI-based radiomics strategy quantitatively analyses contrast-enhanced US images to predict personalized responses to primary TACE in HCC. There is potential for better selection of Barcelona Clinical Liver Cancer stage B patients receiving hepatic TACE and for better optimization of treatment planning and follow-up monitoring in the HCC management process[37].

Identifying a robust survival subgroup for HCC would also significantly improve patient care. Currently, few studies have integrated multiomics data to definitively predict HCC survival in a multipatient cohort. The survival-sensitive subtype model-deep learning model is of importance for the prognostic prediction and treatment intervention of HCC[38].

CONCLUSION

AI has become an important part of liver disease research, improving diagnostic accuracy, improving decision-making by enhancing predictive power, increasing efficiency through automation, and even predicting liver disease prognosis. Analysis of key biomarkers using ML can also provide deeper insights into the pathophysiology of liver disease. Despite the challenges, the application of AI in the field of liver disease is promising and worthy of further study. Researchers need to further develop new models of AI in liver disease diagnosis and precise treatment and conduct clinical verification to improve the accuracy of the results and promote the clinical application of AI. However, we must also be wary of over-reliance on such algorithms. AI will support rather than replace doctors, although computers and healthcare workers will have to work together. Ultimately, healthcare workers will have to make decisions for their patients based on their preferences, circumstances and ethics.

ACKNOWLEDGMENTS

The authors thank all the participants and staff who contributed to this study.

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Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
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E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
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ISSN 2644-3236 (online)

Artificial Intelligence in *Gastroenterology*

Artif Intell Gastroenterol 2021 December 28; 2(6): 141-156

Published by Baishideng Publishing Group Inc

A I G

Artificial Intelligence in Gastroenterology

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AIMS AND SCOPE

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

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

INDEXING/ABSTRACTING

There is currently no indexing.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
Artificial Intelligence in Gastroenterology

ISSN
ISSN 2644-3236 (online)

LAUNCH DATE
July 28, 2020

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Rajvinder Singh, Ferruccio Bonino

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2644-3236/editorialboard.htm

PUBLICATION DATE
December 28, 2021

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Artif Intell Gastroenterol 2021 December 28; 2(6): 141-156

DOI: 10.35712/aig.v2.i6.141

ISSN 2644-3236 (online)

REVIEW

Artificial intelligence in pathological evaluation of gastrointestinal cancers

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Author contributions: Alpsoy A and Yavuz A performed the data acquisition; Elpek GO designed the outline and coordinated the writing of the paper; all authors equally contributed to the writing of the paper and preparation of the tables.

Conflict-of-interest statement: There is no conflict of interest to disclose.

Country/Territory of origin: Turkey

Specialty type: Pathology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): D, D
Grade E (Poor): 0

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Abstract

The integration of artificial intelligence (AI) has shown promising benefits in many fields of diagnostic histopathology, including for gastrointestinal cancers (GCs), such as tumor identification, classification, and prognosis prediction. In parallel, recent evidence suggests that AI may help reduce the workload in gastrointestinal pathology by automatically detecting tumor tissues and evaluating prognostic parameters. In addition, AI seems to be an attractive tool for biomarker/genetic alteration prediction in GC, as it can contain a massive amount of information from visual data that is complex and partially understandable by pathologists. From this point of view, it is suggested that advances in AI could lead to revolutionary changes in many fields of pathology. Unfortunately, these findings do not exclude the possibility that there are still many hurdles to overcome before AI applications can be safely and effectively applied in actual pathology practice. These include a broad spectrum of challenges from needs identification to cost-effectiveness. Therefore, unlike other disciplines of medicine, no histopathology-based AI application, including in GC, has ever been approved either by a regulatory authority or approved for public reimbursement. The purpose of this review is to present data related to the applications of AI in pathology practice in GC and present the challenges that need to be overcome for their implementation.

Key Words: Digital image analysis; Digital pathology; Colorectal cancer; Gastric cancer; Machine learning; Deep learning

Core Tip: Recently, based on improvements in efficient computational power and learning capacities, various artificial intelligence applications, such as image-based diagnosis and prognosis prediction, have emerged in many fields of pathology. This

Received: December 6, 2021
Peer-review started: December 6, 2021
First decision: December 13, 2021
Revised: December 19, 2021
Accepted: December 27, 2021
Article in press: December 27, 2021
Published online: December 28, 2021

P-Reviewer: Balakrishnan DS, Li ZS
S-Editor: Liu M
L-Editor: Wang TQ
P-Editor: Liu M

review comprehensively summarizes the current status of artificial intelligence applications in gastrointestinal cancers. The present data are promising for the use of artificial intelligence to diagnose tumors, evaluate prognostic parameters, and detect biomarker/genetic alterations. However, many challenges hinder the implication of artificial intelligence models in real pathological practice. Therefore, these challenges and suggested solutions are also briefly presented to improve the accuracy and relevance of artificial intelligence in pathological practice, including in gastrointestinal cancers.

Citation: Alpsoy A, Yavuz A, Elpek GO. Artificial intelligence in pathological evaluation of gastrointestinal cancers. *Artif Intell Gastroenterol* 2021; 2(6): 141-156
URL: https://www.wjgnet.com/2644-3236/full/v2/i6/141.htm
DOI: https://dx.doi.org/10.35712/aig.v2.i6.141

INTRODUCTION

Pathology is a medical specialty that performs morphological evaluations of organs, tissues, and cells to provide a definitive diagnosis of diseases and contributes to treatment by determining the critical parameters in their course[1]. Although histopathological assessment under a light microscope is considered a cornerstone, especially in oncology, the search for more objective criteria to overwhelm the subjectivity related to interobserver and intraobserver variations and to diminish the increased workload and time consumption has led to the development of image analysis-based digital pathology (DP), which plays a crucial role in modern pathological practice[2,3].

Following the considerable advances of slide scanner technology that can quickly digitalize whole pathological slides at high resolution (whole-slide images, WSI), in 2017, the approval of the Philips IntelliSite whole-slide scanner (Philips Electronics, Amsterdam, Netherlands) by the Food and Drug Administration (FDA) in the United States allowed a comprehensive evolution in DP[4]. This digitization not only facilitated the application of telepathology and created a valuable resource for education but also yielded the analysis of a large spectrum of morphological parameters and biomarkers/genetic alterations[5-7]. In addition, such digital images are constituted from matrices of numbers that contain much more information that is not accessible to the human eye[8,9]. Indeed, it may be possible to extract predictive and prognostic biomarkers from such digitized slides by computer-based image analysis. These methods are particularly of direct interest to "computational pathology", a relatively new pathology field driven by artificial intelligence (AI) that is expected to transform and improve the diagnosis and staging of cancers[3,10]. As a result, pathological AI models have evolved from expert systems to traditional machine learning (ML) and, finally, deep learning (DL)[11]. While the traditional supervised ML allows the production of data output from previously labeled training sets that can be corrected by the users, labeling big data can be time-consuming and challenging[12]. In addition, the accuracy depends heavily on the quality of feature extraction. In contrast, unsupervised ML is a time-saving model because it provides automatic detection of patterns[13]. However, input data that are not labeled by users pose challenges during interpretation, leading to varying results.

On the other hand, DL extracts features directly from the raw data and utilizes multiple layers of hidden data for the output[14-16]. Compared to expert systems and handcrafted ML models, DL models are simpler to conduct, have higher precision, and are more cost-effective[9,17] (Table 1). Furthermore, a considerable increase in computational processing capacity and the development of algorithms, such as convolutional neural networks (CNNs), fully CNNs, recurrent neural networks (RNNs), and generative adversarial networks, have resulted in numerous investigations on the application of DL-based AI in pathological practice[7,18,19]. The strengths and weaknesses of typical ML methods are summarized in Table 1.

In addition, the use of AI in pathology has led to the emergence of many DL-based applications[20]. Proscia, DeepLens, PathAI, and Inspirata are DL-based applications for the detection, diagnosis, and prognosis of several cancer subtypes[21-25]. In addition, Inspirata and PAIGE.AI are spending substantial time and resources on

Table 1 Strengths and weaknesses of machine learning methods in development of artificial intelligence models for gastrointestinal pathology

AI model	Advantages	Disadvantages
Traditional ML (supervised)	Allows users to produce a data output from the previously labeled training set	Labeling big data can be time-consuming and challenging
	Users can reflect domain knowledge features	Accuracy depends heavily on the quality of feature extraction
Traditional ML (unsupervised)	Users do not label any data or supervise the model	Input data is unknown and not labeled by users
	Can detect patterns automatically	Users cannot get precise information regarding data sorting
	Save time	Challenges during interpreting
CNN	Detects the important information and features without labeling	A large training data is required
	High performance in image recognition	Lack of interpretability (black boxes)
FCN	Provides computational speed	Requires large amounts of labeled data for training
	Automatically eliminates the background noise	High labeling cost
RNN	Can decide which information to remember from its past experience	Harder to train the model
	A deep learning model for sequential data	High computational cost
MIL	Does not require detailed annotation	A large amount of training data is required
	Can be applied to large data sets	High computational cost
GAN	Generates new realistic data resembling the original data	Harder to train the model

AI: Artificial intelligence; ML: Machine learning; CNN: Convolutional neural networks; FCN: Fully convolutional neural networks; RNN: Recurrent neural networks; MIL: Multi-instance learning; GAN: Generative adversarial networks.

creating large libraries of digital WSI for use in training AI algorithms[21,24]. Interestingly, the landscape of DP is, in parallel, also undergoing important innovation and rapid changes[10].

It is also notable that some institutions are digitizing their entire pathology workflow, suggesting the routine use of AI-based systems in many areas of pathology soon[26,27]. Indeed, many studies have suggested that the integration of AI provides benefits for diagnosing and subtyping tumors, detecting histopathological parameters related to prognosis, and even identifying biomarker/genetic alterations in many fields of pathology[28]. On the other hand, the existence of a broad spectrum of difficulties, from AI-based pathology laboratory infrastructures to the robustness of algorithms, indicates that there are still many obstacles to be resolved before introducing AI applications in real-life pathology practice[29]. Nonetheless, AI-based approaches have the potential to contribute to pathological practice by improving workflows, eliminating simple errors, and increasing diagnostic reproducibility.

Regarding the gastrointestinal system, the accumulated data indicate that AI-based models might provide diagnostic assistance, prognosis prediction, and biomarker development for gastrointestinal cancer (GC). There have been few studies in the recent past that have addressed the effectiveness of AI models in GC[8,30]. However, effective implementation of these methods in real-life pathology practice requires further reviews comparing the results of previous studies and highlighting the challenges to be overcome.

This review presents recent data about the AI-based pathological evaluation of GC and current challenges for its implementation in gastrointestinal pathology practice with future directions to consider.

AI-BASED APPLICATIONS IN DIAGNOSIS OF GC

Recent studies on the use of AI models in the histopathological classification of gastric cancer are summarized in Table 2. Although the models used differ among studies, the results support that AI-based classification can be used in histopathological

Table 2 Artificial intelligence-based applications in gastric cancer

Ref.	Task	No. of cases/data set	Method	Performance
Duraipandian *et al*[89]	Classification	700 slides	GastricNet	Accuracy (100%)
Cosatto *et al*[72]		> 12000 WSIs	MIL	AUC (0.96)
Sharma *et al*[31]		454 cases	CNN	Accuracy (69%)
Qu *et al*[90]		9720 images	DL	AUCs (up to 0.97)
Yoshida *et al*[32]		3062 gastric biopsies	ML	Overall concordance rate (55.6%)
León *et al*[91]		40 images	CNN	Accuracy (up to 89.7%)
Liang *et al*[92]		1900 images	DL	Accuracy (91.1%)
Sun *et al*[93]		500 images	DL	Accuracy (91.6%)
Tomita *et al*[94]		502 images[1]	Attention-based DL	Accuracy (83%)
Wang *et al*[95]		608 images	Recalibrated multi-instance-DL	Accuracy (86.5%)
Iizuka *et al*[33]		1746 biopsy WSIs	CNN, RNN	Accuracy (95.6%), AUCs (up to 0.98)
Bollschweiler *et al*[41]	Prognosis	135 cases	ANN	Accuracy (93%)
Hensler *et al*[42]		4302 cases	QUEEN technique	Accuracy (72.73%)
Jagric *et al*[43]		213 cases	Learning vector quantization NN	Sensitivity (71%), specificity (96.1%)
Lu *et al*[36]		939 cases	MMHG	Accuracy (69.28%)
Jiang *et al*[37]		786 cases	SVM classifier	AUCs (up to 0.83)
Liu *et al*[40]		432 tissue samples	SVM classifier	Accuracy (up to 94.19%)
Korhani Kangi and Bahrampour[38]		339 cases	ANN, BNN	Sensitivity (88.2% for ANN, 90.3% for BNN)Specificity (95.4% for ANN, 90.9% for BNN)
Zhang *et al*[39]		669 cases	ML	AUCs (up to 0.831)
García *et al*[44]	Tumor infiltrating lymphocytes	3257 images	CNN	Accuracy (96.9%)
Kather *et al*[56]	Genetic alterations	1147 cases[2]	Deep residual learning	AUC (0.81 for gastric cancer)
Kather *et al*[47]		> 1000 cases[3]	NN	AUC (up to 0.8)
Fu *et al*[57]		> 1000 cases[4]	NN	Variable across tumors/gene alterations. Strongest relations in whole genome duplications

[1]Esophageal adenocarcinoma and Barrett's esophagus.
[2]Gastric and colorectal cancers.
[3]Gastric, colorectal, esophageal, and liver cancers.
[4]Gastric, colorectal, and pancreatic cancers.
AI: Artificial intelligence; GastricNet: The deep learning framework; WSIs: Whole slide images; MIL: Multi-instance learning; AUC: Area under the curve; CNN: Convolutional neural networks; DL: Deep learning; ML: Machine learning; RNN: Recurrent neural networks; ANN: Artificial neural network; QUEEN technique: Quality assured efficient engineering of feedforward neural networks with supervised learning; NN: Neural network; MMHG: Multimodal hypergraph learning framework; SVM: Support vector machine.

evaluations based on the accuracy and area under the curve (AUC) values determined. Different models are considered together in a few studies. For example, in a study where two DL-based methods were used to diagnose gastric cancer, the mean accuracy of both models was shown to be up to 89.7%[31]. In another study that compared the classification results of experienced pathologists with those of the ML-based program created by NEC Corporation, in gastric biopsy specimens, the agreement rate for biopsy specimens negative for neoplastic lesions was found to be as high as 90.6%[32]. More recently, Iizuka *et al*[33], who aimed to classify gastric biopsies as gastric adenocarcinoma, adenoma, or nonneoplastic mucosa by using AI algorithms based on CNNs and RNNs, revealed that the AUC for gastric adenocarcinoma classification was 0.9, supporting that AI-based models could be helpful in the diagnosis of gastric cancer. Although these results suggest that AI can be used to diagnose gastric

cancer, it is difficult to relate these data to performance comparisons alone. In research, parameters such as the size of the dataset, resolution of detection, multisite validation, the number of categories to be classified, and most importantly, the presence of lesions other than malignancies that require diagnosis are also critical variables. In particular, the latter could be a potential limitation of AI-based models in actual practice. Indeed, a gastric biopsy is evaluated not only for malignancy but also for lesions such as gastritis and metaplasia. Therefore, an AI model used only for malignancy screening in gastric pathology will not reduce the pathologist's workload, as other findings also need to be reviewed.

AI applications have also been developed to diagnose colorectal cancer (CRC), which may allow classification of lesions as normal, hyperplasia, adenoma, adenocarcinoma, and histological subtypes of polyps or adenocarcinomas (Table 3). In an elegant study, Korbar *et al*[34] observed that their AI models could classify five colorectal polyp types with a 93% accuracy. In another study, a created DL model was able to reclassify colorectal polyps in a manner comparable to those of the pathologist, even in datasets from other hospitals[35]. From this perspective, the results of most studies are encouraging for the use of AI models in the diagnosis of CRC. However, this does not exclude the fact that comparing the performance of those models reliably necessitates a common task using a standardized dataset with standardized annotations because each model is derived from different datasets with different explanations and is focused on different tasks in current studies.

AI-BASED APPLICATIONS FOR PROGNOSTICATION OF GC

Because gastric cancer has more complex and heterogeneous morphological features than CRC, most AI-based studies performed on these tumors focus on diagnosis rather than prognostication studies (Table 2). Nevertheless, there is some evidence showing that AI models can be helpful to evaluate histopathological parameters, such as differentiation and lymphovascular involvement, which are essential in determining the survival time[36-38], recurrence risk[39,40], metastasis[41-43], and, accordingly, treatment of gastric cancer. In the survival analysis, a higher predictive accuracy for overall survival and disease-free survival than the tumor-node-metastasis staging system defined by the American Joint Committee on Cancer by SVM application has been demonstrated[37]. In addition, this method can also be used to predict adjuvant chemotherapeutic benefits, which can facilitate individualized therapy. Another study combining the demographics, pathological indicators, and physiological characteristics of the study group found that a method using a new multimodal hypergraph learning framework to improve the accuracy of survival prediction outperformed random forests and SVM in survival prediction[36]. Furthermore, when the artificial neural network and Bayesian neural network (BNN) values were compared in survival estimation, it was shown that BNN was superior to the artificial neural network method[38].

The application of neural networks significantly improves the prediction of lymph node metastasis[41]. In addition, in a study to determine the microenvironment that can predict tumor behavior, García *et al*[44]observed that a CNN model could be used to detect tumor-infiltrating lymphocytes (accuracy, 96.9%). However, the number of these studies should be increased to draw a better conclusion about the application of AI-based DP in the prognostication of gastric cancer.

In CRC, DL was found to be effective in predicting prognosis at all stages. For example, in a study where RNN analyzed tissue microarrays to predict 5-year disease-specific survival, the hazard ratio and AUC were determined to be 2.3 and 0.69, respectively[45]. In another study, a 99% accuracy was observed in estimating the course of the disease using more than 1000 histological images collected from three institutions[46]. Finally, in comparing five separate DL networks using 934 cases, Kather *et al*[47] observed that the hazard ratio was 1.99 in determining overall survival. In studies investigating the microenvironment with AI-based models in these tumors, AUC values ranged from 0.91 to 0.99[47-49]. In another interesting study, Weis *et al*[50] pointed out that detecting tumor bud hot spots with CNN may influence determining tumor budding, which plays a role in determining tumor behavior. The characteristics of these studies are briefly presented in Table 3. Although this needs to be supported and standardized by further comparative studies, all these findings suggest that AI can be applied for determining the behavior of CRC.

Table 3 Artificial intelligence-based applications in colorectal cancer

Ref.	Task	No. of cases/data set	Method	Performance
Xu *et al*[96]	Classification	717 patches (N, ADC subtypes)	AlexNet	Accuracy (97.5%)
Awan *et al*[97]		454 cases (N, ADC grades LG *vs* HG)	NN	Accuracy (97%, for 2-class; 91%, for 3-class)
Haj-Hassan *et al*[98]		30 multispectral image patches (N, AD, ADC)	CNN	Accuracy (99.2%)
Kainz *et al*[99]		165 images (benign *vs* malignant)	CNN (LeNet-5)	Accuracy (95%-98%)
Korbar *et al*[34]		697 cases (N, AD subtypes)	ResNet	Accuracy (93.0%)
Yoshida *et al*[100]		1328 colorectal biopsy WSIs	ML	Accuracy (90.1% for adenoma)
Wei *et al*[35]		326 slides (training), 25 slides (validation) 157 slides (internal set)	ResNet	157 slides: Accuracy 93.5% *vs* 91.4%(pathologists) 238 slides: Accuracy 87.0% *vs* 86.6%(pathologists)
Ponzio *et al*[101]		27 WSIs (13500 patches) (N, AD, ADC)	VGG16	Accuracy (96%)
Kather *et al*[47]		94 WSIs[1]	ResNet18	AUC (> 0.99)
Yoon *et al*[102]		57 WSIs (10280 patches)	VGG	Accuracy (93.5%)
Iizuka *et al*[33]		4036 WSIs (N, AD, ADC)	CNN/RNN	AUCs (0.96, ADC; 0.99, AD)
Sena *et al*[103]		393 WSIs (12565 patches) (N, HP, AD, ADC)	CNN	Accuracy (80%)
Bychkov *et al*[45]	Prognosis	420 cases	RNN	HR of 2.3, AUC (0.69)
Kather *et al*[46]		1296 WSIs	VGG19	Accuracy (94%-99%)
Kather *et al*[46]		934 cases	DL (comp. 5 networks)	HR for overall survival of 1.63-1.99
Geessink *et al*[104]		129 cases	NN	HR of 2.04 for disease free survival
Skrede *et al* [105]		2022 cases	Neural networks with MIL	HR 3.04
Kather *et al*[47]	Genetic alterations	TCGA-DX (93408 patches)[1] TCGA-KR (60894 patches)	ResNet18	AUC (0.77), TCGA-DXAUC (0.84), TCGA KR)
Echle *et al*[55]		8836 cases (MSI)	ShuffleNet DL	AUC (0.92-0.96 in two cohorts)
Kather *et al*[47]	Tumor microenvironment analysis	86 WSIs (100000)[1]	VGG19	Accuracy (94%-99%)
Shapcott *et al*[48]		853 patches and 142 TCGA images	CNN with a grid-based attention network	Accuracy (65-84% in two sets)
Swiderska-Chadaj *et al*[49]		28 WSIs	FCN/LSM/U-Net	Sensitivity (74.0%)
Alom *et al*[106]		21135 patches	DCRN/R2U-Net	Accuracy (91.9%)
Sirinukunwattana *et al* [107]	Molecular subtypes	1206 cases	NN with domain-adversarial learning	AUC (0.84-0.95 in the two validation sets)
Weis *et al*[50]	Tumor budding	401 cases	CNN	Correlation R (0.86)

[1]Gastric, colorectal, esophageal, and liver cancers.

AI: Artificial intelligence; N: Normal; ADC: Adenocarcinoma; LG: Low grade; HG : High grade; NN: Neural networks; AD: Adenoma; CNN: Convolutional neural networks; WSIs: Whole slide images; ML: Machine learning; VGG: Visual geometry group; AUC: Area under the curve; RNN: Recurrent neural networks; HR: Hazard ratio; DL: Deep learning; MIL: Multi-instance learning; TCGA: The cancer genome Atlas; MSI: Microsatellite instability; FCN: Fully convolutional neural networks; LSM: Locally sensitive method; DCRN: Densely connected recurrent convolutional network; R2U-Net: Recurrent residual U-Net.

AI-BASED APPLICATIONS FOR GENETIC AND MOLECULAR TESTING IN GC

In routine practice, evaluating surgical and biopsy specimens of GI cancers is essential

for identifying molecular biomarkers that predict the response to targeted therapies. This evaluation requires the use of immunohistochemistry or advanced molecular techniques.

The detection of genetic alterations called microsatellite instability (MSI), especially in CRC, is very important for treatment with immunomodulators[51-53]. In addition, it is possible to determine the MSI-related phenotype and identify conditions that require family information and close follow-up of the patient, such as Lynch syndrome [54]. The revelation that some of the genetic events in these cancers are associated with certain morphological events has led to several attempts to use AI-based algorithms in WSIs. Furthermore, due to the large number of samples available, CRC was seen as a prototype for these studies. In this context, accumulated data indicate that AI-based models are influential in determining both MSI and other genotypic changes[47,55-57]. In particular, the DL algorithm developed by Echle *et al*[55] to detect MSI in CRC using more than 8800 images recently showed an AUC of 0.96 in the multi-institution validation cohort (Table 3).

There have been other attempts to develop models that directly predict gene mutations from the WSI of gastric cancer. In addition, it has been observed that AI could also predict gene expression and RNA-seq data, and these models have remarkable potential for clinical translation[47,56,57] (Table 2).

However, further additional and prospective validation studies are necessary for GI cancers before applying AI in real life to reduce the molecular testing workload and allow testing in health care centers with limited resources.

CHALLENGES AND IMPLEMENTATION OF AI-BASED APPLICATIONS IN REAL-LIFE PRACTICE

In general, the need for a close review of the steps involved in ethics, design, financing, development, validation and regulation, implementation, and impact on the workforce in the application of AI in pathology has been highlighted[58].

From this perspective, although AI-based models are likely to play a critical role in gastrointestinal pathology, including GC, in the future, several problems similar to those in other fields of pathology need to be addressed to ensure implementation. Brief information about the difficulties encountered in applying AI models in pathology, including GC, and suggested solutions are presented in Table 4.

Ethical considerations

Although consent can be obtained from patients to use data for research purposes, a lack of approval for commercial use can cause problems in developing AI models[59]. Some researchers argue that this can be resolved by developing a framework for global data sharing by obtaining approvals that convey the possibility of commercial use for research and product development[30].

Design of AI models

The primary expectation of AI in pathology is to fill gaps and address unmet needs in the daily workflow. These needs mainly include workload-intensive and repetitive procedures, such as calculating tumor necrosis, mitotic count, and lymph node metastases, and diagnosing lesions prone to interobserver variabilities. The main goal to consider in developing AI applications in pathology is to solve a real clinical need. However, the development of models for AI application in this field of medicine involves a variety of stakeholders, including not just pathologists but computer scientists, IT, and pharmaceutical companies, which inevitably leads to different expectations and perspectives. For example, some may have academic publishing purposes, while others may be profitable commercial products. Therefore, an expected solution in pathology may not meet the expectations in finance, leading to the company not preferring to develop. To overcome these challenges and develop AI algorithms that are effectively used in DP, GC, pathologists, academic professionals who can develop technology, and companies that will promote the product must collaborate in harmony.

Development of AI models

Once AI models are designed and built, their development requires an accurate definition of the output, straightforward design of the algorithm, collection of a large follow-up sample or even pilot data, data disclosure and processing, and statistical

Table 4 Summary of challenges and suggested solutions in development process of artificial intelligence applications

Process	Challenges	Suggested solutions
Ethical considerations	Lack of patient's approval for commercial use	Approval for both research and product development
Design of AI models	Underestimation of end-users' needs	Collaboration with skate holders
Optimization of data-sets	CNN: Large amounts of images	Augmentation techniques, transfer learning
	Rare tumors: Limited number of images	Global data sharing
	Variations in preanalytical and analytical phases	AI algorithms to standardize staining, color properties, and WSIs quality
Annotation of data-sets	Interobserver variations in diagnosis	MIL algorithms
	Discrepancies among performances for trained algorithms	
Validation	Presence of ground truth without objectivity	Multicenter evaluations that include many pathologists and data-set
Regulation	Lack of current regulatory guidance specific for AI tools	New guidelines and regulations for safer and effective AI tools
Implementation	Changes in work-flow	Selection of AI applications that will speed up the work-flow
	IT infrastructure investment	Augmented microscopy directed to the cloud network service
	The relative inexperience of pathologists	Training about AI, integration of AI in medical education
	AI applications that lack interpretability (Black-box)	Constructions of interpretable models, generating attention heat map
	Lack of external quality assurance	Sheme for this purpose should be designed
	Legal implications	The performance of AI algorithms should be assured for reporting

CNN: Convolutional neural networks; MIL: Multi-instance learning.

analysis.

From this perspective, high-quality dataset optimization can be considered one of the biggest obstacles to the development of AI in DP. CNNs require a large number, even thousands, of pathological image datasets, to perform adequately[60]. Especially in rare tumors, the inability to obtain a very high number of images is quite limiting. To overcome this situation, the use of data augmentation techniques and learning methods is recommended. In contrast, Jones *et al*[61] indicated that small-scale datasets of < 100 digital slides might be sufficient in the case of transfer learning. Recently, it was proposed to develop publicly available datasets for global data sharing. However, it cannot be ruled out that very few such datasets are available in pathology, partially due to privacy, copyright, and financial issues[62]. Although The Cancer Genome Atlas provides many WSIs and associated molecular data, it does not contain enough cases for training AI applications for clinical practice[63,64]. Hartman *et al*[63] pointed out that another potential source of datasets could be public challenges provided for developing DL algorithms.

Again, developing high performance in AI applications in DP requires training on large datasets, which can be affected by the preanalytical (variations in fixation protocols and variations in the thickness of tissue sections) and analytical (variations in staining techniques and scanning protocols) phases applied to acquire digital images[65,66]. Indeed, converting a glass slide to WSI is not a simple task, and color modifications may influence the accuracy of AI. For this purpose, several AI algorithms have emerged to standardize data in recent years, including staining and color properties[67-69]. In addition, several automated algorithms have also been provided to standardize WSI quality, which automatically detects regions of optimum quality and removes out-of-focus or artifact-related regions, such as DeepFocus[70,71].

Annotation of the dataset

The curation of the dataset should be followed by annotation, which is another complex task. The limits of this annotation are broad, depending on AI, ranging from classification at the slide level to labeling at the pixel level[7,30]. For pathologists, the task of annotating many images is a time-consuming, sometimes challenging effort that can affect the accuracy of the models being trained, especially when the task is complex, especially if, as in gastrointestinal pathology, the disease selected for diagnosis differs significantly among observers (*e.g.*, intramucosal carcinomas) and if

the accuracy of dataset descriptions cannot be warranted[72]. Moreover, the trained algorithm may not produce the same performance in the dataset when used in other medical centers. Recently, many efforts have been made to solve the annotation problems that hinder the application of AI in pathology practice[67,73]. The data support that multi-instance learning (MIL) algorithms can be applied without detailed annotation. In particular, there is evidence that MIL can be effective when there is a large dataset and detailed annotations are impossible to obtain[60].

Validation and regulation

The preparation of the annotated dataset is followed by the model development process (preparation of the datasets for training, testing, and validation) and the selection of the learning method with the ML technique. In this context, the validation of AI-based technologies requires an evidence-based approach, and it is emphasized that analytical validation should also be considered in a laboratory-centered medical discipline, such as pathology[58,73]. Therefore, it is essential to establish steps and criteria for validating new tests according to the standards. For example, to validate the image analysis used to determine the expression of a biomarker, the technique can often be compared to a detailed manual tumor assessment. However, the performance of the AI technique compared with that of pathologists is not straightforward, given the intraobserver and interobserver variability. Today, there are difficulties associated with determining "ground truth" to AI applications. This situation leads to the need for repeated validation of the robustness and reproducibility of AI applications in large and variable patient groups[30].

There may be a relative lack of validation cohorts in the development of AI-based applications in DP. This shortcoming is also contributed by the potential limitation in sharing histopathological sections. Although the interobserver variability and subjectivity in the evaluations of pathologists also indicate the uncertainty of "ground truth" in this aspect, the best measure to overcome this obstacle may be multicenter evaluations that include more than one pathologist and dataset. From the perspective of GC, the lack of external validation in a substantial number of studies for AI applications may limit the practical use of AI.

Regulation of AI

Although appropriate regulations are necessary for the safe and effective use of AI in pathology, as highlighted by Allen[74], regulatory approval should be structured to define the risk-benefit balance, reduce potential harm, produce appropriate verification standards, and encourage innovation. On the other hand, the presence of various challenges should not be ignored in this regard.

Various regulatory authorities [such as the FDA, Centers for Medicare and Medicaid Services (CMS), and the European Union Conformité Européenne (EUCE)] are not yet fully prepared for the implementation of AI applications in clinical medicine. As a result, AI-based devices are being controlled by old and potentially outdated guidelines for testing medical devices.

Currently, in the United States, the FDA is working on new regulations to make AI-based devices safer and more effective[75]. On the other hand, appropriate validation for all laboratory tests using human tissue prior to clinical application is required by CMS regardless of FDA approval, and this organization has no specific regulations to validate AI applications. Furthermore, the EUCE reported that *in vitro* diagnostic medical device directives will be replaced by *in vitro* diagnostic regulations in May 2022[76]. In addition, it is necessary to take into account the regulatory trends of the country where AI is implemented.

Implementation

The implementation of AI models in daily pathology practice depends on meeting specific requirements by overcoming various challenges. First, a laboratory infrastructure equipped to enable AI applications in a time frame that does not interfere with patient care is essential. Currently, many pathology laboratories only use tissue sections for diagnostic evaluations. However, the implementation of AI models will require new DP-related equipment, software, a specific data management system, data storage facilities, and, more importantly, a substantial investment to cover their cost[77]. In addition, an institutional IT platform is required to enable practitioners to operate on-site and cloud-based computing systems. Thus, DP applications may require significant investment, hindering the implementation of these technologies. It has been demonstrated that augmented microscopy directly connected to the cloud network service can solve the whole slide scanner setup problem[78]. The

cloud-based AI application developed by GOOGLE can also aid in the search for morphologically similar features in a target image, regardless of the annotation status [79].

The relative inexperience of pathologists with AI-based technologies should not be overlooked. Therefore, pathologists need to improve their knowledge of both the installation of DP systems and the application of AI. Another problem is that, given the reported performance of some algorithms, automated AI models are believed to outperform pathologists, causing pathologists to be hesitant about these applications [79-81]. However, current results suggest that AI models are more likely to help improve the overall quality of pathological diagnosis and provide relevant additional information rather than replacing pathologists[82,83]. Indeed, there will always be a need for pathologists to audit technologies and control systems in AI implementation. Therefore, pathologists must be aware of the long-term risk-benefit balance of AI applications[84]. Since current DL-based AI applications lack interpretability, it may be helpful to develop AI solutions that end-users can interpret, thus providing them with detailed explanations of how their predictions are made. Although DL's "black box" problem has not been fully resolved, several solutions have been reported, such as constructing an interpretable model, generating an attention heatmap, and constructing an external interpretive model[85-88].

While AI assistance in pathological diagnosis may reduce the opportunities for learning diagnostic skills during pathology training, resident pathologists should be trained and encouraged to learn the utility, limitations, and pitfalls of AI application as an adjunct method to improve the quality and precision of clinical diagnoses. Therefore, some reforms may be required in pathology training, starting with medical education followed by a pathology education program to address a more accurate and safer implementation of AI in pathology practice[84].

Like other clinical tests, quality assurance is an important issue for the effective use of AI in DP, and consequently, a scheme of external quality assurance for applications should be urgently prepared for its implementation. Furthermore, laboratory staff should be aware of the quality management system.

Beyond all this, the legal implications of signing a report prepared by a pathologist using AI should not be ignored. Therefore, to include AI findings in a pathological report, the performance of the algorithm must be assured. This legal issue also supports the notion that AI cannot replace pathologists but that AI can be used to support pathologists in clinical trials.

CONCLUSION

AI-based approaches have the potential to contribute to the pathological diagnosis and staging of GC by improving workflows, eliminating simple errors, and increasing diagnostic reproducibility. It is also the case that it encourages biomarker discovery by revealing impossible predictions using traditional visual methods. However, there are many hurdles to overcome, including infrastructure and the generalization of algorithms. Overcoming these obstacles requires the efforts of computer scientists, pathologists, and clinicians, who will deal with each challenge separately and cooperate in harmony. In this way, AI applications that are user-friendly, explainable, manageable, and cost-effective can play a crucial role in the development of pathological assessments to be used in the diagnosis, prognosis, and treatment of GC.

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